

# Against Vibration Theory of Olfaction

## BSE656A - Neurobiology

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## 1 Introduction

**Olfaction** is the sense of smell. It is the phenomenon of receptors detecting certain properties about the molecules that are known as odorants. The perception of an odour is the result of an extraordinary complex cascade of events. The very first steps of this perception involves the interaction of chemicals with our olfactory neurons [7]. Odour is a property that depends on several highly variable factors. There is a many to many mapping between these factors. Cracking the *combinatorial code* is, of course, the first step towards our understanding of the complex mechanism involved in the perception of smell. Such a function is performed by the central part of our olfactory system (the olfactory bulb, olfactory cortices, etc.). Beyond that, so-called peri-receptor events, notably implying proteins present in the olfactory mucus, likely contribute to the subtlety of our perception by modulating how the quality, the quantity and the kinetics of the odourant signal are coded. [8, 10]

**Vibratory theory** [1], first proposed by Dyson in 1928, states that it is the vibrational frequency of the molecules in the infrared range which is detected by the receptors and interpreted as odour. It is often contrasted with the **shape theory** of olfaction which believes that the receptors detect the molecular shape of the odorant molecules. The vibration theory harps on the idea that the vibrational energy possessed by a molecule must be equal to the difference in energy between two energy levels of the receptor. This synchronization lets the odorant molecule tunnel through and triggers the signal transduction pathway.

**Shape theory** [2] on the other hand is a simple molecular "lock and key" mechanism. According to this theory, the odorant molecule fits into a *gap* in the receptor molecule in the nasal epithelium. These molecular interactions reflect the chemical features of the interacting molecule: molecular size, shape, and functional groups combinations of atoms such as hydroxyl (OH) or carbonyl (C=O) that possess special chemical reactivity.

## 2 Experimental evidence supporting our position

The early set of tests to determine whether the vibration theory of olfaction would hold were mostly psychophysical, the most prominent one being the study done by Vosshall and Keller [3], where they presented to their subjects acetophenone and its deuterated (replacing C-H bonds by C-D bonds, which leads to same structure but different vibrational energy characteristics) counterpart, and the human subjects largely failed to distinguish between the two.

A more recent study done by Block et. al [4], was a biophysical study as opposed to psychophysical. The researchers' main question was whether receptors specialized for musk detection could distinguish musk isotopomers (deuterated musks). The answer would be the affirmative according to the vibration theory. A receptor, OR5AN1, highly receptive to musks was identified and DNA encoding it was introduced into tissue culture cells. The degree of receptor activation was linked to amount of light emissions, which is easily quantified. When OR5AN1 was exposed to isotopomers of highly purified musk, no change in the level of light emission was seen, indicating identical response. The same was true of nine other odor receptor molecules. This was an indication that the receptor molecules responded to the structure of odorant molecules, and not the vibrational energies.

### 3 Rebuttals

**Dyson's initial theory** [1] that olfactory organs might be detecting molecular vibrations of the odorant molecules was modified by *Wright* and others [8], who suggested that molecular vibrations of the odorant molecules must be mechanically detected. However, this implies that only the vibrational modes dominant at room temperature can be detected which implies that only molecular vibrations below  $500\text{ cm}^{-1}$  can be detected which precludes the detection several distinct smelling, inorganic molecules such as ammonia, hydrogen sulphide and hydrogen cyanide which vibrate in the range  $700\text{--}3500\text{ cm}^{-1}$ . Further, mechanisms that can possibly detect molecular vibrations mechanically haven't been discovered.

Luca Turin proposed a mechanism for vibrational spectroscopy based on inelastic electron tunneling [5]. In this mechanism, electrons tunneling across a gap between two different energy levels, can interact with a small molecule present in the gap. Electrons in a higher energy, while passing across the gap, interact with the molecule present in the gap and excite one of the vibrational modes of the molecule, thereby losing energy and tunneling to the lower energy level. The presence of the odorant molecule in the gap thus increases the conductance of the tunneling junction. Turin also suggested certain protein motifs and cellular signal transduction pathways which may connect the electron tunneling activity to ordinary electron traffic in the cell (soluble electron source and an electrochemical reaction as the final step). However, Turin's model of vibrational spectroscopy does not take into consideration possible, and quite probable interactions between the protein residues near the electron source and sink, and the electrons tunneling across the gap. The model treats all the degrees of freedom of the olfactory receptor site as being classical, apart from the vibrational modes of the odorant molecule. A detailed theoretical analysis of Turin's model by Brookes *et al* [4, 10] suggests that quantum fluctuations of the bath (protein residues near the electron source and sink sites) would obscure the vibrational modes of the odorant molecule.

Several studies indicate the ability of olfactory organs in ***Drosophila melanogaster*** as well as in humans to differentiate between isotopomers - odorant molecules with the same chemical structure but with a different isotope of one of the elements, such as deuterium atoms instead of hydrogen atoms [11, 12]. However, such outcomes in studies involving humans have been attributed to psychophysical factors. It is difficult to draw precise conclusions from smell-tests in humans due to the presence of a large number of confounding factors that can influence decisions of test subjects.

Olfactory membranes can contain, embedded in them, a number of enzymes capable of chemically altering different organic and inorganic molecules. The chemical action of these highly specific enzymes will be different on different isotopomers. The odorants, with the same chemical structure, can be chemically altered into different chemical species. Thus, differentiating between isotopomers will not require any vibrational spectroscopic activity. Further, isotopomers utilized in smell-tests can often contain small traces of impurities that manage to escape gas chromatography (the technique commonly used to purify odorant molecules). These traces of impurities could contribute towards the ability of olfactory organs to differentiate between isotopomers. In light of such factors, Luca Turin himself admits that the only conclusive proof for such an eccentric theory of olfactory action will be a direct detection of the electron current elicited by odorant binding in the receptors [13].

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