Could Humans Recognize Odor by Phonon Assisted Tunneling?

Jennifer C. Brookes,[*] Filio Hartoutsiou,[†] A. P. Horsfield,[‡] and A. M. Stoneham[§]

Department of Physics and Astronomy, University College London, Gower Street, London WC1E 6BT, United Kingdom
(Received 10 July 2006; published 16 January 2007)

Our sense of smell relies on sensitive, selective atomic-scale processes that occur when a scent molecule meets specific receptors in the nose. The physical mechanisms of detection are unclear: odorant shape and size are important, but experiment shows them insufficient. One novel proposal suggests receptors are actuated by inelastic electron tunneling from a donor to an acceptor mediated by the odorant, and provides critical discrimination. We test the physical viability of this mechanism using a simple but general model. With parameter values appropriate for biomolecular systems, we find the proposal consistent both with the underlying physics and with observed features of smell. This mechanism suggests a distinct paradigm for selective molecular interactions at receptors (the swipe card model): recognition and actuation involve size and shape, but also exploit other processes.

PACS numbers: 87.16.Xa, 82.39.Jn, 87.16.Ac, 87.14.Ee

Our sense of smell affects our behavior profoundly. Discrimination between small molecules, often in very low concentrations, allows us to make judgments about our immediate environment [1] and influence our perceptions. Even though odorants are key components of many commercial products [2], the biomolecular processes of olfaction are inadequately understood: scent design is not straightforward. We know that odor detection involves several types of receptors for a given odorant, and understand how a receptor signal is amplified and processed [3,4]. However, the initial selective atomic-scale processes as the scent molecule meets its nasal receptors are not well understood. Odorant shape and size are certainly important, but experiment shows these are insufficient. Here we assess the novel proposal that a critical early step involves inelastic electron tunneling mediated by the odorant. We test the physical viability of this mechanism [5] using electron transfer (ET) theory, with values of key parameters in line with those for other biomolecular systems. The proposed mechanism is viable (there are no physics-based objections and it is consistent with known features of olfaction) provided the receptor has certain general properties. This mechanism has wider importance because it introduces a distinct paradigm for selective actuation of receptors: whereas lock and key models [6] imply size, shape, and nonbonding interactions (the docking criteria) are all, in our swipe card model recognition and actuation involve other processes in addition to docking. Thus it encompasses and goes beyond mechanisms such as proton transfer, discussed by us previously [7].

All current theories agree that selective docking of odorants is important [2]. However, odorants are small molecules (rarely more than a few tens of atoms [2]), and it is improbable that docking criteria alone offer sufficient discrimination. For example, molecules with almost identical shapes can smell very different: replacing carbon with its isosteres Si, Ge, and Sn invariably markedly alter odor character [8]. Something more is needed for olfaction,

leading to early suggestions that odorant vibration frequencies were critical [9,10], though without specific mechanisms. Both infrared and inelastic electron tunneling [11,12] (IETS) spectroscopies distinguish very precisely between different molecules through vibrational frequencies and intensities, which makes the proposal appealing. The first specific mechanism (based on IETS) was Turin's [13] idea that there is odorant mediated inelastic tunneling of an electron at the receptor: inelastic tunneling between receptor electronic states differing in energy by $\hbar\omega$ that occurs only when energy is conserved by emission of an odorant phonon of the right energy, hence selectivity. Clearly, the vibration must also couple to the electronic transition.

Experiment offers several tests of Turin's idea. It explains why certain molecules with very different shapes can smell similar (e.g., boranes and thiols), but also why some molecules of essentially identical shape smell utterly different (e.g., 1,1-dimethylcyclohexane and its sila counterpart) because of frequency or coupling changes. The question of whether humans can distinguish between a molecule and its deuterated counterpart is still controversial. There is evidence both for [13,14] and against [15]. In animals, isotope discrimination is well documented [16]. Both left- and right-handed forms of enantiomers should have the same vibrational spectrum. The odors of some enantiomer pairs are the same (type 1) while others differ (type 2) [17]. Type 2 can be explained by docking criteria (different chiralities fit different receptors), while type 1 is naturally explained by vibrational frequency. However, docking and frequency together can account for both because chirality will affect the intensity of response of receptors to the enantiomers (the helices that form the walls of the receptors are chiral). Quantitative support for the theory comes from the successful correlation of odor character with tunneling frequency spectrum [18] for a range of odorants. Indeed, vibrational frequency has been found to correlate better with odor than structure [19].

Thus a molecule's vibrational spectrum appears closely linked to its odor. We now test whether the physical processes underlying Turin's proposed mechanism for detecting the frequency are credible.

First we focus on the odorant and perform a simple test of whether odor can be related to vibrational frequency and to coupling to the odorant charges (as required by IETS). We computed the vibrational spectra of H_2S and four boranes (decaborane, *m*-, *o*- and *p*- carborane). The boranes are structurally similar, but all quite distinct from H_2S. However, H_2S and decaborane smell sulfuraceous, while the carboranes smell camphoraceous. Using GAUSSIAN 03 [20] we computed vibrational frequencies and infrared (IR) couplings, defined as $|\partial\vec{p}/\partial Q_i|^2$ with $\vec{p}$ the dipole moment and Q_i a displacement along normal mode i. The sulfuraceous smell of H_2S is associated with vibrations in the region of 2600 cm^{-1} [21]. In this region decaborane has IR couplings that are one to 2 orders of magnitude greater than the carboranes. Assuming that the IR couplings are a good estimate of the electron-oscillator coupling in an olfactory receptor, this could explain sulfuraceous and less sulfuraceous odors.

Turning to the combined odorant and receptor system, we must determine whether ET is possible on the relevant time scale, and if so whether the discriminating electron transfer rate (with excitation of the critical odorant mode) is sufficiently large relative to rates for nondiscriminatory transfer channels (without excitation of the critical mode). This is necessary because most IETS experiments observe inelastic tunneling with phonon emission as a weak adjunct to the elastic component, detected only by complex post-processing of a type unlikely in a nasal environment. Too little is currently known about the atomic and electronic structure of real odorant receptors for full-scale calculations. Instead, we make general assumptions about the nature of the receptor, the odorant, and their interaction. These assumptions relate to a series of characteristic times corresponding to the required physical processes (see Fig. 1).

Turin's theory requires a source of electrons or holes to allow charge flow to take place. The precise biological origin is not known, but may well consist of reducing (oxidizing) species (X) in the cell fluid [2]. These molecules diffuse through the aqueous medium and arrive with an average interval of τ_X. Using a standard approach for computing reactant collision rates in solution from the diffusion equation and the Stokes-Einstein relation for the diffusion coefficient [22] we get $\tau_X = 3\eta/2n_X k_B T$ where η is the viscosity of water (0.891×10^{-3} kg m^{-1} s^{-1}), n_X is the concentration of X, k_B is Boltzmann's constant, and T is the temperature. Note that this result is independent of the nature of X or the receptor. Because n_X will probably lie in the range $1\ \mu$M $\rightarrow 100\ \mu$M, we get a range of values for τ_X of $10\ \mu$s $\rightarrow 1$ ms. The charge now has to cross from the molecule to the receptor molecule, a process that can be
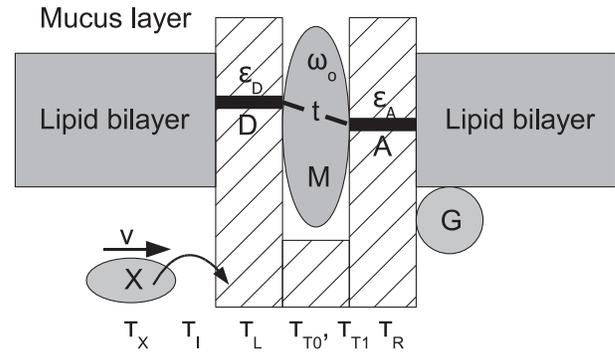

FIG. 1. The olfactory receptor is a G protein coupled receptor with seven hydrophobic helices that span the cell membrane. It responds to the arrival of a recognized odorant by releasing the α subunit of a neighboring G protein, which in turn initiates a large influx of Ca ions into the cell, a signal that can be communicated to the brain. This figure represents the model of the receptor we use to describe its action. The electron (hole) source X is likely to be a reducing (oxidizing) agent in the cell fluid. It arrives at a site on the outside of the receptor protein where it can exchange charge after an average interval τ_X. Once in place, it exchanges a charge with a characteristic time τ_I. The charge then travels to the donor D in one transmembrane helix of the protein over an average time of τ_L, from where it then hops to the acceptor A (possibly in a different helix) with either an average time τ_{T0} for nondiscriminating ("elastic") tunneling or an average time τ_{T1} for discriminating ("inelastic") tunneling. Only the inelastic contribution is sensitive to the odorant (M) oscillator frequency ω_0, and so needs to dominate the elastic contribution ($\tau_{T0} \gg \tau_{T1}$). The electron then travels from A to trigger the release of the G protein (G) over a time τ_R. Note that the terms elastic and inelastic refer *only* to energy exchange with the odorant.

described by Marcus theory [23–25], and characterized by a time τ_I. In proteins times range from about 1 ms down to about 1 μs [26]. The injected charge has to propagate through to the donor (D). The route is not known, but probably involves hopping transport. Thus the journey time is likely be in the ms to μs range as for charge injection. The next step is the inelastic tunneling from D to A (the acceptor), and it is this charge movement that actuates the receptor. Now the charge must reach the mechanism that releases the G protein which in turn initiates the signal that is sent to the brain. Again, we do not know the route taken but is likely to involve charge hopping. So the characteristic time τ_R will probably be in the range ms to μs. Thus, overall charge injection and extraction together are likely to occur on typical biological time scales of μs to ms.

For the mechanism to work there must be essentially no tunneling from D to A in the absence of the odorant, either because the distance is too great or energy conservation is problematic. The odorant must make inelastic transmission possible by a mechanism coupling electron movement from D and A to vibrational excitation in the odorant. In IETS there is a strong contribution to this coupling from the Coulomb interaction between partial charges associated with oscillating atoms and a mobile electron [27,28].

This same mechanism allows us to account for observed features of olfaction including the detection of oscillators buried inside a molecule (e.g., 2,6 di-t-butyl phenol [2]), and is compatible with our swipe card model: the long-ranged interaction can couple the mobile electron to the oscillator even with a loose fit.

The times characterizing elastic (τ_{T0}) and inelastic (τ_{T1}) ET from D to A are central to the success or failure of Turin's mechanism. We treat D and A as single molecular orbitals with energies ε_D and ε_A, coupled to each other by a weak hopping integral t, but not coupled to other electronic states. Because the hopping between D and A is slow on electronic time scales, the remaining electronic couplings must be very weak to prevent electron leakage. However, D and A will be coupled to oscillators in the odorant, receptor protein, and the wider environment. The ET rate from D to A can be computed from standard theory [23–25,29–31] but with the odorant oscillator treated explicitly. We consider one odorant oscillator of frequency ω_o which couples with strength γ_D (γ_A) to D (A). The environment is treated as many oscillators with frequencies ω_q and coupling strengths γ_{qD} and γ_{qA}. The complete system is described by the Hamiltonian $\hat{H} = \hat{H}_D + \hat{H}_A + \hat{v}$, where $\hat{H}_X = |X\rangle\langle X|(\varepsilon_X + \hat{H}_{\text{osc}} + \hat{H}_{e-\text{osc},X})$ (X is D or A), $\hat{v} = t(|D\rangle\langle A| + |A\rangle\langle D|)$ and $|D\rangle$ ($|A\rangle$) is an electronic state on D (A). $\hat{H}_{\text{osc}} = (\hat{a}^\dagger\hat{a} + \frac{1}{2})\hbar\omega_o + \sum_q(\hat{a}_q^\dagger\hat{a}_q + \frac{1}{2})\hbar\omega_q$ is the oscillator Hamiltonian for the odorant and environment, and $\hat{H}_{e-\text{osc},X} = \gamma_X(\hat{a} + \hat{a}^\dagger) + \sum_q\gamma_{qX}(\hat{a}_q + \hat{a}_q^\dagger)$ couples the electron to the oscillators. The eigenstates of $\hat{H}_{\text{osc}}$ are $|nN\rangle$, where n is the odorant oscillator occupancy and N corresponds to a set of environment oscillator occupancies $\{n_q\}$. The eigenstates of $\hat{H}_X$ are $|\Psi_{XnN}\rangle = \exp[u_X(\hat{a} - \hat{a}^\dagger) + \sum_q u_{qX}(\hat{a}_q - \hat{a}_q^\dagger)]|XnN\rangle$ and have eigenvalues $E_{XnN} = \varepsilon_X + (n + \frac{1}{2} - u_X^2)\hbar\omega_o + \sum_q(n_q + \frac{1}{2} - u_{qX}^2)\hbar\omega_q$. The states $|XnN\rangle$ are products of unperturbed electronic and oscillator basis states, $u_X = \gamma_X/\hbar\omega_o$ and $u_{qX} = \gamma_{qX}/\hbar\omega_q$. The times τ_{T0} and τ_{T1} follow from the standard golden rule result for the coupling of the system with the electron on D and odorant oscillator in its ground state to that with the electron on A and odorant oscillator in excited state $|n\rangle$: $1/\tau_{Tn} = (2\pi/\hbar)\sum_{NN'}P_N|\langle\Psi_{D0N}|\hat{v}|\Psi_{AnN'}\rangle|^2$ where P_N is the probability that the system starts in state $|\Psi_{D0N}\rangle$. After making standard approximations for an electron coupled to a bath of phonons [31,32], and taking the background fluctuations to be of low frequency, we get the Marcus-type expression

$$\frac{1}{\tau_{Tn}} = \frac{2\pi}{\hbar}t^2\frac{\sigma_n}{\sqrt{4\pi k_B T\lambda}}\exp\left(-\frac{(\epsilon_n - \lambda)^2}{4k_B T\lambda}\right) \quad (1)$$

where $\sigma_n = \exp(-S)S^n/n!$, $S = (u_D - u_A)^2$ (a Huang-Rhys factor), $\epsilon_n = \varepsilon_D - \varepsilon_A - n\hbar\omega_o$, $\beta = 1/k_B T$, $\lambda = \sum_q S_q\hbar\omega_q$ (reorganization energy), and $S_q = (u_{qD} - u_{qA})^2$.

We now estimate values for the parameters (Table I). The interesting range for $\hbar\omega_o$ in olfaction is about 70 meV

TABLE I. Estimated values for the physical quantities needed to compute τ_{T0} and τ_{T1}. See text for explanation of their values.

Quantity	$\hbar\omega_o$	S	λ	$|t|$ Value
Value	200 meV	0.01	30 meV	1 meV

to 400 meV [18], so a typical value is 200 meV. To estimate the Huang-Rhys factor S we introduce a physical mechanism for the electron-oscillator interaction based on the long-ranged electrostatic interaction between the electron and odorant atomic partial charges. The definition $S = (u_D - u_A)^2$ is equivalent to $S = \Delta F^2/2\hbar M_o\omega_o^3$ where ΔF is the change in force on the odorant oscillator as a result of the electronic transition [33,34]. We treat the oscillator as a dipole with charges $\pm qe$ and compute the forces on the oscillator when the electron is on A and D (treated as pointlike), giving

$$S = 4q^2\frac{m_e}{M_o}\left(\frac{\text{Ry}}{\hbar\omega_o}\right)^3\left(\frac{\hat{R}_D \cdot \hat{p}}{(R_D/a_0)^2} - \frac{\hat{R}_A \cdot \hat{p}}{(R_A/a_0)^2}\right)^2 \quad (2)$$

where $\hat{p}$ is the direction of the dipole, $\vec{R}_D$ is the vector from D to the dipole, $\vec{R}_A$ is the vector from A to the dipole, m_e is the electron mass, Ry the Rydberg, and a_0 the Bohr radius. Setting $q = 0.2$ (a typical partial atomic charge in a polar molecule), $m_e/M_o = 1/15\,000$ (using a representative atomic mass for light elements), $\hbar\omega_o = 200$ meV, $\hat{R}_D \cdot \hat{p} = -\hat{R}_A \cdot \hat{p} = 1$ and $R_D = R_A = 6a_0$ gives $S \sim 0.01$.

We assume the odorant (M) contacts D and A but interacts with them only weakly with hopping integral v. By considering the resulting admixtures of an M state with energy ε_M with those of D and A we obtain an effective hopping integral between D and A [$t = v^2/(\varepsilon_M - \varepsilon_A)$]. If ε_M corresponds to a lowest unoccupied molecular orbital while ε_D and ε_A correspond to highest occupied molecular orbitals then the difference $\varepsilon_M - \varepsilon_A$ can be as large as 10 eV. The hopping integrals can be estimated for known molecular structures. While the odorant structure is known, the donor and acceptor structures interacting with it are unknown, and we have to make an educated guess. If the bonds between M, and D and A are no stronger than hydrogen bonds, we can put a rough upper bound on the associated hopping integrals of order 0.1 eV, and hence obtain $t \sim 1$ meV. Our final conclusions are not sensitive to this value.

Reorganization energies are typically of the order of 1 eV, especially in hydrated systems, which would result in the elastic channel being much faster than the inelastic. But much smaller values have been found, and olfactory receptors are hydrophobic. Experiments on charge separation in mutant reaction centers of the photosynthetic bacteria *Rhodobacter capsulatus* show reorganization energies at room temperature below 0.03 eV [35]. A generally low value for odorant receptors would be a result of evolutionary optimization leading to almost no reorganization during the transition. This requires that D and A are not too

close to the aqueous medium in the cell to prevent significant coupling to the polarization of the water; thus we conjecture that D and A must lie well within the lipid bilayer region (see Fig. 1). The reorganization energy can also be reduced if electronic states on D and A are extended in space [29], so residues with delocalized electrons may be candidates. (For example, the conserved [36] tryptophan on helix 4 and 3 phenylalanines on helix 3. The surrounding highly variable residues could modify their redox potentials, producing different receptors). We take a value for the reorganization energy of 0.03 eV for the table of values.

Substituting the values in Table I into Eq. (1) for the case of resonance ($\varepsilon_D - \varepsilon_A = \hbar\omega_o$) we get $\tau_{T0} \sim 87$ ns and $\tau_{T1} \sim 1.3$ ns, which satisfies the condition $\tau_{T1} \ll \tau_{T0}$, and shows that the overall time for odor recognition is not limited by the discrimination process. Increasing the reorganization energy to just 50 meV would make $\tau_{T1} > \tau_{T0}$. Thus, provided the reorganization energy can be made not much bigger than $k_B T$, we can obtain a large signal to noise ratio. We note that the theory remains unaltered if a proton tunnels from D to A, but the parameters t, ε_D, and ε_A will be modified.

Our analysis indicates that humans could indeed recognize odor using phonon-assisted tunneling, provided the receptor has certain properties that are well within ranges known from other biomolecular systems. Our model shows that the overall charge transfer rate is sufficient to permit detection on the observed time scales, and the inelastic signal can be made sufficiently large relative to the elastic signal for there to be an acceptable signal to noise ratio. Lack of information on local receptor structure limits what can be verified. Our model illustrates a more general idea of how molecules can actuate receptors selectively. Lock and key models rely on docking for discrimination, and mechanical mechanisms for actuation. Selective docking does have a role in our class of swipe card models, but the crucial discrimination and nonmechanical actuation processes are different.

---

*Electronic address: j.brookes@ucl.ac.uk
†Electronic address: to_milaraki@hotmail.com
‡Electronic address: a.horsfield@ucl.ac.uk
§Electronic address: a.stoneham@ucl.ac.uk

[1] J. C. Leffingwell, Leffingwell Repts. **5**, 1 (2001).
[2] *Chemistry and Technology of Flavours and Fragrances*, edited by D. Rowe (Blackwells, Oxford, 2005), Chap. 11.
[3] R. Axel, Angew. Chem., Int. Ed. **44**, 6110 (2005).
[4] L. Buck, Angew. Chem., Int. Ed. **44**, 6128 (2005).
[5] W. Bialek, Annu. Rev. Biophys. Biophys. Chem. **16**, 455 (1987).
[6] R. B. Silverman, *The Organic Chemistry of Enzyme-Catalyzed Reactions* (Elsevier, New York, 2002).
[7] D. Wallace, A. M. Stoneham, A. Testa, A. H. Harker, and M. M. D. Ramos, Mol. Simul. **9**, 385 (1993).
[8] D. Wrobel, U. Wannagat, and U. Harder, Chem. Monthly **113**, 381 (1982).
[9] G. M. Dyson, Chem. Ind. **57**, 647 (1938).
[10] R. H. Wright, *The Sense of Smell* (CRC Press, Boca Raton, Florida, U.S.A., 1982).
[11] J. Lambe and R. C. Jaklevic, Phys. Rev. **165**, 821 (1968).
[12] C. J. Adkins and W. A. Phillips, J. Phys. C **18**, 1313 (1985).
[13] L. Turin, Chem. Senses **21**, 773 (1996).
[14] L. J. W. Haffenden, V. A. Yaylayan, and J. Fortin, Food Chem. **73**, 67 (2001).
[15] A. Keller and L. B. Vosshall, Nat. Neurosci. **7**, 337 (2004).
[16] B. R. Havens and C. E. Meloan, in *Food Flavors: Generation, Analysis and Process Influence: Proceedings of the 8th International Flavor Conference, Cos, Greece, 1994*, edited by George Charalambous (Elsevier, Amsterdam, 1995.), Vol. 37, p. 497.
[17] E. Brenna, C. Fuganti, and S. Serra, Tetrahedron: Asymmetry **14**, 1 (2003).
[18] L. Turin, J. Theor. Biol. **216**, 367 (2002).
[19] S.-y. Takane and J. B. O. Mitchell, Org. Biomol. Chem. **2**, 3250 (2004).
[20] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, and J. C. Burant *et al.*, GAUSSIAN 03, *Revision C.02* (Gaussian, Inc., Wallingford, CT, 2004).
[21] *CRC Handbook of Chemistry and Physics*, edited by D. R. Lide (CRC Press, Boca Raton, Florida, U.S.A., 2005), 86th ed.
[22] P. Atkins and J. de Paula, *Atkins' Physical Chemistry* (OUP, New York, 2002).
[23] R. A. Marcus, Annu. Rev. Phys. Chem. **15**, 155 (1964).
[24] J. Ulstrup, *Charge Transfer Processes in Condensed Media*, *Lecture Notes in Chemistry* Vol. 10 (Springer-Verlag, Berlin, 1979).
[25] *Protein Electron Transfer*, edited by D. S. Bendall (Bios Scientific Publishers, Abington, 1996).
[26] H. B. Gray and J. R. Winkle, Annu. Rev. Biochem. **65**, 537 (1996).
[27] J. R. Kirtley, D. J. Scalapino, and P. K. Hansma, Phys. Rev. B **14**, 3177 (1976).
[28] J. R. Kirtley and P. Soven, Phys. Rev. B **19**, 1812 (1979).
[29] R. A. Marcus, J. Chem. Phys. **24**, 966 (1956).
[30] R. A. Marcus, J. Chem. Phys. **43**, 679 (1965).
[31] X. Song and R. A. Marcus, J. Chem. Phys. **99**, 7768 (1993).
[32] C. P. Flynn and A. M. Stoneham, Phys. Rev. B **1**, 3966 (1970).
[33] K. Huang and A. Rhys, Proc. R. Soc. A **204**, 406 (1950).
[34] A. M. Stoneham, *Theory of Defects in Solids* (Oxford University Press, New York, 2001).
[35] Y. Jia, T. J. DiMagno, C.-K. Chan, Z. Wang, M. Du, D. K. Hanson, M. Schiffer, J. R. Norris, G. R. Fleming, and M. S. Popov, J. Phys. Chem. **97**, 13 180 (1993).
[36] T. Fuchs, G. Glusman, S. Horn-Saban, D. Lancet, and Y. Pilpel, Hum. Genet. **108**, 1 (2001).