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COMMENTARY

A Silicon Olfactome

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Abstract

In this issue of *Chemical Senses*, Galizia et al publish an important new tool for the chemosensory research community in general and for olfactory-oriented scientist in particular. The primary aim of the tool is to make it possible to compare results regarding the response specificity of *Drosophila melanogaster* olfactory receptors (DOrs) from different laboratories. These results have often been arrived at by the use of varying stimulation paradigms and different response registration methods. By building an impressive algorithm, the authors have created a web-based resource, where all extant response spectra have been entered, already now providing a very comprehensive overview of key ligands and tuning width of the DOrs. The web resource is highly attractive, as the authors make it freely available to the scientific community, with an open structure allowing new results to be entered as they emerge. The general structure of the program also allows its application to other species, such as other drosophilids, mice, and humans. Even though the application, as the authors themselves point out, still has its shortcomings, we find it to be a very important step forward in correlating the strong universal effort in understanding *Drosophila* olfaction.

Key words: *Drosophila*, olfaction, receptor

Commentary

One of the major challenges in science of today is to get a grasp of the overall image from the plethora of publications emerging (Hansson et al. 2009). During the last 10 years, this has indeed been true for studies of the *Drosophila melanogaster* olfactory receptors (DOrs). Already before the actual identification of the DOrs themselves in 2000 (Clyne et al. 1999; Vosshall et al. 1999), the first studies of ligand specificity emerged and since then an ever-increasing number of studies have added data, making the DOrs more and more well characterized. The problem is that the studies have been performed in laboratories all over the world. These laboratories often make use of different recording methodologies, different stimulation paradigms, and also test different stimulus spectra. The methodologies used can mainly be divided into extracellular recordings, functional imaging both peripherally and centrally, and studies of DOrs expressed both in "empty" *Drosophila* sensory neurons and heterologously expressed in, for example, HEK293, SF9, or *Xenopus* cells. The stimulus spectra have ranged from off-the-shelf odors to fractionated volatile collections from key resources as, for example, fruit and yeast. The stimulation paradigms range from hand puffing of odors to computer-controlled stimulus delivery systems or stimulation via a gas chromatograph.

Why is it then especially urgent to find new ways of interlacing data from different sources in studies of olfaction? Compared with the other senses, olfaction depends on central nervous processing of information coming from a very large number of channels. These channels are formed by sensory neurons expressing different types of receptor proteins. The high number of channels is very likely the consequence of the nature of the chemical information detected. In the nonchemical senses, one type of stimulus, albeit at different frequencies and intensities, is detected, and a small number of receptors can be used. In olfaction, an immense number of molecules, each one a unique entity, needs to be detected. Genomes characterized have in correspondence been found to code for a very large number of olfactory receptors; in insects usually between 50 and 150, in humans around 350, and in

mouse over 1000 (Bargmann 2006). By combinatorial coding, these receptor repertoires can code extremely high numbers of different odors (Malnic et al. 1999). To reach an understanding of such complicated detector systems, it becomes highly important to integrate knowledge from all investigating laboratories and also from different disciplines involved.

In this issue of *Chemical Senses*, Galizia et al. (2010) present an interesting new tool. The Database of Odor Responses (DoORs) is a software platform that provides consensus response profiles for almost all the 60 fly olfactory receptors (ORs). The DoOR constitutes a novel approach that enables the comparison and combination of odor response profiles from multiple data sets, in spite of these being obtained through a variety of techniques (functional imaging [e.g., Wang et al. 2003], electrophysiology [e.g., Hallem et al. 2004], and heterologous expression analysis [e.g., Smart et al. 2008]) and with the use of partially nonoverlapping sets of screened odorants. To merge these heterogeneous data sets, Galizia et al. (2010) relied on the simple assumption that for any given OR and for any methodological approach, the OR response profile conforms to the same basic principle, namely that an odor ligand that is more active in one data set should also be a better ligand in another data set.

The DoOR program enables the user to obtain a consensus response profile of a given OR (Figure 1a), or vice versa, and most useful, for a given odorant, obtain the OR activation pattern (Figure 1b). Having had access to the program for some time, we have found it to be an excellent resource, and we are certain that the field in general will feel the same. Importantly though is naturally that the DoOR gets updated to encompass new information as it becomes available. Herein lies also a responsibility of DoOR users to make their data accessible. Moreover, and as stated by Galizia et al. (2010), it would certainly be interesting if future versions of the DoOR would also include other species. A fair guess is that *Anopheles gambiae* will be the insect next in line for which multiple OR (and iontotropic receptor [IR] [Benton et al. 2009]) response profile data sets will be available. Extensive data already exists (Carey et al. 2010; Wang et al. 2010), and more is surely to come. Other mosquito disease

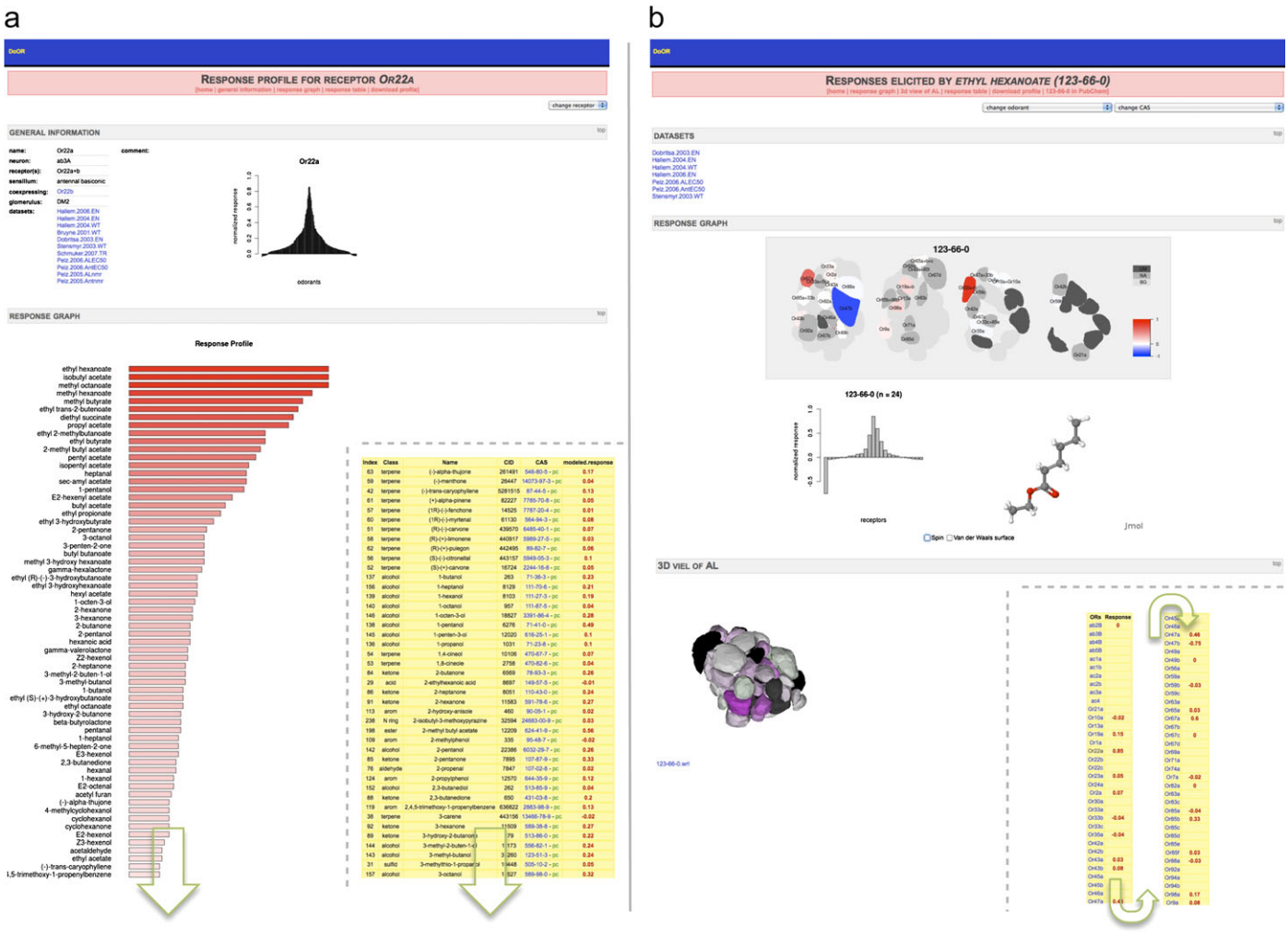

Figure 1 The 2 sides of the DoOR. For any given OR, the DoOR portal provides consensus response profiles (A), and for a given odorant, the OR activation pattern.

vectors will certainly follow suit. Hopefully, completely deorphaned OR/IR sets from nondipteran insects will also be published, allowing for more robust comparisons of the evolution of olfactory coding in insects.

Evident from the DoOR is that our knowledge regarding the receptive range and ligand tuning of the flies' chemoreceptor makeup, although extensive in comparison with other animals, is far from complete. For certain receptors, no or virtually no information exists, and for many of them the key ligands appear missing. The DoOR thus clearly points to the holes in our knowledge. It is interesting to note that several receptors appear to be highly specific, which could indicate that these genes fulfill important and specific functions, akin to, for example, the "vinegar" receptor Or42b (Semmelhack and Wang 2009), apparently critical for the detection of alcoholic fermentation. We could envision that several additional labeled line input channels occur, for example, ORs/IRs mediating oviposition cues or host unsuitability. Overall, establishing the ecological and evolutionary relevance of the respective response profiles, that is, establishing the functional significance of a given OR/IR responding to a given odorant, should be a task for future studies. In these aspects, the DoOR is clearly a helpful tool, pointing toward candidate receptors. The consensus response profiles provided via the DoOR could in combination with chemometrics (Haddad et al. 2008) also be used to predict new and more efficient ligands, and also the other way around, to predict which receptor/receptors most likely will interact with any given odor.

This is the first version of the DoOR, and as such it at once raises new demands on coming ones. The authors themselves point out several important points that in the long run should be included. The tool now to a large extent disregards concentration coding. In future versions, this will be a very important aspect to include, as each receptor has unique concentration response characteristics for the ligands it is interacting with. Secondly the tool does not take time-related events into consideration. Is a response phasic or tonic? Does it follow the time of the odor stimulation? Temporal patterns of activity has been shown to be a parameter highly important both in coding the actual occurrence of odor molecules but also in providing neural information (Stopfer et al. 1999). The tool also lacks possibilities to let odor stimuli interact on the same receptor, that is, blend interactions cannot be entered into the database or predicted by the tool. These 3 factors are important features to be added in future versions of the DoOR. An additional dimension is the behavioral responses elicited by the activation of different DOrs and/or by different ligands. More and more sophisticated behavioral assays are being developed all over the world, allowing more and more fine-scaled analyses of *Drosophila* behavior (Hansson et al. 2009). Future versions should also be able to take this information into account, thus allowing elimination of nonsense stimuli and enabling us to concentrate on what is behaviorally relevant for the fly.

In conclusion, the DoOR web-based tool to create consensus response profiles of DOrs will very likely become a highly used resource in the olfactory community. Initially, it will be used to combine data from all the laboratories working on DOr specificity, but in the longer run it can in combination with chemometrics also be used to predict new stimuli. As new species get incorporated the tool can also become highly useful for predicting, for example, activating or inhibiting olfactory receptor ligands allowing us to manipulate the behavior of pest or vector insects or blocking molecules for malodors in the human olfactory environment.

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