Extended Abstract

1. Summary & Objectives

The PhD thesis of M.A. Teixeira was developed at the Laboratory of Separation and Reaction Engineering (LSRE) at the Faculty of Engineering of the University of Porto, under the supervision of Professor Alírio E. Rodrigues. M.A. Teixeira was approved by unanimity with distinction and this research was part of the Doctoral Program in Chemical and Biological Engineering in which he also obtained a classification of merit in three courses (Proposal Research, Dissertation, and Pharmaceutical and health care products). In the final part of his PhD, it was also developed a partnership work with the Procter & Gamble Company (UK). Overall, the research performed during 4 years resulted in a series of experimental data, together with new methodologies, theoretical models and innovative tools that seek to describe, assess, quantify and predict the way we perceive odours and fragrance chemicals.

The main motivation for this PhD relied in two key topics that we explore ahead: first, fragrances are present everywhere, being part of the formulation of more than 75% of household consumer products (*e.g.* cosmetics, toiletries, perfumes); and second, their design or incorporation into end-user products is still based on the empirical knowledge of perfumers, leading to countless trial-and-error formulations, which, consequently, raise products' cost and time to market. For the former motivation, it should be said that consumers are extremely attracted to perfumed products because they influence their image and mood. Consequently, it is no surprise that the Flavour & Fragrance (F&F) business is a multi-billion dollar market spread all over the world (Leffingwell & Leffingwell, 2011). For the latter, note that the knowledge in this field is limited due to the secrecy imposed by major companies in such a profitable business, but also because it still remains as an art. Nevertheless, the latter problem is perhaps a consequence of the lack of knowledge in understanding the sense of olfaction. Moreover, the chemical complexity arising from perfumes is mainly due to the desire of their creators to deliver perceptual complexity and intensity to consumers which adds significantly to the costs.

However, recent works suggest that it is possible to reduce the number and quantity of chemicals used in product formulation through the use of scientific principles, without any measurable reduction in perceptual complexity (Cussler *et al.*, 2010; Bagajewicz *et al.*, 2011). This was something that M.A. Teixeira was also developing before. Although this is a complex process to be achieved, there is no doubt that an opportunity shows up for new tools aimed at the optimization of fragrance product development by implementation of predictive models together with human perception. All the aforementioned are reasons enough to draw the conclusion that the perception of perfumed products is indeed complex, especially when the number of available chemicals involved is high. But it is also a window of opportunities.

When M.A. Teixeira started his PhD it was clear that the main objectives were focused on the development of tools for the optimization of the design, performance and classification of perfumed products in a scientific way. Such would come together with the evaluation and, ultimately, the prediction of the performance of perfumed products, thus contributing to lower production costs and manufacturing time at the industrial level.

2. Research framework and approach

2.1. From Product to Perfume Engineering

Recalling perfume mixtures, these are generally highly complex liquid solutions of hundreds of odorant chemicals dissolved in solvents (plus stabilizers, antioxidants, UV filters, colouring agents). The former compounds evaporate and diffuse at different rates through air over time and distance until airborne molecules reach our nose and get noticeable with some intensity and character. The study of this chain of processes includes multidisciplinary sciences, starting from thermodynamics to transport phenomena, and from biochemistry to psychophysics. Thus, the combination of these sciences (or parts of them) for their application to perfume design, can be performed through Product Engineering, an emerging paradigm of the last decade (Ulrich & Eppinger, 2000; Cussler & Moggridge, 2001; Costa *et al.*, 2006; Bagajewicz, 2007; Wei, 2007; Wesselingh *et al.*, 2007; Teixeira *et al.*, 2011b; Teixeira *et al.*, 2012a). In fact, Chemical Engineering can be viewed as two interrelated fields: what we want to produce, that is Product Engineering or Product Design, and how we should produce it, which is the scope of Process Engineering. Without a doubt, nowadays, the development of many novel products to meet consumer needs comprises these two fields of knowledge. Figure 1 illustrates this relationship within Chemical Engineering. First and foremost, such products have to go through several stages till reaching the market: needs, ideas, design, development, optimization, production, and testing (Charpentier, 1997; Cussler & Moggridge, 2001; Ulrich & Eppinger, 2003). This is the reason why product engineers need to have knowledge and expertise in multiple scientific fields, but also about customer needs and marketing (Wesselingh, *et al.*, 2007). Extending the current limits of product's performance has now become a key factor for Product Engineers who must hand out innovative and valued products, technologies and services to the market.

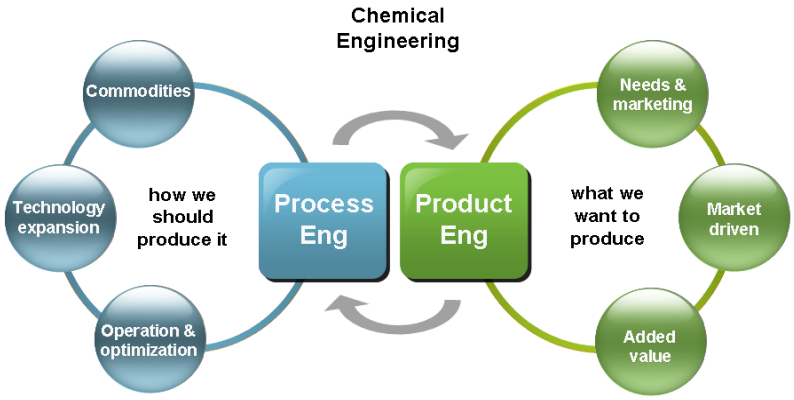

Figure 1 - Relationship between Product and Process Engineering within Chemical Engineering.

Hence, the development of Perfume Engineering itself represents a particular case in the field of Product Engineering, inside the F&F industry, with the main objective of implementing scientific knowledge into a so far empiric and experimental area. To address the proposed problem for Perfume Engineering, in terms of design, performance and classification of fragrance products, a model was developed to account for fragrance perception starting from product's formulation to the olfactory perception of odours.

2.2. Odour perception model

At the basis it was considered that a perfume can be approximated to a liquid mixture of *N* fragrance ingredients and solvents that is evaporating into the air above it. For that part, it is known that fragrance molecules have different physicochemical properties and that interactions will be occurring at the molecular level, influencing the release rate of each. Then, odorant molecules will diffuse in air until they reach the human nose where they solubilise in the mucus layer, partitioning to the nasal epithelium to reach the olfactory neurons. There they bind to olfactory receptor (OR) proteins, triggering a response to the olfactory bulb in the brain which is interpreted as an odour fingerprint. As the concentration rises, it is expected that the perceived sensation magnitude will also increase following some relationship. Within a mixture of odorant molecules some will be more strongly perceived than others, thus defining the character or quality of the mixture. Figure 2 schematically represents the steps involved in this model.

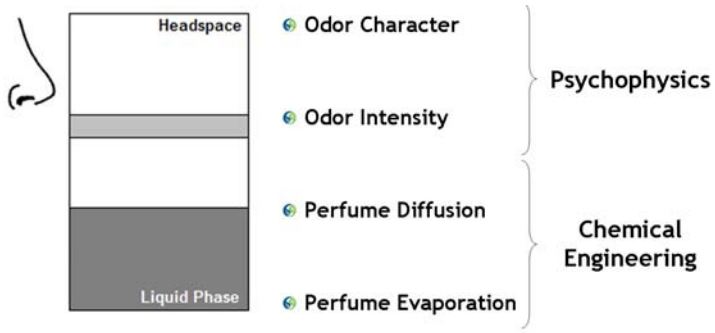

Figure 2 - Schematic representation of the steps involved in the odour perception model.

2.3. Perfumery Quaternary-Quinary Diagram (PQ2D®)

However, once defined our approach, how could we possibly represent in a graphical way the odour perceived from a simple fragrance mixture? The answer for this question, started to be sketched within the parallelism found between the classic perfume pyramid structure (which has top, middle and base notes) (Carles, 1962) and ternary phase diagrams, commonly used in engineering and physical-chemistry. The result was the Perfumery Ternary Diagram (PTD®), a graphical software tool for the prediction of perceived dominant odours for any possible ternary mixture (Mata *et al.*, 2005; Teixeira, 2011). In order to calculate the perceived odour intensity and character of any single mixture, a model is required to calculate its magnitude from vapour concentrations like the concept of Odor Value (OV) or the Stevens' Power Law (Ψ) (Stevens, 1957; Calkin & Jellinek, 1994; Teixeira *et al.*, 2010a). For its part, the OV is a quantitative parameter, that defines the strength of an odorant as the ratio between its concentration in the headspace (C_i^g) and its odour detection threshold in air (ODT_i) (Calkin & Jellinek, 1994; Zwislocki, 2009; Ohloff *et al.*, 2012):

$$OV_i = \frac{C_i^g}{ODT_i} \quad (1)$$

For the Power Law, the relationship is raised to a power exponent (n_i) and defined as:

$$\Psi_i = \left(\frac{C_i^g}{ODT_i} \right)^{n_i} \quad (2)$$

The ODT, for its part, represents the minimum concentration of an odorant that can be perceived by the human nose. From this point, the concentration of the different fragrant components in the gas phase above the liquid (C_i^g), can be calculated from Thermodynamics using the general equation for vapour-liquid equilibria (VLE):

$$y_i \phi_i P = x_i \gamma_i P_i^{sat} \quad (3)$$

where y_i and x_i are the vapour and liquid mole fractions of component *i*, while ϕ_i and γ_i are the vapour and liquid activity coefficients of *i*, respectively. *P* is the total pressure and P_i^{sat} is the saturation pressure of pure component *i*. At atmospheric pressure, ideal gas behaviour can be assumed so that eq. 3 can be simplified by considering $\phi_i = 1$. Consequently, the concentration of odorant species in the headspace (C_i^g) can be calculated:

$$C_i^g = \frac{y_i M_i P}{RT} = \gamma_i x_i \frac{P_i^{sat} M_i}{RT} \quad (4)$$

where M_i is the molecular mass of component *i*, *R* is the universal gas constant and *T* is the absolute temperature. Thus, combining eq. 4 with the OV or Power Law models, it is possible to calculate the perceived odour intensity. Activity coefficients can be calculated with the UNIFAC method for prediction of the VLE (Poling *et al.*, 2004).

However, when considering a perfume with *N* fragrant components, there will be *N* different odorants in the headspace. To account for the odour perception of multi-component mixtures, the Strongest Component model can be applied. It states that the mixture odour intensity can be approximated to the maximum odour intensity of its components, although there is a mixture of perceived scents in the air (Laffort & Dravnieks, 1982):

$$OV_{mix} = max\{OV_i\} \quad or \quad \psi_{mix} = max\{\psi_i\}, \; i = 1,\ldots N \quad (5)$$

Although the PTD® tool is suitable for ternary mixtures comprising a top, middle and base note it does not allow viewing the whole perspective of a quaternary mixture comprising a solvent in its formulation. For that purpose, M.A. Teixeira developed another graphical tool called Perfumery Quaternary-Quinary Diagram (PQ2D® - see Figure 4b) (Teixeira *et al.*, 2009b). The PQ2D® uses the same approach described before but it is suitable for quaternary and quinary mixtures, and if some constraints are defined it is suitable to show the behaviour of octonary ones (Teixeira, 2011). It uses 3-D tetrahedrons to map the perceived odour and introduces the concepts of Perfumery Binary Surfaces (PBS) and Perfumery Ternary Lines (PTL), composition points where two and three components share the maximum odour intensity, respectively.

2.4. Perfume performance & diffusion model

Nevertheless, despite the relevance of the PTD® and PQ2D® methodologies for prediction of the perceived odour, there was not yet, in the literature, any approach that could predict the performance of a fragranced product. In order to achieve that goal, it was developed a diffusion model based on Fick's Law and it was coupled with perfumery performance parameters. The developed model is presented in equations 6 and 7, together with defined initial and boundary conditions. It was implemented in the MATLAB software and was later validated using a diffusion tube built for that purpose (Teixeira *et al.*, 2009a).

$$\frac{\partial y_i}{\partial t} = D_{i,air}\frac{\partial^2 y_i}{\partial z^2} \tag{6}$$

$$\frac{dn_i}{dt} = D_{i,air}A_{lg}c_T\left.\frac{\partial y_i}{\partial z}\right|_{z=0} \tag{7}$$

where y_i and $D_{i,air}$ are the mole fraction of species *i* and diffusivity of component *i* in the gas phase in the gas phase, respectively. Moreover, *t* is the time variable, n_i is the number of moles of component *i* in the liquid phase and A_{lg} is the area of the liquid-gas interface.

Initial Conditions (IC)

Gas Phase

$$t = 0: \quad y_i = y_{i_0} = 0 \tag{8}$$

Liquid Phase

$$t = 0: \quad n_i = n_{i_0} \text{ or } x_i = x_{i_0} \tag{9}$$

Boundary Conditions (BC)

$t > 0:$

$$z = 0: \; y_i = \frac{\gamma_i P_i^{sat}}{P}x_i = \frac{\gamma_i P_i^{sat}}{P}\frac{n_i}{\sum_i n_i} \tag{10}$$

$$z = z_{max}: \; y_i = 0 \tag{11}$$

Knowing vapour concentrations, it is possible to convert them into odour intensities using the previous Psychophysics models and, thus, evaluate the perceived odour over time and distance using performance parameters. These are presented in Figure 3 and provide a picture of the propagation of a given fragrance in air, allowing the comparison of the effectiveness of different ingredients or formulations.

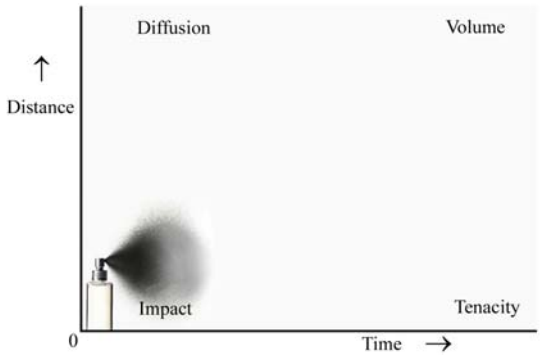

Figure 3 – Parameters used by perfumers to evaluate the performance of a perfume as a function of the intensity and character of the perceived odour with time and distance.

This model was applied to several perfume mixtures and experimentally validated to predict fragrance performance from liquid composition only (Teixeira, 2011). Moreover it was applied to textiles impregnated with scented microcapsules for a product like perfumed man suits, allowing to model the release and propagation of a perfume scent in air (Teixeira, *et al.*, 2011b).
Furthermore, from the two approaches presented before, it becomes clear that there are two relevant topics that must be carefully addressed: the ODT and the VLE of fragrance mixtures. ODTs are at the bottom of the perceived intensity scale and so their experimental determination is laborious and dependent of physiological variability. Consequently, the prediction of ODTs would be of great interest and economic value. For that purpose, M.A. Teixeira assumed that at low concentrations, odorant-OR interactions would not be the limiting step, since most of the ORs would be available. Thus, the controlling step would be the transport processes from air through the mucus to the epithelium. Furthermore, assuming transport phenomena is fast, then equilibrium between air/mucus and mucus/OR phases would be reached and the question is reduced to partitioning of odorants between the different phases. Consequently, a new predictive equation using three physical properties of odorants was developed: saturation pressure, water solubility and 1-octanol/water partition coefficient (Rodríguez *et al.*, 2011). On the other hand, VLE of fragranced products is a key process to evaluate both their odour intensity and character. For that purpose, several predictive G^E methods based on the group contribution concept (UNIFAC, UNIFAC-Dortmund, ASOG and A-UNIFAC) were evaluated (simulation and experimental data) for the prediction of multi-component VLE (Teixeira *et al.*, 2011a).
Finally, M.A. Teixeira developed, in the final part, of his PhD two different topics: on one hand, the odour perception model previously presented was validated for the first time with experimental olfactory evaluations using perfumers and non-trained panellists (Teixeira *et al.*, 2012b). This work was done in collaboration with the Procter & Gamble. On the other hand, a novel tool called Perfumery Radar was designed to predict the classification of perfumes into olfactory families, reducing interpersonal variability of olfactory evaluations from experts, as happens in the industry. It can be structured into the following steps: 1. Classification of pure fragrances in olfactory families; 2. Prediction of the odour intensity for each fragrance using the OV concept; 3. Determination of the OV for each olfactory family and representation in the Perfumery Radar. The PR uses typical terms for classification of fragrances (which can be adapted or updated at demand) and the models depicted before for the prediction of main olfactory families of a perfume, thus reducing the controversy with perfumers' classifications.

3. State of the art

Despite the fact that this thesis comprises transversal topics for the design, performance and classification of fragranced products, it is also true that some of them are quite different. Accordingly, here, we will attempt to resume the state of the art (where it applies) in the most relevant ones. Note, however, that some of the topics addressed, like the PQ2D®, result from the combination of models from different sciences and, thus, have no comparison in the literature.

Considering the different steps in the developed odour perception model, it is important to address all the phenomena involved in the formulation, behaviour, release, diffusion and perception of fragrances: *i)* the evaluation of both vapour-liquid and liquid-liquid (or even vapour-liquid-liquid) equilibrium of mixtures composed by fragrance ingredients at different temperatures which may provide important information for fragrance development (Arce, et al., 2002; de Doz, et al., 2008); *ii)* measurement of phase interactions for multi-component mixtures composed by surfactant(s), water, and fragrance ingredient(s) is also valuable for the industry (Tokuoka, et al., 1994; Friberg, et al., 2009); *iii)* other studies concerned with the solubility of fragrance materials in water and alcohols were of great importance to evaluate skin disorders, since they are used in a number of cosmetic products (Domanska, et al., 2008; Domanska, et al., 2010); *iv)* additionally, studies involving humans are of relevance for estimating evaporation and absorption of fragrances from the skin, evaluation of the kinetics for fragrance ingredients applied onto the human skin *in vitro* as well as modelling these phenomena (Kasting and Saiyasombati, 2003). Concerning the evaporation of fragrances from other media, there are several studies using polymeric microcapsules containing fragrance chemicals, some of which were tested for impregnation into fabrics and posterior evaluation of the released materials using headspace gas chromatography, cryogenic systems coupled with chromatography, electronic noses, or olfactory evaluations (Haefliger *et al.*, 2010).

In terms of fragrance propagation in air the first preliminary study is probably that of Calkin and Jelinek with the empiric definition of performance parameters like impact, tenacity, diffusion and volume as well as important properties for the evaluation of performance like the odor value, odor threshold or log P (Calkin & Jellinek, 1994). Gygax *et al.* (Gygax & Koch, 2001) combined headspace measurements with olfactometry data and correlated physicochemical properties for evaluation of fragrance performance. Furthermore, Stora *et al.* (Stora *et al.*, 2001) evaluated perfume performance based on the chemical structure and physicochemical properties of the single species. Finally, it is worth mention some patented methods for formulation of fragranced products to mask malodors or perfume compositions designed for use in wash-off systems. Despite the relevance of these studies, it was lacking a supporting theory or model to explain the experimental data they measured.

Concerning the perception of odours at the threshold level there were few studies attempting to predict ODTs. It can be resumed to the works of Abraham *et al.* (Abraham *et al.*, 2002) and Hau (Hau & Connell, 1998) with QSAR methods using multiple descriptors to correlate ODTs with physical properties. Although the relevance of these well known approaches, the fact that they were only able to deal with very few chemicals (< 10 components) is a major drawback because there are hundreds of different fragrance chemicals that can be used in perfumery products. More recently, Kraft and Eichenberger developed the olfactophore model for the correlation of structure-odour properties for a small class of 20 marine odorants (Kraft & Eichenberger, 2003).

In what concerns to the classification of perfumes, several attempts have been made in the past trying to associate such complex mixtures to olfactory families. An extensive study from the

survey of all perfumed products developed since 1782, lead to the "*Classification des Parfums et Terminologie*" developed by the French Society of Perfumers. Besides, some fragrance companies like Avon or Firmenich classify perfumes into different families, each one comprising subfamilies or *nuances*. Furthermore, the Fragrance Wheel developed by the acclaimed perfumer Michael Edwards (1983) considers four standard family notes having each one three subfamilies. Despite the relevance of these classifications, they are also purely experimental with lack of predictive power and so subjected to (large) interpersonal variability, even when performed by perfumers.

On the other hand, Psychophysics is a science that has been dealing with the perception of odours for long. There are numerous studies in the literature regarding the correlation between the odour intensity of single fragrance ingredients or (simple) mixtures of them with olfactory evaluations (Cain *et al.*, 1995; Chastrette, 1998). Nevertheless, studies addressing odour intensity of multi-component mixtures or simply odour quality are still scarce and puzzling.

4. Key innovations & Applications

In brief, the main achievements from the PhD thesis of M.A. Teixeira are devoted to the development of novel tools, models and data which are aimed at optimizing the formulation of fragranced products by speeding up its process and, simultaneously, reducing consumption of raw materials and products' cost. Ahead are highlighted the most relevant topics.

4.1. The Perfumery Quaternary & Quinary Diagram (PQ2D®)

The PQ2D® is a purely predictive graphical tool capable of showing the odour character of any multi-component fragrance mixture for all its possible compositions (Teixeira, *et al.*, 2009b). Because it presents the range of compositions where each fragrance ingredient dominates the odour space (Figure 4b) it serves as guidance for perfumers when creating their scents.

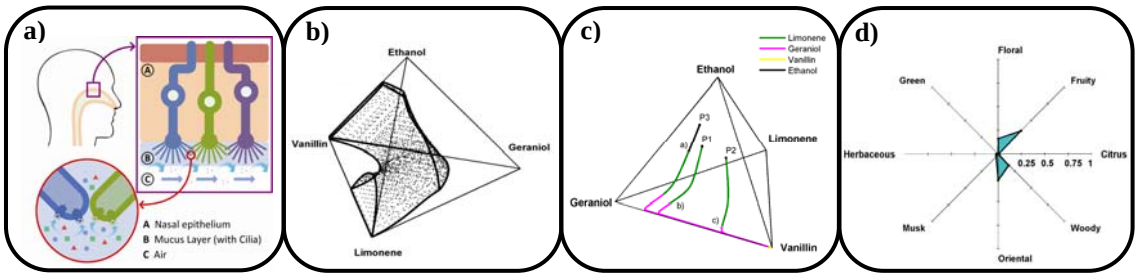

Figure 4 - a) Scheme for the perception of fragrances by the OR cells in humans; b) PQ2D® representing compositions where one fragrance dominates the overall odour; c) Evaporation lines for the evolution of the scent; d) Perfumery radar for the classification of commercial perfumes into olfactory families.

The key advantage of PQ2D® is that it uses purely predictive models without the need to perform experimental measurements of odour intensities using panellists. It is perfectly suited for perfumed products with a simple composition of top, middle and base notes diluted in solvents. An additional feature is that when combined with a diffusion model, the composition

and odour evolution of the perfume mixture over time can be represented (Figure 4c). The same approach of the PQ2D® methodology is now currently applied in top F&F companies (although under other name), aiming to reduce time for product formulation and waste of raw materials.

4.2. Perfume Diffusion & Performance

The analysis of fragrance performance is done through a series of parameters that are a function of time and distance. The developed diffusion model, together with the perception models used are suitable to account for fragrance performance. This was validated experimentally with different perfume mixtures (single, binary, quaternary and multi-component with up to 11 chemicals for the first time) in a specifically designed diffusion tube, similar to the Stefan tube. Additionally, a new graphic tool, called performance plot, was developed to present both time and distance effects on the perceived smell using odour iso-intensity lines (Figure 5). It was observed a very good agreement between our purely predictive model and experimental concentration data either for pure components or mixtures. Finally, the predicted odour intensities (Ψ) proved to be extremely close to experimental ones.

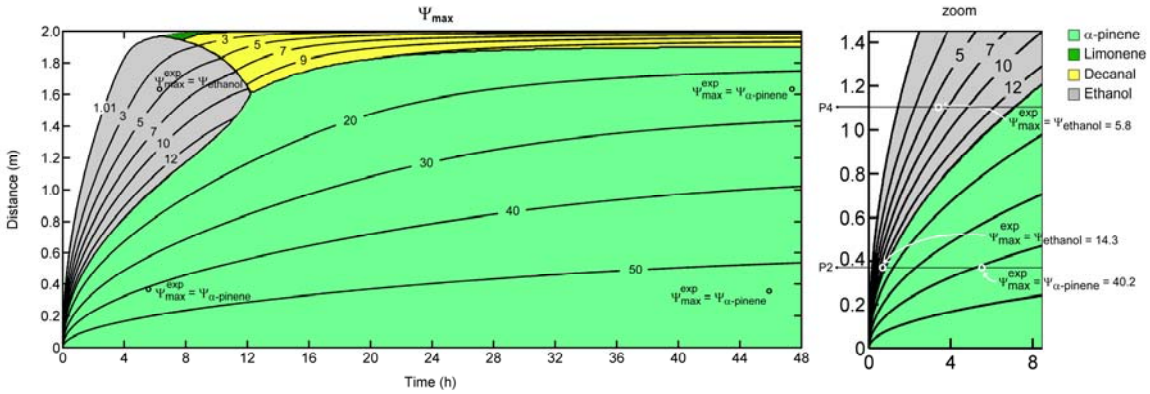

Figure 5 - Performance plot for a multi-component mixture (11 chemicals) where the dominant odorant is represented over time and distance. Odour iso-intensity lines are represented to show the relative intensities of each fragrance chemical. Points represent experimental data.

4.3. Odour Threshold Prediction

In this field, a novel equation was developed to predict ODTs (Figure 4a) instead of measuring those using panellists (which is dependent on panel inter-personal variability, has high costs and is time consuming). As previously said, whenever it is intended to potentiate some fragrance or masking undesirable ones, the ODT is the key parameter for fragrance design. The developed model uses three physical properties readily available in the open literature (saturation pressure, water solubility and octanol/water partition coefficient) to predict ODTs with good accuracy and was applied to 121 chemicals. Indeed, in most cases, the predicted value is within the range of experimental data available in the literature. The regression was first applied to ODTs measured from different authors separately and then with the whole pool of data, showing similar parameters statistically significant (p-value << 0.05) (Rodríguez, *et al.*, 2011).

4.4. The Perfumery Radar (PR)

The PR methodology was designed to classify perfumes into olfactory families using purely predictive models and representing it graphically into radar plots (Figure 4d). It was first applied to more simple products like four essential oils (orange, lemon, jasmine and thyme) revealing an extraordinary agreement with perfumers. Then it was applied to 25 commercially-available perfumes (14 feminine and 11 unisex) and the obtained PR classifications were compared with 6 empirical classifications from the market with very successful results (Teixeira *et al.*, 2010b). Due to that fact, the PR methodology collected the attention of the media worldwide (*e.g.* it was highlighted in *The Economist*), which demonstrates the interest of industry and of market.

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