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Exploring the Odorant-Determined, Molecular Basis for Olfactory Perception

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ABSTRACT

The mechanistic underpinnings of olfactory receptor (OR)-odorant interactions have yet to be completely understood. This stymies our understanding of how we perceive specific odors, odorants or combinations of odorants. We used computational methodologies to address OR-odorant interactions from a novel perspective-that of the odorant. In this study, odorants that elicit a hedonistic olfactory response were identified. We used machine learning methodologies to cluster 85 odorant molecules that are perfumes, active ingredients in perfumes or fillers in perfumes. Our clustering process used neural networks, which leveraged structural (inter-atomic distances-bonded as well as non-bonded) and electronic (NMR chemical shifts) specific features from our odorant cohort. Chemical shifts were theoretically determined using ab initio Density Functional Theory (DFT)- methods. Intra-molecular distances were obtained following geometry optimization using the above DFT methods. The 85-odorant cohort was then clustered into five sub-groups, based on similar electronic and structural features. To provide this electronic-structural basis for olfactory "hedonistic" perception, we tested whether the perceptions of odors, based on super-smeller responses, were also similarly clustered. Odor- perceptions within the clusters matched odor types with very few overlaps. Outliers arose from odorants that have shown multiple perceptive responses.

This proof-of-concept experiment will go a long way towards elucidating the combinatorial and promiscuous nature of odorant-olfactory receptor interactions. The perspective of the odorant is a novel approach to identifying olfactory receptor-odorant interactions.

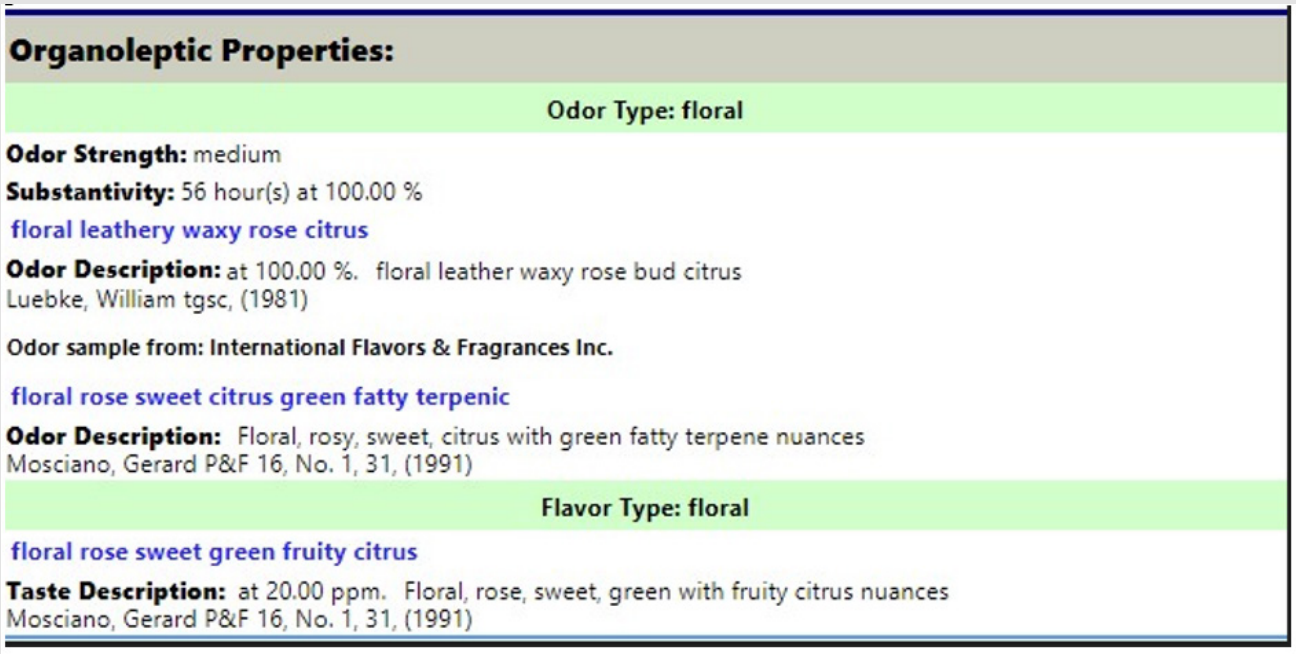
Introduction

The discovery of olfactory receptors has been relatively recent [1]. The impact of this discovery is particularly critical for two reasons: the 2004 Nobel Prize in Medicine and Physiology [2]; and the identification of the olfactory receptor gene family being the largest in all the human and mammalian genomes [3-6]. Olfactory receptors (OR) reside in the cilia of the mucous membrane of the nostrils, each of which is associated with a single olfactory neuron [7]. An olfactory receptor's interaction with an odorant marks the first step of olfaction. This OR-odorant interaction catalyzes a not well-understood signal transduction process that results in the perception of an odor [8]. The human genome has an olfactory receptor gene family consisting of approximately 400 receptor proteins [3,9,10]. Several hundred receptors are responsible for the discrimination of several thousand odorants and odors (combination of odorants-contributing to a particular odor). Elucidating the mechanism by which these odorants interact with and activate the olfactory receptors would

provide molecular-level insights into how one can relate the odorant, its complementarily interacting olfactory receptor and the resulting odor-perception. Functional assessments that would result in the identification of specific odorants that will target one or more OR are limited. There exists no acceptable rational basis for testing a panel of odorants against an OR. Experimental efforts at functionally characterizing ORs have been made, with some success [11,12]. These studies have been few and far between.

Results of these efforts indicate that the nature of OR-odorant interactions is promiscuous in nature: one receptor will interact with several odorants, while several receptors will interact with the same odorant. An overarching mechanism at a molecular level to address these interactions from experimental, functional analyses, however, is stymied. Olfactory receptors are membrane-bound and-because of the nature of these proteins-are difficult to express and purify. The crystal structure of an olfactory receptor is currently not available. Several studies have used homology modeling methodologies to develop structures of ORs. Some of these studies also involve molecular dynamics simulations of the interactions between ORs and odorants [13-16]. Here, we used a novel approach towards elucidating OR-odorant interactions, from the perspective of the odor. Our aim was to identify aspects of an odorant that are likely to bind specific ORs–namely the odorant's structural and electronic features. Our methodologies went beyond merely looking at functional groups or overall molecular size or structure of the odorant. We identified specific interatomic distances and electronic features associated with atoms that are common to specifically perceived odors. To achieve this, we rigorously optimized the molecular geometries and performed electronic charge distribution studies of perfume odorants using quantum chemistry calculations using density functional representations of the atom in molecules.

Variants of these methodologies have been used in drug design--to identify features of a putative pharmaceutical product that is likely to bind and activate a receptor protein--an interaction that mirrors that of an odorant and olfactory receptor. Indeed, most protein receptors for drug-compounds are Class A GPCRs. This is the presumed structure of an olfactory receptor [17]. We used machine learning ideations that leveraged the intra-molecular distances and the NMR-shifts of 85 odorant molecules from quantum chemistry studies to cluster odorants. Five clusters were generated. The odorant molecules in each cluster were then matched to their perceptions–which were determined by "smell experts" from companies that manufactured these odorant compounds.


Organoleptic Properties:

Odor Type: floral

Odor Strength: medium

Substantivity: 56 hour(s) at 100.00 %

floral leathery waxy rose citrus

Odor Description: at 100.00 %. floral leather waxy rose bud citrus
Luebke, William tgsc, (1981)

Odor sample from: International Flavors & Fragrances Inc.

floral rose sweet citrus green fatty terpenic

Odor Description: Floral, rosy, sweet, citrus with green fatty terpene nuances
Mosciano, Gerard P&F 16, No. 1, 31, (1991)

Flavor Type: floral

floral rose sweet green fruity citrus

Taste Description: at 20.00 ppm. Floral, rose, sweet, green with fruity citrus nuances
Mosciano, Gerard P&F 16, No. 1, 31, (1991)

Figure 1: A partial screen capture from the link, http://www.thegoodscentscompany.com/data/rw1007032.html, which is the page for Citronellol in the Good Scents resource. The figure shows that perceived odors from two different sources.

Methods

Identification and Acquisition of Perfume Odorants

Eighty-five odorant molecules were identified from a search using the term "perfume" from the Good Scents resource http://www.thegoodscentscompany.com/. (Figure 1) shows a screen capture of a partial page for the odorant, Citronellol (Chemical Abstracts Service [CAS] number: 106-22-9; IUPAC name: 3,7-dimethyloct-6-en-1-ol). The Good Scents Company is a comprehensive resource that informs the users of the chemical nature of the compound. It also lists the perceived odor and flavor of the compound from all available sources, as determined by smell and taste experts. For Citronellol, the perceived odor information is from two different sources. Source 1: floral, leathery, waxy, rose, and citrus. Source 2: floral, rose, sweet, citrus, green, fatty, and terpenic. The flavor for this compound is listed as: floral, rose, sweet, green, fruity, and citrus. (http://www.thegoodscentscompany.com/data/rw1007032.html-- Figure 1). For every odorant identified using the search term "perfume" from The Good Scents resource, the perceived odors were cataloged. (Table 1) lists all the compounds and their perceived odors. (Table 2), the converse of (Table 1), lists the compounds for the different perceived odors. The three-dimensional structural coordinates for every compound were downloaded from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) resource in the SDF (Structure Data Files) format.

Table 1: The odorants selected based on a search on keywords "perfume" in The Good Scents resource and the odor perceptions from every available resource for each odorant.

Odorant	Perceived Odors
Ambroxide	amber, ambergris, paper, musk, woody, cedar, pine, green, seedy
Anethole	sweet, anise, licorice, mimosa, medicinal, herbaceous, strong, warm, spice
Anisic_aldehyde	sweet, herbaceous, hawthorn, vanilla, spicy, powdery, minty, mimosa, hawthorne, fruity, floral, creamy, cinnamon, chocolate, cherry, berry, balsam, aromatic, anise, anis, almond
Anisole	anise, phenolic, gasoline, ethereal
Alpha santalol	woody, sandalwood
Benzoin	medicinal, balsamic, vanilla, camphereous
Benzyl acetate	sweet, floral, fruity, fresh
Benzyl alcohol	floral, phenolic, balsamic, rose
Benzyl benzoate	sweet, floral, balsamic, fruity, almond, cheese, strawberry, oily, herb
Benzyl cinnamate	sweet, floral, balsamic, fruity, pineapple, spicy, cherry, powdery, apricot, chocolate, peach, cinnamic
Benzylacetone	floral, aromatic, sweet, balsamic, jasmine, herbal, fruity, chemical, benzyl, acetate
Beta santalol	woody
Beta vetivone	cassis, grapefruit, woody, medicinal
Beta pinene	woody, green, spicy, pine, hay, resinous, minty, peppery, nutmeg, camphoraceous, eucalyptus, watery
Bisabolol	floral, balsamic, peppery, chamomile
Boisvelone	amber, ambergris, woody, floral, velvety, lemony, citrus, violet
Bourgeonal	green, sweet, sandalwood, fresh, watery, muguet, lillies
Calone	green, fruity, fresh, ozone, melon, moss, marine
Camphene	woody, pine, green, camphereous, spicy, herbal, minty, citrus, lavender, coniferous, harsh
Camphor	camphoraceous
Cashmeran	amber, musk, woody, sweet, floral, fruity, spicy, powdery, pine
Chavicol	medicinal, phenolic, herbal
Cinnamyl alcohol	green, sweet, floral, balsamic, spicy, cinnamon, hyacinth, honey, yeasty
Cis-3-hexenal	green, floral, fruity, pineapple, strawberry, herb, grassy, apple, sharp, vegetable, orange, lilac
Citral	green, sweet, fresh, tart, hesperidic, lemony, sharp, tangy
Citronellol	green, sweet, floral, fruity, rose, menthol, leather, waxy, fatty, citrus, geranium
Civet	balsamic, fatty, powdery, honey, fecal, urine, animal
Cuminaldehyde	green, spicy, herbal, vegetable, cumin
Cyclododecanone	camphereous
Cyclohexadecanone	powdery, animal, musk

Cyclopentadecanolide	musk, anise, vanilla, fruity, heliotrope, tobacco, powdery, animal
Cyclopentadecanone	musk, fatty, powdery, animal
Cyclopentanone	minty
Damascenone	woody, earthy, green, sweet, fruity, rose, plum, berry, tobacco, spicy, herbal, grape, raspberry, sugar, citrus, nutty
Damascone	floral rose apple fruity blackcurrant, spicy, plum, minty metallic, fruity, sweet
Delta octalactone	green, sweet, dairy, tropical, coconut, fatty, oily, spicy, creamy, hay, caramel
Estragole	green, weedy, anise, sassafras, sweet, phenolic, spicy, herbal, celery, basil, minty
Furan-2-yl-methanethiol	coffee, sulfurous, burnt, roasted, onion, meaty, smoky, savory, oily, nutty, waxy, rubbery, herbaceous, garlic, fishy, fatty, eggy, cooked, chocolate, chicken, caramel
Furaneol	candy floss, sweet, walnut, butterscotch, fruity, pineapple, strawberry, sugar, caramel
Gamma decalactone	sweet, vanilla, fruity, fresh, cocoa, coconut, buttery, fatty, oily, creamy, apricot, peach
Gamma nonalactone	sweet, dairy, orchid, fruity, cocoa, coconut, buttery, waxy, fatty, oily, creamy, apricot
Geraniol	green, sweet, floral, metallic, pear, fruity, rose, waxy, peach, citrus, geranium
Geranyl acetate	green, floral, pear, rose, waxy, herbal, lavender
Grapefruit mercaptan	woody, tropical, onion, garlic, pungent, sulfur, grapefruit, resinous
Helional	green, floral, fresh, hay, watery, muguet, ozone, marine
Heptyl acetate	woody, green, rummy, pear, fruity, fresh, apricot, wine, citrus
Hexyl cinnamaldehyde	green, floral, jasmin, tropical, fruity, waxy, spicy, powdery, herbal, citrus
Hydroxycitronellal	green, sweet, floral, tropical, fresh, waxy, citrus, muguet, melon, lilac
Indole	floral, camphereous, pungent, musty, fecal, animal
Irone	woody, floral, berry, powdery, violet, orris
Isopropyl salicylate	green, orchid, clover, vine
Isovanillin	spicy, phenolic
Jasmine lactone	oily, fruity, petal, floral, jasmine, tuberose, peach, apricot, coconut
Lilial	green, floral, powdery, watery, muguet, cumin
Linalool	woody, green, blueberry, sweet, floral, rose, waxy, citrus, lavender, coriander, orange
Lyral	woody, sweet, floral, rhubarb, cyclamen, muguet, lilac
Massoia lacto	green, sweet, dairy, fruity, coconut, creamy, peach, herbal
Menthone	woody, sweet, fresh, menthol, minty
Methyl benzoate	cananga, floral, tuberose, cherry, pit, fruity, wintergreen, almon
Methyl butyrate	banana, sweet, fruity, pineapple, creamy, apple
Methyl isobutyrate	sweet, floral, fruity, ethereal, pineapple, tutti, apple
Methyl mercaptan	onion, garlic, sulfur, oily, cabbage, cheesy, creamy
Muscone	musk, sweet, floral, fatty, powdery, animal
Myrcene	woody, balsamic, rose, plastic, spicy, herbal, celery, carrot, peppery, vegetable
Nerol	woody, green, tea, neroli, sweet, floral, fresh, rose, waxy, spicy, herbal, lemony, magnolia, citrus, marine
Nerolidol	woody, green, tea, floral, waxy, herbal, citrus
Ocimene	woody, green, sweet, floral, tropical, herbal, citrus, terpene
Oct-1-en-3-one	mushroom, earthy, vegetable, savory, musty, metallic, herbal, fishy, dirty, chicken, cabbage, broccoli
Ortho vanillin	vanilla
Patchoulol	patchouli, earthy, camphereous, powdery
Perillaldehyde	green, sweet, fresh, spicy, clove, herbal, minty, citrus, grassy, orange, cumin
Phellandrene	turpentine, minty
Phenethyl alcohol	bread, sweet, floral, fresh, rose, honey
P menthane	pine
Pomarose	fruity, rose, plum, raisin, dried, apple

Pulegone	camphereous
Raspberry ketone	seedy, sweet, floral, berry, raspberry
Rhodinol	sweet, floral, tropical, rose, waxy, fatty, spicy, powdery, lemony, citrus, orange, geranium
Safrole	woody, anise, sassafrass, sweet, floral, spicy
Sandalore	woody, sweet, amyris, sandalwood, waxy, creamy
Skatole	fecal, animal
Sotolon	coffee, candy floss, sweet, sugar, caramel
Thujone	cedar
Thymol	medicinal, phenolic, herbal, camphoraceous, thyme
Vanillin	vanilla

Table 2: The perceived odors of odorants selected based on a search on keywords "perfume" in The Good Scents resource. This is the converse of (Table 1). 162 unique perceived odors were identified for the 85 odorants.

Perceived Odor	
Amber	ambroxide, boisvelone, cashmeran
Ambergris	ambroxide, boisvelone
Paper	ambroxide
Musk	musk xylol, muscone, ambroxide, cashmeran, cyclodexadecanone, cyclopentadecanolide, cyclopentadecanone
Woody	sandalore, safrole, pathchoulol, ocimene, nerolidol, myrcene, menthone, lyral, linalool, irone, heptyl acetate, grapefruit mercaptan, damascenone, ambroxide, anisic aldehyde, alpha-santalol, benzyl acetone, beta-vetivone, beta-pinene, boisvelone, boisvelone, camphene, cashmeran
Cedar	thujone, ambroxide
Earthy	pathchoulol, 1-octen-3-one, damascenone
Pine	ambroxide, camphene
Green	perillaldehyde, ocimene, nerolidol, nerol, massoia lactone, linalool, lilial, isopropyl salicylate, hydroxycitronellal, hexyl cinnamaldehyde, heptyl acetate, helional, geranyl acetate, geraniol, estragole, delta-octalactone, damascenone, ambroxide, benzyl acetone, beta-pinene, bourgeonal, calone, camphene, camphene, cinnamyl alcohol, cis-3-hexenal, citral, citronellol, cuminaldehyde, cyclamen
Seedy	raspberry ketone, ambroxide
Tea	nerolidol
Blueberry	linalool
Rummy	heptyl acetate
Weedy	estragole
Anise	safrole, estragole, anethol, anisic aldehyde, anisole, cyclopentadecanolide
Licorice	anethol
Coffee	sotolon, furfuryl mercaptan
Sassafrass	safrole, estragole
Candy-floss	furaneol, sotolon
Cananga	methyl benzoate
Medicinal	thymol, anethol, benzoin, chavicol
Banana	methyl butyrate
Neroli	nerol
Fennel	para-menthane
Bread	phenethyl alcohol
Sweet	sotolon, sandalore, safrole, rhodinol, raspberry ketone, phenethyl alcohol, perillaldehyde, ocimene, nerol, musk xylol, muscone, methyl isobutyrate, methyl butyrate, menthone, massoia lactone, lyral, linalool, hydroxycitronellal, geraniol, gamma-nonalactone, gamma-decalactone, furaneol, estragole, delta-octalactone, damascenone, anisic aldehyde, benzyl acetate, benzyl benzoate, benzyl cinnamate, anethol, bourgeonal, cashmeran, cinnamyl alcohol, citral, citronellol

Floral	safrole, rhodinol, raspberry ketone, phenethyl alcohol, ocimene, nerolidol, nerol, muscone, methyl isobutyrate, methyl benzoate, lyral, linalool, lilial, jasmin lactone, irone, indole, hydroxycitronellal, hexyl cinnamaldehyde, helional, geranyl acetate, geraniol, anisic aldehyde, benzyl acetate, benzyl alcohol, benzyl benzoate, benzyl cinnamate, benzyl acetone, bisabolol, boisvelone, boisvelone, cashmeran, cinnamyl alcohol, cis-3-hexenal, citronellol, cyclamen
Phenolic	thymol, estragole, anisole, benzyl alcohol, chavicol
Dairy	massoia lactone, gamma-nonalactone, delta-octalactone
Orchid	isopropyl salicylate, gamma-nonalactone
Jasmine	jasmine lactone, hexyl cinnamaldehyde
Tuberose	methyl benzoate, jasmine lactone
Cherry	methyl benzoate
Clover	isopropyl salicylate
Metallic	geraniol, 1-octen-3-one
Gasoline	anisole
Tropical	rhodinol, ocimene, hydroxycitronellal, hexyl cinnamaldehyde, grapefruit mercaptan, delta-octalactone
Walnut	furaneol
Vine	isopropyl salicylate
Butterscotch	furaneol
Pear	heptyl acetate, geranyl acetate, geraniol
Ethereal	anisole
Amyris	sandalore
Sandalwood	sandalore , alpha-santalol, bourgeonal
Balsamic	myrcene, benzoin, benzyl alcohol, benzyl benzoate, benzyl cinnamate, benzyl acetone, bisabolol, cinnamyl alcohol, civet
Vanilla	ortho-vanillin, gamma-decalactone, benzoin, cyclopentadecanolide, cyclopentadecanolide
Camphereous	pathchoulol, indole, benzoin, camphene, camphor, cyclododecanone
Fruity	pomarose, methyl isobutyrate, methyl butyrate, methyl benzoate, massoia lactone, jasmin lactone, hexyl cinnamaldehyde, heptyl acetate, geraniol, gamma-nonalactone, gamma-decalactone, furaneol, damascenone, benzyl acetate, benzyl benzoate, benzyl cinnamate, benzyl acetone, beta-vetivone, calone, cashmeran, cis-3-hexenal, citronellol, cyclopentadecanolide, cyclopentadecanolide
Fresh	phenethyl alcohol, perillaldehyde, nerol, menthone, hydroxycitronellal, heptyl acetate, helional, gamma-decalactone, benzyl acetate, bourgeonal, calone, citral, cyclamen
Rose	rhodinol, pomarose, phenethyl alcohol, nerol, myrcene, linalool, geranyl acetate, geraniol, benzyl alcohol, citronellol, damascenone
Heliotrope	cyclopentadecanolide
Ethereal	methyl isobutyrate
Plastic	myrcene
Plum	pomarose, damascenone
Raisin	pomarose
Dried fruit	pomarose
Petal	jasmine lactone
Cocoa	gamma-nonalactone, gamma-decalactone
Menthol	menthone, citronellol
Linden	cyclamen
Leather	citronellol
Berry	raspberry ketone, irone, damascenone
Tobacco	damascenone, cyclopentadecanolide, damascenone
Rhubarb	lyral, cyclamen
Wintergreen	methyl benzoate
Almond	methyl benzoate, benzyl benzoate
Coconut	massoia lactone, jasmine lactone, gamma-nonalactone, gamma-decalactone, delta-octalactone

Buttery	gamma-nonalactone, gamma-decalactone
Waxy	sandalore, rhodinol, nerolidol, nerol, linalool, hydroxycitronellal, hexyl cinnamaldehyde, geranyl acetate, geraniol, gamma-nonalactone, gamma-nonalactone
Cheese	benzyl benzoate
Savory	furfuryl mercaptan
Meaty	furfuryl mercaptan
Rubbery	furfuryl mercaptan
Chicken	1-octen-3-one, furfuryl mercaptan
Onion	methyl mercaptan, , grapefruit mercaptan, furfuryl mercaptan
Garlic	methyl mercaptan, grapefruit mercaptan
Pungent	indole, grapefruit mercaptan
Sulfur	methyl mercaptan, grapefruit mercaptan, furfuryl mercaptan
Fatty	rhodinol, musk xylol, muscone, gamma-nonalactone, gamma-decalactone, furfuryl mercaptan, delta-octalactone, citronellol, civet, cyclopentadecanone
Pineapple	methyl isobutyrate, methyl butyrate, furaneol, benzyl benzoat, benzyl cinnamate, cis-3-hexenal
Strawberry	furaneol, benzyl benzoate, benzyl acetone, cis-3-hexenal
Oily	methyl mercaptan, jasmin lactone, gamma-nonalactone, gamma-decalactone, furfuryl mercaptan, benzyl benzoate, delta-octalactone
Herb	benzyl benzoate, cis-3-hexenal
Cabbage	1-octen-3-one, methyl mercaptan
Cheesy	methyl mercaptan
Tutti frutti	methyl isobutyrate
Burnt	furfuryl mercaptan
Smoky	furfuryl mercaptan
Spicy	safrole, rhodinol, perillaldehyde, nerol, myrcene, hexyl cinnamaldehyde, estragole, delta-octalactone, damascenone, benzyl cinnamate, beta-pinene, camphene, cashmeran, cinnamyl alcohol, cuminaldehyde
Cherry	benzyl cinnamate
Creamy	sandalore , methyl mercaptan, , methyl butyrate, massoia lactone, gamma-nonalactone, gamma-decalactone, delta-octalactone
Powdery	rhodinol, pathchoulol, muscone, lilial, irone, hexyl cinnamaldehyde, benzyl cinnamate, cashmeran, civet, cyclhexadecanone, cyclopentadecanolide, cyclopentadecanone
Apricot	jasmin lactone, heptyl acetate, gamma-nonalactone, gamma-decalactone, benzyl cinnamate
Chocolate	benzyl cinnamate
Clove	perillaldehyde
Peach	massoia lactone, jasmin lactone, geraniol, gamma-decalactone, benzyl cinnamate
Tart	citral
Wine	heptyl acetate
Hesperidic	citral
Terpentine	phellandrene
Cinnamic	benzyl cinnamate
Herbal	thymol, perillaldehyde, 1-octen-3-one, ocimene, nerolidol, myrcene, massoia lactone, hexyl cinnamaldehyde, geranyl acetate, estragole, damascenone, benzyl acetone, camphene, chavicol, cuminaldehyde
Grapefruit	grapefruit mercaptan, beta-vetivone
Grape	damascenone
Mushroom	1-octen-3-one
Raspberry	raspberry ketone, damascenone
Sugar	sotolon, furaneol, damascenone
Cassis	beta-vetivone
Pine	beta-pinene, cashmeran
Celery	myrcene, estragole

Basil	estragole
Carrot	myrcene
Hay	helional , beta-pinene, delta-octalactone
Resinous	grapefruit mercaptan, beta-pinene
Caramel	sotolon, furaneol, delta-octalactone
Minty	phellandrene, perillaldehyde, menthone, estragole, beta-pinene, camphene, cyclopentanone
Peppery	myrcene, beta-pinene, bisabolo
Nutmeg	beta-pinene
Camphoraceous	thymol, beta-pinene, pulegone
Thyme	thymol
Peppermint	pulgone
Eucalyptus	beta-pinene
Watery	lilial, helional , beta-pinene, bourgeonal, cyclamen
Chamomile	bisabolol
Musty	1-octen-3-one, indole, cyclamen
Cyclamen	lyral
Velvety	boisvelone
Fishy	1-octen-3-one
Lemony	rhodinol, nerol, boisvelone, citral
Magnolia	nerol
Citrus	rhodinol, perillaldehyde, ocimene, nerolidol, nerol, linalool, hydroxycitronellal, hexyl cinnamaldehyde, heptyl acetate, geraniol, damascenone, boisvelone, camphene, citronellol
Violet	irone, boisvelone
Nutty	furfuryl mercaptan, damascenone
Egg	furfuryl mercaptan
Muguet	lyral , lilial, hydroxycitronellal, helional, bourgeonal
Lillies	bourgeonal
Ozone	helional, calone
Melon	hydroxycitronellal, calone, cyclamen
Moss	calone
Marine	nerol, helional, calone
Lavender	linalool, geranyl acetate, camphene
Coniferous	camphene
Harsh	camphene
Coriander	linalool
Cinnamon	cinnamyl alcohol
Hyacinth	cinnamyl alcohol
Honey	phenethyl alcohol, cinnamyl alcohol, civet
Yeasty	cinnamyl alcohol
Grassy	perillaldehyde, cis-3-hexenal
Apple	pomarose, methyl isobutyrate, methyl butyrate, cis-3-hexenal
Sharp	cis-3-hexenal, citral
Orris	irone
Terpene	ocimene
Broccoli	1-octen-3-one
Vegetable	1-octen-3-one, myrcene, cis-3-hexenal, cuminaldehyde, cyclamen

Orange	rhodinol, perillaldehyde, linalool, cis-3-hexenal
Lilac	lyral, hydroxycitronellal, cis-3-hexenal
Tangy	citral
Geranium	rhodinol, geraniol, citronellol
Fecal	skatole, indole, civet
Urine	civet
Animal	skatole, muscone, indole, civet, cyclhexadecanone, cyclopentadecanolide, cyclopentadecanone
Cumin	perillaldehyde, lilial, cuminaldehyde

Quantum Chemistry--NMR and Geometries

Coordinates of the SDF files were used as a starting point for the geometry optimization calculations. These SDF files were converted into x, y, z coordinates using the Open Babel resources (https://openbabel.org/) and then to Gaussian input files using customized bash scripts. Density functional theory calculations were carried out on the initial structures using the software Gaussian (version 16.A.03) [18] with the hybrid functional B3LYP and basis set 6-31G(d) for all the atoms, first to optimize the geometry and then to determine NMR chemical shifts for the carbon and nitrogen atoms. Shielding and isotropic coupling constants were computed using the gauge-including atomic orbitals (GIAOs) implemented in the Gaussian software. Isotropic shielding values were extracted, and the chemical shift values were calculated for each of the atoms. Optimized structures were then converted into SDF files and used for further clustering analysis [19].

Creating Feature Matrix

The data from the ab initio, quantum chemistry experiments were integrated into a feature matrix, which was the result of the elements of three matrices:

1) An adjacency matrix stored the bonded connectivities of the atoms from the odorants using Python libraries, Spektral and NetworkX;

2) A distance matrix comprised all intra-molecular distances (irrespective of whether the atoms were bonded or not) using the Python library, molmod; and

3) An NMR matrix. The NMR matrix elements were binned into blocks of chemical shifts of 20 ppm (parts per million). For Carbon-13, the blocks ranged from 0 ppm to 220 ppm. 20 ppm blocks were also used for Nitrogen-15. To account for the entire range of chemical shifts for nitrogen, the NMR matrix included nitrogen bins ranging from 0 ppm to 400 ppm. All the matrices were combined into a single matrix. This features matrix comprised 1638 features.

Clustering

In our customized Python program, we used three neural networks: a Graph Attention Neural Network (GANN) that mapped an odorant's atomic connectivities from its positional coordinates [20]; a deep neural network (DNN) [21] that comprehensively extracted interatomic-bond distances; and a DNN that extracted electronic features of bonded and surrounding atoms within an odorant from the 13C and 15N NMR chemical shifts. We used K-means unsupervised learning algorithm to cluster the structural and electronic features from the feature matrix. The algorithm groups observations with similar attribute values together by measuring the Euclidian distance between points. As proof of concept, we tested the system on creating five clusters from the 85-odorant list.

Results

(Table 3) illustrates the distribution of the odorant molecules among the five clusters. Cluster 1 had four molecules, cluster 2–by far the largest–had 60, cluster 3 had 16, cluster 4 had four, and cluster 5 had six odorants. For each cluster, the top ranked perceived odors are highlighted in (Table 4). In cluster 1–the smallest cluster–the representative odors are woody and powdery. In cluster 2, the top-ranking odors are sweet, green, camphereous, floral, herb and spicy. For cluster 3, the odors are floral, woody, powdery and amber. For cluster 4, the top-ranking are powdery, animal, fruity and musk. For cluster 5, the odors related to specific fruits predominate: apple, fruity, pineapple, and creamy.

Table 3: The distribution of the cohort of odorants in the five clusters following clustering analysis.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Alpha santalol, beta santalol, cyclopendecanone, hexyl cinnamaldehyde	Anethole, anisic aldehyde, benzylacetone, benzyl alcohol, benzyl benzoate, beta pinene, bourgeonal, calone, camphene, camphor, chavicol, cinnamyl alcohol, citral, citronellol, cuminaldehyde, cyclamen aldehyde, cyclododecanone, damascenone, delta octalactone, furaneol, gamma decalactone, gamme nonalactone, geraniol, geranyl acetate, grapefruit mercatan, helional, heptyl acetate, hydroxycitronellal, indole, isppropyl salicylate, isovanillin, jasmine lactone, linalool, massioa lactone, menthone, methyl benzoate, myrcene, nerol, ocimene, oct-1-en-3-one, ortho vanillin, p-menthane, perillaldehyde, phellandrene, phenethyl alcohol, pomarose, pulegone, raspberry ketone, rhodinol, safrole, skatole, sotolon, thujone, thymol, vanillin	ambroxide, benzoin, benzyl acetate, beta vetivone, bisabolol, boisveline, cashmeran, civet, irone, lillial, lyral, muscone, musk xylene. Nerolidol, patchoulol, sandalore	benzyl cinnamate, cyclohexadecone, cyclopentadecanolide, cyclopentanone	Cis-3-hexenal, furan-2-yl-methanethiol, methyl butyrate, methyl isobutyrate, methyl mercaptan

Table 4: The top ranked perceived odors for each cluster following clustering analysis.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
powdery, woody	sweet, green, floral, herb, spice, camphereous, fruity, woody	floral, woody, powdery, amber, sweet, balsamic, green	powdery, animal, fruity, musk	apple, fruity, pineapple, creamy, floral

Discussion

To put the perceived odors into perspective of our methodology, it means that specific structure-electronic features of the molecules, which were the data fed through the feature matrix into the machine learning system are reproduced across the odorants that are in each cluster. For the electronic features, the NMR chemical shifts were considered for C-13 and N-15 atoms. NMR chemical shifts for H-1 were not determined. None of the cohorts of odorants had a phosphorus atom. The chemical shifts were binned into 20 ppm blocks and covered the entire range of the chemical shift spectrum in ppm–observed for every possible connectivity and electronic environment for carbon and nitrogen odorant atoms. Odorants that elicit a specific response, e.g., a fruity odor, possess one or more atom-pairs, each of which are separated by the same distance and have the same NMR chemical shift. The structure matrix consisted only of all intra-molecular distances and intra-molecular bond connectivities. No information related to functional groups, size of molecule, or structural features such as straight chains or rings were included. We explored the possibility that the reproducing "atom-pairs" as mentioned above, responsible for a perceived odor, go beyond bonded atom-pairs. The eventual goal is to identify specific atoms-pair(s) as being responsible for generating a specific olfactory response. (Table 4) only includes perceived odors that had high counts. This meant that a particular odor was elicited by most of the odorants in the cluster.

(Table 1) shows every possible odor identified by a smell-expert from The Good Scents resource, which was used in this work. Some odorants, e.g. Citronellol, have several odors (Figure 1), some of which are closely related and conceivably have perceptual overlaps, e.g., green vs. herb-like, or, sweet vs. floral. Some of the perceived odors also overlap across clusters (Table 4). Benzyl acetone (Cluster 2) has been identified as having the odors of: floral, aromatic, sweet, balsamic, jasmine, herbal, fruity, and chemical. Benzyl alcohol, from the same cluster has the odors: floral, phenolic, balsamic, and rose. In each case, the experts have been able to discern between floral and jasmine, and between floral and rose. The Good Scents resources identifies the odor perception based on the source of the expertise–and indeed, these differ, in some cases, depending on the expert. It, however, does not identify the specific concentration of the odorant used during the smell test. There is evidence that odor-perception changes with concentration [21,22]. An increasing body of evidence shows that odorant perception changes between demographic populations and often depends on the geographical region of an individual [23,24]. Epigenetic factors also likely influence odor perception. Expert smellers can presumably discriminate between can distinguish between green and herbal, oily and fatty, sweet and floral. But it is likely that the perceptions of highly similar odors are weighed by opinion.

Odors identified as watery (lilial, helional, beta-pinene, bourgeonal, cyclamen) or fresh (phenethyl alcohol, perillaldehyde, nerol, menthone, hydroxycitronellal, heptyl_acetate, helional, gamma-decalactone, benzyl_acetate, bourgeonal, calone, citral, cyclamen) are also vague, and likely vary among smell and taste experts. One possible future remedy is to only include as perceived odors for an odorant those that are common among experts. There is an overlap in some odors between clusters: woody (Cluster 1 and 3), powdery (Cluster 1, 3 and 4), and fruity (Cluster 4 and 5). Cluster 2 with many odorants is distinguishable because the top-ranking odor perceptions are gen-

erally sweet-smelling. Cluster 5 is distinguishable because of the predominance of specific fruit odors, in addition to the generic "fruity" odor. Our clustering software allows the programmer to determine the number of clusters in which to place the odorants. For this proof-of-concept effort, we chose the creation of five clusters. It is likely that some of the overlap is because of the limited number of clusters which forced slightly different odorants into the same cluster. Future work would necessitate the need of re-clustering the odorants into 10, 15, 20 and 25 clusters to ascertain the ideal number of clusters for an odorant cohort of this size, while fine tuning the software's ability to discriminate subtler electronic-structural differences. Another possible methodology would be to create 3-5 clusters of odorant molecules by iterating the clustering analysis over 25-50 random selected odorants out of the 85 tested.

This randomization process would remove any biases in determining the exact number of clusters needed. In depth analysis would also be required to pinpoint the exact electronic structural feature of the odorant specifically responsible for a olfactory perceptive response.

Conclusion

We present here a novel methodology of correlating electronic and structural features in odorants with odor perception. Our atom-pairs are not restricted to bonded atoms. This means that we can identify features that are not obvious from merely observing the overall structure of an odorant. These notions are like those advanced in the drug-design of putative pharmaceutical products domain. Drug design methods use Quality Structure Activity Relationships QSAR [25] and Spectral Data Activity Relationship (1-D, which used NMR, and 3-D, which used distances) to associate electronic structural features with drug-activity [26,27]. In the pharmaceutical industry, a drug's activity is determined by quantification of pharmacophore or toxicophore effects of the compound on human subjects. In drawing a parallel between these methodologies and the ones described in this paper, activity in the case of odorants is the elicited perceived odor from the perspective of the expert-smeller. We have shown that our system can discriminate between perceived odors. One issue that needs to be further addressed is fine-tuning the methodology to determine the ideal number of clusters per odorant cohort and pinpointing specific structural features responsible for specific olfactory responses.

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