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Physics of Smell

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Abstract:

Quantum mechanics in biology is becoming increasingly important. Only in the last few years experimental equipment became powerful enough to allow observation and measurement of quantum effects in biological systems. New and very promising theories started to arise showing biological processes in a very different way that we were used to. Among three main quantum theories in biology to this time (magnetic sensing, photosynthesis and olfaction) olfaction theory will be presented in this seminar. Basic anatomical and biological properties of olfaction system in human will be reviewed. Historically important theories in this area will be mentioned along with pro et contra experimental facts. Physical model with all important parameters and approximations will be presented. In the end, there will be discussion and future perspective.

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1 Introduction

The physical phenomena behind the most important human sensory systems, seeing and hearing, are generally well understood also among non physicists as they involve very basic physical phenomena. When going further to tasting and touch, the broader understanding of the processes starts to faint to the point, when there is no “official” understanding at all.

Smell is still the elusive sense. To this time there is no widely excepted theory about how does it work, what responses are triggered by which stimuli and how and why does this happen. From the literature it is clear, that process could not be “chemical” as there is no irreversible chemical reaction involved in the process – it has to be something “physical” [1], which is why supposedly chemistry theme appears in a physics seminar.

This seminar will focus on the very same question: what is it about the molecule that makes it smell and how is this property detected. The theory that will be presented is not widely accepted yet but it already has some very important affirmations in measurements and successful applicative results.

2 Biological background

2.1 Anatomy and general properties

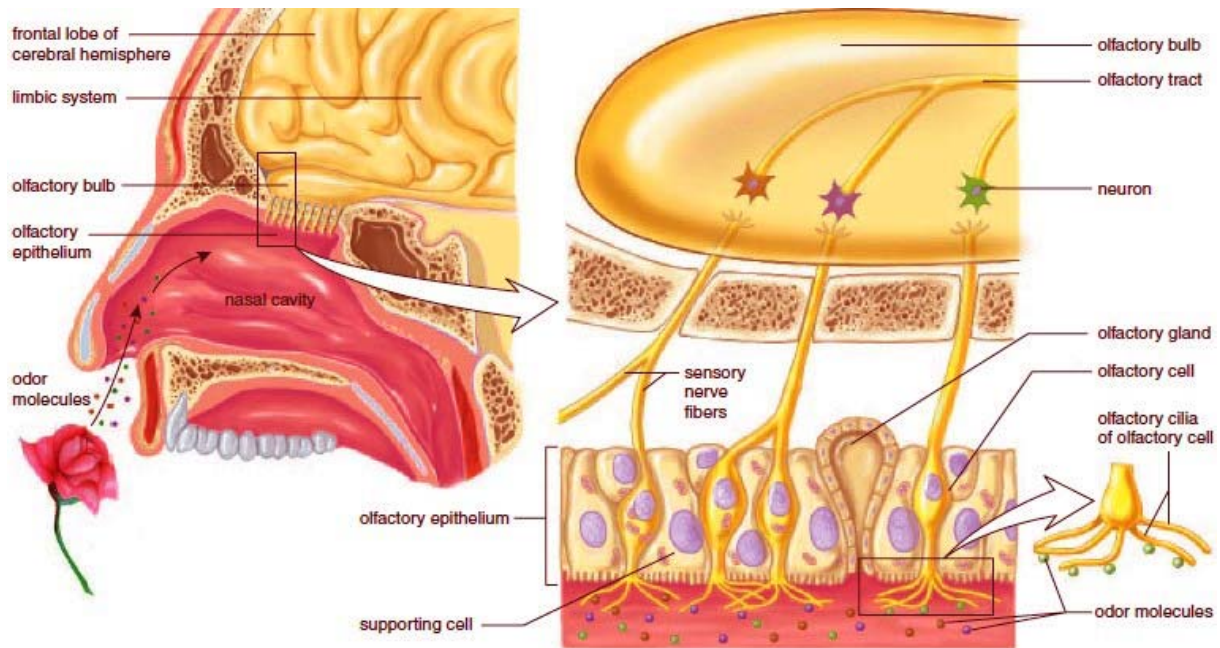


Figure 1: Position (left) and anatomy (right) of human olfaction system.

The sensory part of olfaction system in human is about 3 cm² in size (on each side) and is located on the roof of the nasal cavity, about 7cm above and behind nostrils [2] (Figure 1, left). Olfactory epithelium (Figure 1, right) consists of supporting cells, stem cells called basal cells (not shown in the figure), olfactory gland and olfactory cells (i.e. olfactory sensory neurons) with olfactory cilia. In total there are about 50 million of olfactory sensory neurons in olfactory epithelium [3], each having about 5-40 cilia at the end [3]. Olfactory receptors, where odor detection takes place, are positioned on cilia. Cilia are separated from the rest of nasal cavity with 10-40 μ m of mucus layer [4] which odor molecules have to penetrate in order to get to the receptors. The basal cells have function of replacing the sensory neurons at least every 30-45 days which is unprecedented in neuron based systems [4].

3 The process of smelling

The *molecular* and *genetic* aspect of olfactory system has been already determined by Richard Axel and Linda Buck for which they won Nobel Prize for medicine and physiology in 2004. For illustrative purposes and better understanding we will take a look on basics of how olfactory system works.

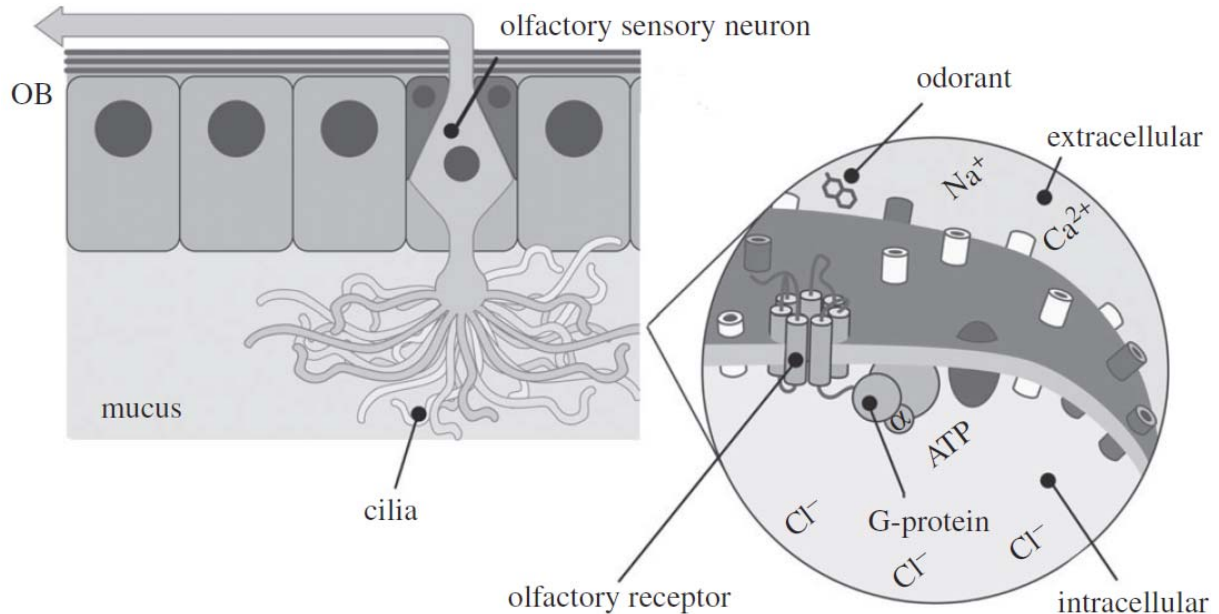


Figure 2: Place where the odorant meets cilia of olfactory sensory neuron is shown. Function of olfactory receptors is to discriminate odor molecules. The signal is triggered only with certain types of attached odor molecules. If triggered, the electric signal is projected onto the olfactory bulb (OB) and then further in brain.

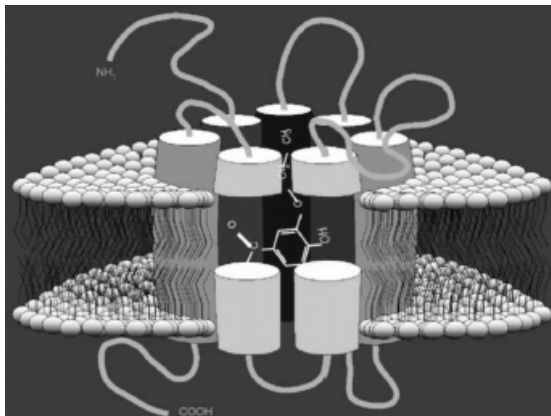


Figure 3: Breer's model of G-protein coupled receptor. Transmembrane helices are presented as barrels. Top membrane surface is outside and bottom membrane surface is inside of olfactory neuron.

Axel and Buck discovered that the odor receptors belong to *G-protein coupled receptor* (GPCR) class. This class consists of seven transmembrane helices connected with flexible loops, forming a socket. Inside the socket odor molecule is attached. Although the class of the olfactory receptor is already decoded, the detailed atomic structure is still unknown [5]. See Breer's model of GPCR in Figure 3 [6] for possible structural representation. In Figure 2 can be seen how the receptor is located in cilia surface. In human there are approximately 350 receptor types [7] that are each tuned to more or less particular odor molecule. Signals from all the receptor types are represented in the brain to what is known as "*combinatorial code*" [8] (Figure 4). Similar to color, mixing different odors can result in odor that is

different from the starting odors. In a commercially available odorants there are typically from 100's to 1000's of different odor compounds.

The odor molecules are typically 10's of atoms in size, volatile, non-reacting and mainly hydrophobic [9] substances that can penetrate layer of mucus covering cilia in the nasal cavity. The biological mechanism of odorant detection is as follows. When odor (the first messenger) is detected, the receptor (GPCR) releases a G-protein unit and second messenger process of transduction ensues that controls a Ca^{2+} and Na^+ ion influx into the cell. Subsequently, Ca^{2+} acts as third messenger that induces Cl^- ions to flow. This in turn causes the olfactory sensory neuron to fire [10].

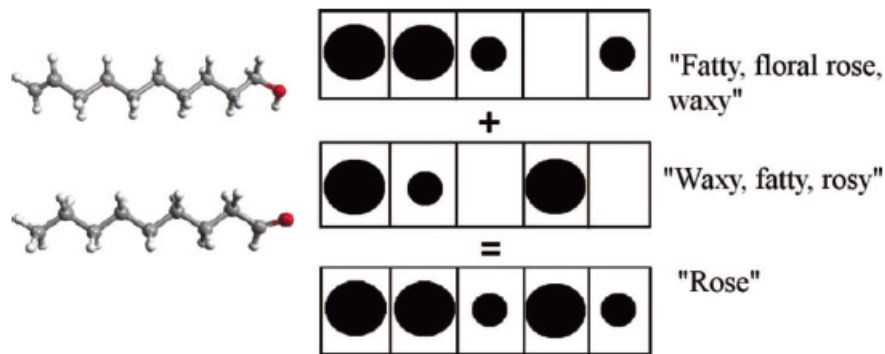


Figure 4: Graphical representation of »combinatorial code«. Two different odors with rose characteristics results in rose odor.

Despite the very detailed knowledge about biological processes involved in olfaction there is still link missing about the very first moment when the odor molecule enters receptor: how receptor discriminate the molecule and what exactly releases G-protein unit. There have been several theories about that and some of them will be presented in the next chapter.

It is also important to stress some other facts. Smell, as all organoleptic senses, is believed to be subjective which could impose a problem in scientific evaluation. Luckily this is only partly the truth. On receptor level we all “smell” the same. It is the *interpretation* of the signal in the brain that makes the smell subjective. There exist measurement methods that make measuring signals on receptor level possible (cell depolarization that is triggered by receptor, fluorescent magnetic resonance imaging of the brain [5]), solving the problem of “subjective” measurements. Contrary to first impression the smell *can* be approached scientifically.

4 A short history of olfaction theories

Olfaction theories can be divided based on supposed discrimination factor into three different categories.

4.2 Molecular shape (“lock and key” model)

Main supporters of this theory were Amoore (1948), Boelens (1974), Ohloff (1991), Rossiter (1996) and Kraft et al. (2000). The theory is based on viewpoint that whatever happens in nose can't be much different from what happens in other similar parts of human body. Most of other receptor systems in biology works by shape: enzymes, antibodies, ... so it is not that unreasonable to presume the same mechanism for olfactory system [11]. However, the shape

theory fails in case of molecules that are structurally very different and smell the same or are structurally almost exactly the same but smell considerably different (Figure 5). In a research, 75 structurally different molecules have been documented to smell of bitter almond [12]. Extensive research of this problem has been also made by C. Sell [13]. Apart from clear difficulties with experimental affirmations, the shape theory also doesn't propose any mechanism that could release G-protein and start the detection process.

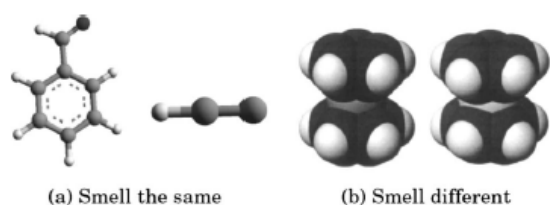


Figure 5: (a) Example of molecules that smell the same while being structurally very different : benzaldehyde (left) and hydrogen cyanide (right) both smell of bitter almonds. (b) Example of molecules that smell different despite being structurally almost identical: ferrocene (left) and nickelocene (right). The difference is in the type of metal ion inside the structure.

4.3 Vibration theory

Main supporters of this theory were Dyson (1938), Wright (1964), Meloan (1981), Turin (1996). It started by noticing correlation between the fact that molecule smells and that it has definitive spectral lines in IR part of vibration spectrum. Luca Turin in 1996 proposed theory based on inelastic electron tunneling. It is very closely related to “swipe-card” model.

4.4 “Swipe-card” model

In “swipe-card” model the previous two theories fuse together. Vibration theory is still fully valid but some aspects of “lock and key” model are also taken into account. Obviously, the shape of the molecule matters to some extent, because molecules can be smelt only if they are small enough to fit into the olfactory receptor. There is also at least one documented case of mirror molecules that according to vibration theory should smell the same but in reality they smell differs. It turns out, that because of the molecule's shape (and subsequently its attachment to the receptor) in one instance not all vibrations are present and structurally same (but mirror) molecule smells different. If the missing vibration is added by mixing with other type of odor molecule, the smells becomes the same [14]. Just like with swipe card, the shape is important (otherwise the card would not fit into the slot) but it is the code in the magnetic band (the vibrations) that triggers the process.

Another good experimental scrutiny for the theory is trying to observe smell differences between two odor molecules with different type of isotopes. The idea is that the molecules are structurally and chemically the same, the only difference is slight shift in vibration modes due to different mass of isotopes (hydrogen and deuterium is used). Experimental affirmation of the model is still somewhat ambiguous. There are some researches that support (see [15]) and others that refute (see [16]) the theory. The findings of the latest research are that people (trained and untrained) can't differentiate between deuterated and nondeuterated *small* molecules, however, they can differentiate if the odor molecules are *larger* [17].

5 Physical model of vibration theory

5.5 Assumptions and parameters of the model

The idea about possible physical model that would include IR vibration modes of odor molecules came from Lambe and Jaklevic paper about inelastic electron tunneling that made inelastic tunneling microscopy (IETS) possible in nanoscale range [18]. For the model to be feasible also with biological materials, some condition has to be considered [12]:

- Contrary to continuous scanning in IETS, in biological system there would be pick up of discrete energies as each type of GPCR receptor is tuned differently.
- One electron may be enough to trigger the detection (contrary to electron flow in IETS).
- Obviously, energy states of materials and temperature effect will be different from normal IETS.
- In IETS the inelastic electron tunneling flow is very faint in comparison with elastic tunneling flow. In biological system the elastic tunneling should be suppressed completely in order to avoid constant receptor “switch-on” and consequently sensory overflow.

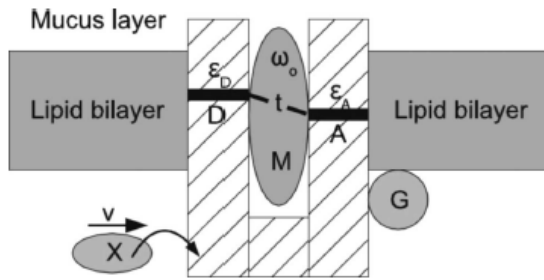


Figure 6: Schematic representation of GPCR olfactory receptor in vibration mechanism physics model. Orientation is the same as in Figure 3. X acts as electron source to donor (D) with Fermi level ϵ_D . If odor molecule (M) has the right vibration mode ω_0 the electrons can tunnel to the acceptor side (A) with Fermi level ϵ_A where they release G-protein (G).

odor molecule.

There are also some other important approximations and considerations that will be introduced step-by-step in the text below.

The olfactory receptor has to be “resistant” to background noise, i.e. vibration modes of molecules that are imbedded in the receptor. Certainly the most common is C-H stretch vibration that occurs at 0,36eV (2911,3cm⁻¹) [19]. Its coupling strength depends on root mean square amplitude of vibration and effective charge. The first parameter we can estimate by:

$$\bar{x}^2 = \frac{1}{2} \frac{\hbar}{M \omega} \coth\left(\frac{\omega \hbar}{2k_b T}\right) \quad (1)$$

For M=1 for hydrogen (in atomic units) and energy $\hbar\omega = 0,36eV$ the result is 0,076Å. The educated guess for the distance between receptor helices (i.e. the distance between D and A)

In order for the physical olfaction vibration model to work also the following conditions has to be fulfilled [9]:

- While olfactory receptor is able to detect many odor molecules, donor (D) and acceptor (A) helices has to be able to return elastically to initial state after detecting the odorant.
- To be able to detect smell within milliseconds (according to experimental measurements) it is mandatory for A and D to replenish in the same time scale. The actual process of tunneling can be faster.
- Energy splitting between D and A has to correspond to $\hbar\omega_0$ vibrational quantum in

is about 8\AA [5]. The “noise” is small enough not to interfere with our model. The original suggestion by Turin is that the frequencies around C-H stretches are “blind spot” (the appropriate receptor type doesn’t exist) [20].

In the physical model we will use standard large body non-radiative theories (Huang-Rhys theory and Marcus theory). We’ll assume that the process is slow enough to use perturbational approaches (Fermi Golden Rule). Also very important observation is that environment of olfactory receptor is hydrophobic which mean that it is very dry. We can safely assume that the only moving charge is in the odorant molecule [5]. Although olfactory receptors can be “tuned” to one or many odor molecule vibration we will simplify the number of “tuned” vibrations to one per receptor only. We also assume that only one electron tunnels at a time.

We start the physical model building by approximating all molecules involved in the system (D, A, M, environment) as set of quantum oscillators. The electron transfer from the initial state D to the final state D is coupled to the vibrations of the odorant molecule M and of the rest of the environment. Estimation of probability P_{ex} for the odor molecule to be in excited state can be done in the following way (*see Appendix for derivation*):

$$P_{ex} = \exp\left(-\frac{\hbar\omega}{k_B T}\right) \quad (2)$$

With parameters for typical odorant molecule with vibrational quantum of $\hbar\omega_0 = 0,2eV$ [5] and normal human temperature ($k_B T = 0,027eV$) we get probability of about 0,0006. We can safely assume that all odorant molecules are in ground vibrational states. Based on what we know about other similar biological systems we can assume that environment is a collection of very low frequency oscillators that are only very weakly coupled to the transient electron and impose no disturbance [5].

Next, we estimate key parameters for electron tunneling events. We have two types of tunneling events: elastic and inelastic with timescales τ_{T0} and τ_{T1} respectively. As already mentioned, the inelastic tunneling must surpass the elastic tunneling in order for our model to be biologically feasible. We also have to estimate spectral resolution and at least crude estimations of absolute rates for elastic and inelastic electron tunneling to be able to check the model against data obtained experimentally.

5.6 The electron tunneling rate equation

After some mathematical formalism that exceeds the scope of this seminar we get the equation for tunneling electron with or without vibrational excitation of the odorant molecule [9]

$$\frac{1}{\tau_{D,0 \rightarrow A,n}} = \frac{2\pi}{\hbar} |t|^2 \frac{\sigma_n}{\sqrt{4\pi k_B T \lambda}} \exp\left(-\frac{(\varepsilon_n - \lambda)^2}{4\pi k_B T \lambda}\right) \quad (3)$$

The abbreviation $\varepsilon_n = \varepsilon_D - \varepsilon_A - n\hbar\omega_0$ is used. $n=0$ is elastic tunneling channel, when the odorant is not excited and $n=1$ the inelastic channel, when the “right” odor molecule is recognized by the receptor and the olfactory system is triggered.

In the equation (3), the *Huang-Rhys factor* (S) is hidden in the relation:

$$\sigma_n = \frac{S^n}{n!} \exp(-S), \quad S = (u_D - u_A)^2 \quad (4)$$

Huang-Rhys factor is a measure of coupling the tunneling transition to the vibrational mode of the odor molecule M. If it is too big ($>0,3$), the 2 and 3 phonon processes start to arise and the discrimination is obscured. If it is too low ($<0,05$), the couplings are not strong enough to be detectable with inelastic electron tunneling. *Huang-Rhys factor* can be accurately calculated for free odorant molecules and it indeed falls into the useful range 0,05-0,03 [5].

λ in the equation (3) is reorganization energy:

$$\lambda = \sum_q S_q \hbar \omega_q, \quad S_q = (u_{qD} - u_{qA})^2 \quad (5)$$

where q runs over all modes. Because the detailed atomic structure of olfactory receptor is not yet known, λ can't be accurately computed. Analogous to other similar biological systems it is reasonable to assume that its value at room temperature will be below 30 meV [5]. Indeed, this value is low enough for the physical model to work (Figure 9).

t in equation (3) is electronic matrix element for non-radiative transition and it is quite possibly negligible when no odor molecule is present. It can be roughly estimated by:

$$t = \frac{v^2}{\varepsilon_M - \varepsilon_A} \quad (6)$$

where v is hopping integral that will usually not exceed 0,1 meV. ε_M corresponds to the lowest unoccupied molecular orbit and ε_A to the highest occupied molecular orbit and the difference $\varepsilon_M - \varepsilon_A$ can be around 10 meV for most of the odor molecules [21]. Value of t can then be approximated as 1 meV. We can cross-check our educated guess for t with experimental data for *C. vinosum* that give us, when we put the data into the equation (3), value of 2,4 meV for the matrix element t . Our estimation for t is close enough [22].

The plot with both values of n can be seen in Figure 9. For typical values (given in Figure 7) we get $\tau_{T0} \approx 87ns$ and $\tau_{T1} \approx 0,15ns$ for elastic and inelastic tunneling respectively. That satisfy the condition $\tau_{T0} \gg \tau_{T1}$ and the physical model is biologically fissile, indeed.

Quantity	$\hbar \omega_0$	S	λ	$ t $
Value	200 meV	0,1	30 meV	1 meV

Figure 7: Estimates values for computing characteristics times for elastic and inelastic electron tunneling.

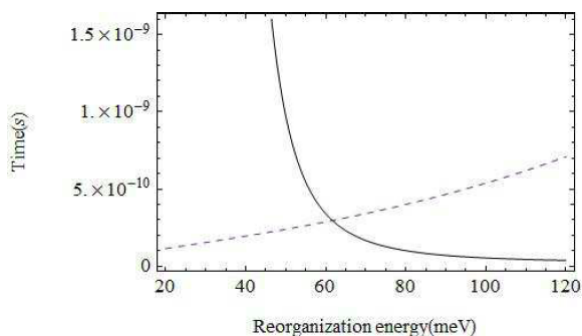


Figure 9: A plot time vs. reorganisation energy (λ). Thick line represents inelastic (discriminating, τ_{T1} , $n = 1$) and dotted line represents elastic (non-discriminating, τ_{T0} , $n = 0$) electron tunneling.

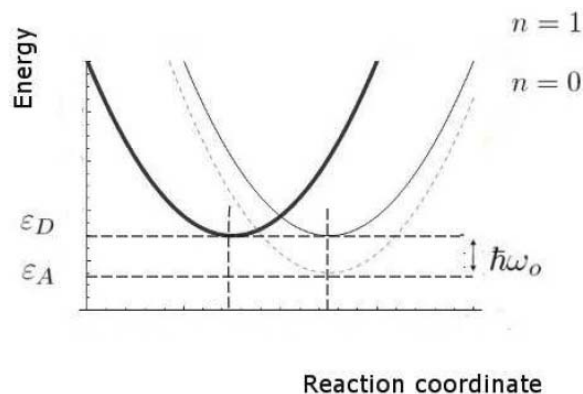


Figure 8: A Configuratio coordinate diagram showing the initial state (D) on the left and the final state (A) on the right. The final state has two options: for elastic ($n=0$, thick line) and inelastic ($n=1$, dotted line) tunneling.

6 Discussion

Despite the vibrational theory of olfaction is still incomplete and it lacks systematic experimental affirmations it already had great impact in industrial sphere.

Traditionally, fragrance companies are developing odors by organoleptic testing of large amount of compounds. That is not only very time consuming but also very expensive and the industry is constantly searching for improvements. To test the vibrational theory in its early stage, the founder of the theory, Luca Turin, was asked by a fragrance company to synthesize surrogate for the widely used odor compound called *coumarine*, which in its original form is carcinogen. By using the theory results (and also by some lucky coincidence as he admits) he managed to do it in just three weeks [11]!

There are still limit cases that vibrational theory can't explain but it is clear that it has potential that is worth exploring and is quantum based. For further physical modeling more data are needed, especially regarding receptor detailed atomic structure.

7 Future perspectives and conclusion

G protein receptors are a family of receptors that are one of the most frequent targets of various drugs. New theoretical findings about their discriminating mechanism might cause revolution in pharmaceutical industry and new approaches in drugs healing [23]

Another very attractive property of smell is that very small quantities (1 part per billion in human and much more in some animals) of unfamiliar molecules can be detected in millisecond timescale without any previous training. With further theoretical understanding of the mechanism revolutionary new methods of chemical analysis and sensory in general could arise.

It appears that olfactory sensing really is, despite initial opposition of mainstream science, based on quantum mechanics. In that sense it is similar to two other very important human senses – hearing and sight – whose *modus operandi* is also known to be quantum mechanic. Our interface to the outer world seems to be quantum mechanic! Despite very unintuitive (at

least to non physicists) we are intimately connected to its properties. In a way quantum mechanics defines our awareness about ourselves and the world around us.

8 Appendix

8.7 Derivation of probability for the quantum oscillator to be in excited state

In this appendix we will derive the probability for the quantum oscillator to be in excited state, i.e. equation (2). The presumption is that the oscillator is free and unperturbed. We start with statistical mechanics according to which the probability for the system to be in the n -th state equals to:

$$\rho_n = \exp[\beta(F - W_n)], \quad \beta = \frac{1}{k_B T} \quad (\text{A.1})$$

where k_B is Boltzmann constant, T the temperature of the system and $\exp[-\beta F]$ partition function, defined with statistical sum as

$$\exp[-\beta F] = \sum \exp[-\beta W_n] \quad (\text{A.2})$$

Energy of the n -th state of quantum oscillator is

$$W_n = (n + \frac{1}{2})\hbar\omega, \quad n = 0, 1, 2, \dots \quad (\text{A.3})$$

We derive the partition function with noticing that it represents infinite geometric series:

$$\begin{aligned} \exp[-\beta F] &= \sum_{n=0}^{\infty} \exp\left[-(n + \frac{1}{2})\beta\hbar\omega\right] = \exp\left[-\frac{1}{2}\beta\hbar\omega\right] \sum_{n=0}^{\infty} \exp[-n\beta\hbar\omega] = \\ &= \exp\left[-\frac{1}{2}\beta\hbar\omega\right] \sum_{n=0}^{\infty} (\exp[-\beta\hbar\omega])^n \end{aligned} \quad (\text{A.4})$$

Infinite sum in (A.4) is geometric series for which we now that holds:

$$\sum_{n=0}^{\infty} a_0 q^n = \frac{a_0}{1 - q} \quad (\text{A.5})$$

From (A.4) we see that $a_0 = 1$ and $q = \exp[-\beta\hbar\omega]$ so the partition function is:

$$\exp[-\beta F] = \frac{\exp[-\frac{1}{2}\beta\hbar\omega]}{1 - \exp[-\beta\hbar\omega]} \quad (\text{A.6})$$

To get the probability that the oscillator is in excited state, we have to sum equation (A.1) over all such states i.e., indices $n=1,2,\dots$. Similar to (A.4) we get geometric series only that time the starting index is 1.

$$P_{ex} = \frac{1 - \exp[-\beta\hbar\omega]}{\exp[-\frac{1}{2}\beta\hbar\omega]} \exp[-\frac{1}{2}\beta\hbar\omega] \sum_{n=1}^{\infty} (\exp[-\beta\hbar\omega])^n \quad (\text{A.7})$$

We can transform equation (A.7) to be similar to equation (A.5) by introducing new, prime index:

$$n' = n - 1 \quad \Rightarrow \quad n = n' + 1 \quad (\text{A.8})$$

With new index the equation (A.7) is written as:

$$P_{ex} = (1 - \exp[-\beta\hbar\omega]) \sum_{n'=1}^{\infty} (\exp[-\beta\hbar\omega])^{n'+1} \quad (\text{A.9})$$

We see that this time the parameters for infinite sum of geometric series are $a_0 = \exp[-\beta\hbar\omega]$ and $q = \exp[-\beta\hbar\omega]$ and the final result is as expected:

$$\begin{aligned} P_{ex} &= (1 - \exp[-\beta\hbar\omega]) \frac{\exp[-\beta\hbar\omega]}{(1 - \exp[-\beta\hbar\omega])} = \exp[-\beta\hbar\omega] \\ &= \exp\left[-\frac{\hbar\omega}{k_B T}\right] \end{aligned} \quad (\text{A.10})$$

9 References

9.8 Figure references

Figure	Reference
Figure 1	“Senses of Taste and Smell.” Accessed May 13, 2013. http://encyclopedia.lubopitko-bg.com/Senses_of_Taste_and_Smell.html .
Figure 2	Brookes, J. C. “Science Is Perception: What Can Our Sense of Smell Tell Us About Ourselves and the World Around Us?” <i>Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences</i> 368, no. 1924 (July 5, 2010): 3491–3502. doi:10.1098/rsta.2010.0117.
Figure 3	Brookes, Jennifer C. “Olfaction: The Physics of How Smell Works?” <i>Contemporary Physics</i> 52, no. 5 (September 2011): 385–402. doi:10.1080/00107514.2011.597565.
Figure 4	Brookes, Jennifer C. “Olfaction: The Physics of How Smell Works?” <i>Contemporary Physics</i> 52, no. 5 (September 2011): 385–402. doi:10.1080/00107514.2011.597565.
Figure 5	Brookes, Jennifer C. “Olfaction: The Physics of How Smell Works?” <i>Contemporary Physics</i> 52, no. 5 (September 2011): 385–402. doi:10.1080/00107514.2011.597565.
Figure 6	Brookes, Jennifer C. “Olfaction: The Physics of How Smell Works?” <i>Contemporary Physics</i> 52, no. 5 (September 2011): 385–402. doi:10.1080/00107514.2011.597565.
Figure 7	Brookes, Jennifer, Andrew Horsfield, and A. Stoneham. “The Swipe Card Model of Odorant Recognition.” <i>Sensors</i> 12, no. 12 (November 12, 2012): 15709–15749. doi:10.3390/s121115709.
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