

Decoding Smell: The Future of Odor Mapping with AI and Molecular Chemistry

BY: LAKSHYA ALAGAN

What do the roses in your garden smell like? Delicate and floral, or perhaps overpowering? While each of us perceives scents in a personal way—an enigma eighteenth-century philosopher Frank Jackson introduced as “qualia”—the majority of individuals share continuities and patterns that allow us to create models of our senses. As a result, new advances in artificial intelligence, combined with growing chemical knowledge, are uncovering a more accurate way to predict smells based on molecular structure. While individual perception still varies widely, this advancement moves us closer to unraveling the mysteries of one of our most complex senses—smell.

UNDERSTANDING SENSORY MAPPING

Before scents were chemically profiled, scientists began to uncover the direct relationships between our senses and modalities. For example, visual perception can be characterized by wavelengths that map out colors; thus, we can directly identify specific colors from the wavelengths alone. Likewise, our hearing, or auditory perception, allows us to identify pitch from the frequency waves directly. Sensory mapping models show how our brain interprets such sensory information, laying out their specific relationships.¹ Once a layout of sensory interpretation is established, it can be applied to a technology for further research and prediction. For example, understanding the relationship between color and wavelength allowed for the creation of

color-blind eyewear, which utilizes special lenses to filter out specific wavelengths of light and help the brain more easily differentiate between colors. In individuals with certain color blindness conditions, such as red-green vision deficiency, these lenses reduce the amount of perceived overlap in red-green wavelengths, allowing them to observe colors that were previously unseen.² In summary, sensory mapping serves to describe the connection and relationship between sensory stimuli and how the human brain interprets them. As a result, sensory mapping serves as a foundation for developing brain maps and potential therapeutics for brain-related conditions.

While vision and audition have distinct linear mappings, odor seems to tell a more complex story. Odor perception has been researched by chemists for several decades, with a focus on how molecular structures and the presence of certain functional groups influence how the molecule smells.^{3,4,5} For example, molecules with an ester functional group tend to have a sweet and fruity scent, while ketones tend to have a more pungent scent.³ Utilizing these patterns, a method of smell-prediction known as odor fingerprinting was created to characterize and compare molecules. Fingerprinting develops a molecule’s chemical scent profile by encoding information about its structural features in

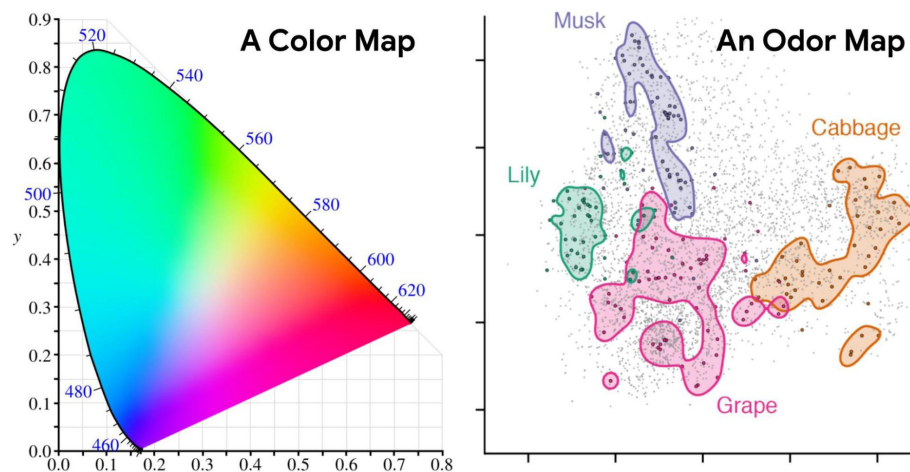


Figure 1. The color map (shown on the left) illustrates how different wavelengths of light correspond to specific colors on a linear scale. The odor map (shown on the right), however, presents a complex, overlapping system of smells, reflecting the nonlinear relationship between odors and molecular structures.

a binary form (a code of zeroes and ones), which accounts for the presence or absence of a specific characteristic.^{6,7}

ODOR MAPPING AND ITS DISCONTINUITIES

Such observational patterns and research have established that there *does* lie a relationship between molecular structure and smell perception, raising the question: Can molecular structure (which includes the presence of certain functional groups) map for odor? To understand this, we must first understand how our brain physiologically perceives and interprets smell. When odorous molecules enter our nose, they bind to specific olfactory receptors in the upper nose which account for a few of about 1000 different types of receptors. These receptors activate olfactory sensory neurons, which relay chemical messages to the olfactory bulb—the region of the brain responsible for scent perception.^{8,9} Thus, what we smell is not only determined by *which* receptors are activated but also by the specific combination of several receptors being activated. As a result, unique combinations of receptor activation trigger different responses for the brain to interpret; this multidimensional system differs from the direct mapping of vision and sound.

However, traditional olfactory fingerprinting methods based on functional groups and molecular structures alone are not able to account for all sensory experiences, as different molecules with the same functional group can sometimes produce differing smells. For example, take 4,4-dimethyl-2-octeno- δ -lactone and 8-methyl-2-noneno- δ -lactone; both molecules contain the lactone functional group and have similar structures, yet very distinctive smells. The former has a minty odor, while the latter has a buttery odor.³ Conversely, molecules with immense structural differences can actually produce similar smells; this is often the case for musk-related odors.^{1,3,4} Furthermore, although functional groups can sometimes accurately predict odor, they can only do so to a limited extent: most functional groups can describe if something is generally sweet, pungent, or minty smelling, but can't specifically describe if it smells like vanilla or garlic.¹

THE PRINCIPLE ODOR MAP (POM)

Due to odor-mapping discontinuities and limitations, researchers have been looking to develop more accurate representations of the complexities that fall within odor prediction. In 2023, researchers created a remarkable machine learning mapping program designed

“While vision and audition have distinct linear mappings, odor seems to tell a more complex story.”

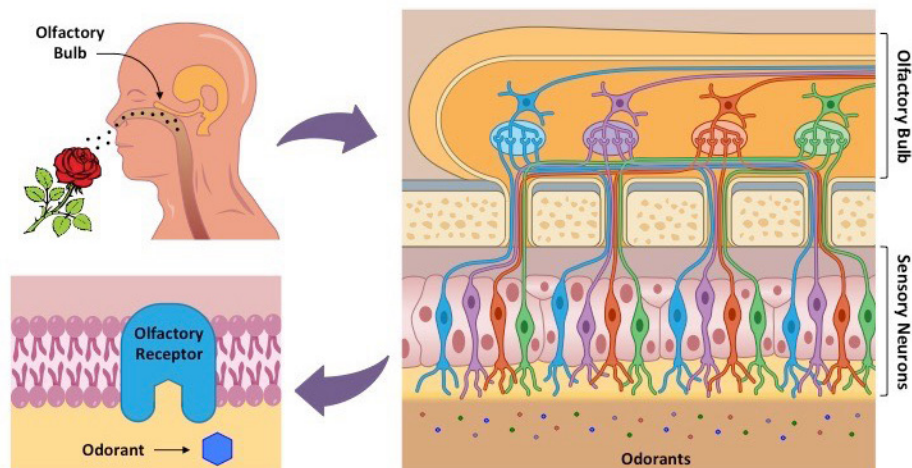


Figure 2. Olfactory System. When odor molecules are inhaled, they travel through your nasal cavity and bind to specific olfactory receptors. When triggered, these receptors send signals through sensory neurons to the olfactory bulb, where the brain processes and interprets the smell.

to eliminate several of these issues: the Principle Odor Map (POM).

Recognizing the importance of chemistry with respect to odor, a team of researchers sought to represent odor-carrying molecules through a type of graph neural network (GNN) that can make predictions based on graph structures: the message-passing neural network (MPNN). In this representation, molecular structures are mapped to odor labels. Neural networks, such as MPNN, are computational models that mimic the processes of the brain, using data and inputs to recognize patterns and relationships.

The model consists of multiple layers, categorized into two types: message-passing

layers and fully connected layers. The penultimate (second to last) layer of this model is known as the POM. In the POM, each molecule is represented by a graph where each atom in that molecule is labeled by various key properties. Furthermore, each bond in that graphed molecule is characterized by its angle's degree, aromaticity, and whether it is part of a carbon ring. In this map, unlike molecular fingerprinting which assigns equal importance to all fragments, the GNN can optimize fragment weights; this means the GNN takes into account that certain fragments are more relevant to scent characterization than others. As a result, when testing the model, the POM could accurately represent perceptual hierarchies and distances, extend beyond the provided scents from the dataset, and adjust to discontinuities in the traditional molecule-odor mapping. After the POM layer, the final layer assigned scent labels to molecular characterizations, interpreting the POM outputs and linking odor descriptors to molecular factors to predict descriptors that an average human might assign.

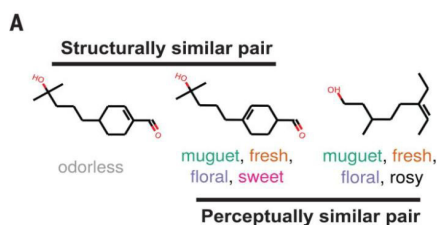


Figure 3: Odor in Structural and Perceptual Pairs. The two molecules on the left are structurally similar but have different odors: the leftmost molecule is odorless, while the middle molecule has a floral scent. In contrast, the two molecules on the right have different structures yet both produce sweet, floral aromas.

To train the model, a dataset with approximately 5,000 molecules was curated from prior databases, each with odor descriptions ranging from "creamy" to "grassy." The odor model was then trained over 150 cycles, getting its parameters fine-tuned throughout the process for optimal performance. By taking the model

through extensive training and test sets, and by employing methods to address prior discontinuities in the molecule-odor relationship, the researchers optimized the model's accuracy. As a result, the model was found to demonstrate impressive consistency and accuracy across various molecules, achieving an area under the receiver operating characteristic curve (AUROC) of 0.89, which is a metric that indicates a strong predictive power—zero representing opposite predictive power, 0.5 representing randomness, and one representing perfect predictive power.¹

Furthermore, scientists tested the model against human panels to compare its predictive power with that of individual human raters. While odor perception varies across individuals, group-average odor ratings were utilized to establish the most prominent smell perception. Then, for each molecule, the median human panelist and POM were both compared to the human mean which served as the “gold standard.” In this study, the model

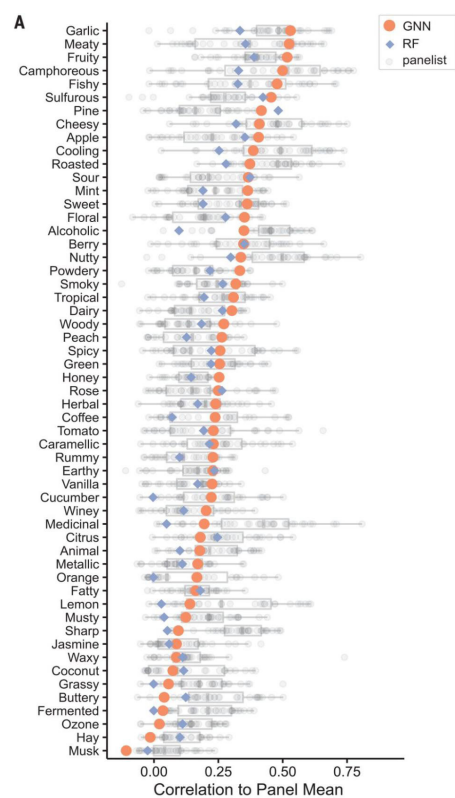


Figure 5. Comparison of Data Sets to Panel Mean. GNN refers to the Principle Odor Mapping (POM) model, RF is a previous odor-predicting model, and the panel represents individuals who described smells. The graph compares how closely GNN (orange), RF (blue), and panelists (gray) align with the panel mean, which serves as the “gold standard” for smell prediction.

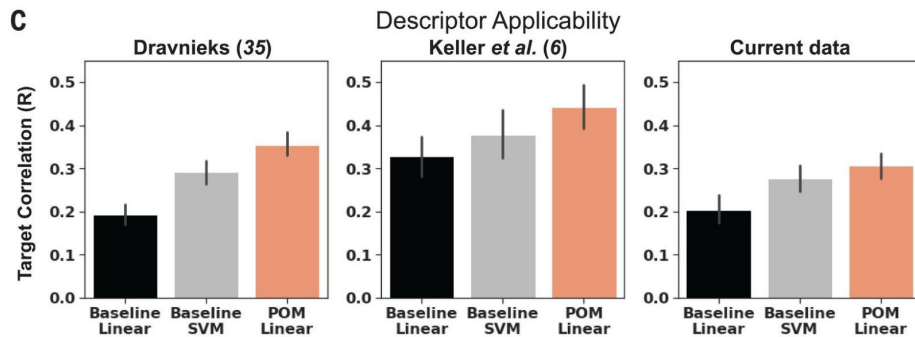


Figure 4: Odor Applicability in Three Odor-Predicting Models. A linear model using POM coordinates (shown by the orange bar) outperformed both a traditional SVM approach (gray bar) and baseline linear models (black bar) in predicting odor applicability. This was demonstrated across three different datasets: Dravnieks, Keller, and the current data.

outperformed the panelists in closeness to the mean results for 53% of the scents. Thus, the POM not only decodes scent but offers a model that surpasses human panels in smell prediction accuracy. This further established its accuracy, especially compared to previous odor maps like fingerprinting-based models, which surpassed median panelists only 41% of the time when trained on the same dataset.¹

olfactory systems can be developed, potentially enabling researchers to map individual smell perception. Branching into individual smell perception would mark a significant step forward in understanding medical conditions like Alzheimer's disease that inhibit or affect smell perception.¹¹ Such research could lead to improved understanding in the context of the neuronal-olfactory relationship, paving the

“Thus, the POM not only decodes scent but offers a model that surpasses human panels in smell prediction accuracy.”

FUTURE IMPLICATIONS OF PRINCIPLE ODOR MAPPING (POM)

With the development of POM technology, new possible avenues in neuroscience and chemistry unveil themselves. A reliable structure map allows researchers to explore the odor space at unperceivable scales; that is, smells that are too faint for the nose to pick up can be explored. Around 40 billion chemicals that have never been synthesized before can now be plotted to reveal their potential smell. Furthermore, understanding odor can have multifaceted applications. This includes benefits for fragrance and flavor companies looking to optimize certain scents for production, and mosquito repellent makers looking to improve their formula for effectiveness.¹⁰

Odor mapping also plays a significant role in neuroscientific discovery; maps of systems such as the hippocampus and auditory cortex were made possible by applying sense-mapping to neural circuitry.¹ Therefore, the relationship between olfactory receptors and neurons allows researchers to explore how we can map odor onto our neurons. By establishing this connection, new maps of

way for faster diagnostics.

Ultimately, advances in odor mapping, as displayed by the POM, allow us to further explore questions researchers and philosophers alike have debated for centuries: What is smell? In seeking answers, we see that odor impacts several aspects of our lives—from detecting diseases to appreciating perfume. As Frank Jackson famously states: “Nothing you could tell of a physical sort captures the smell of a rose.”¹² While that may still be true, it's becoming increasingly likely in the twenty-first century that the physical can, in fact, predict it.

ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude to Dr. Alexis Shusterman, Professor of Chemistry at UC Berkeley, Dr. Alex Wiltschko, CEO of Osmo, and UC Berkeley PhD candidate in Computational Biology, Kailey Ferger, for their invaluable insights, guidance, and thorough review throughout this project. Their expertise, dedication, and support have been instrumental in shaping this work, and I am deeply grateful for their expertise and encouragement.

REFERENCES

1. Lee, B. K., Mayhew, E. J., Sanchez-Lengeling, B., Wei, J. N., Qian, W. W., Little, K. A., Andres, M., Nguyen, B. B., Moloy, T., Yasonik, J., Parker, J. K., Gerkin, R. C., Mainland, J. D., & Wiltschko, A. B. (2023). A principal odor map unifies diverse tasks in olfactory perception. *Science*, 381(6661), 999–1006. <https://doi.org/10.1126/science.ade4401>
2. Team, T. H. N. (2022, April 19). *How Do Colorblindness Glasses Work?* | Sharp HealthCare. <https://www.sharp.com/health-news/color-me-awestruck-how-colorblindness-glasses-work>
3. Genva, M., Kenne Kemene, T., Deleu, M., Lins, L., & Fauconnier, M.-L. (2019). Is It Possible to Predict the Odor of a Molecule on the Basis of its Structure? *International Journal of Molecular Sciences*, 20(12), 3018. <https://doi.org/10.3390/ijms20123018>
4. February 2009, S. C. (n.d.). *If it smells—It's chemistry*. RSC Education. Retrieved October 29, 2024, from <https://edu.rsc.org/feature/if-it-smells-its-chemistry/2020168.article>
5. *Smell*. (n.d.). Retrieved October 29, 2024, from <https://www.chm.bris.ac.uk/motm/irone/smell.htm>
6. Yang, J., Cai, Y., Zhao, K., Xie, H., & Chen, X. (2022). Concepts and applications of chemical fingerprint for hit and lead screening. *Drug Discovery Today*, 27(11), 103356. <https://doi.org/10.1016/j.drudis.2022.103356>
7. Chall, S. (2024, June 9). Molecular Fingerprint. *Medium*. <https://medium.com/@santuchal/molecular-fingerprint-1693111d7b96>
8. Glezer, I., & Malnic, B. (2019a). Olfactory receptor function. In *Handbook of Clinical Neurology* (Vol. 164, pp. 67–78). Elsevier. <https://doi.org/10.1016/B978-0-444-63855-7.00005-8>
9. Sharma, A., Kumar, R., Aier, I., Semwal, R., Tyagi, P., & Varadwaj, P. (2019). Sense of Smell: Structural, Functional, Mechanistic Advancements and Challenges in Human Olfactory Research. *Current Neuropharmacology*, 17(9), 891–911. <https://doi.org/10.2174/1570159X17666181206095626>
10. News, N. (2023, September 2). AI Cracks the Code on Odor Perception. *Neuroscience News*. <https://neurosciencenews.com/odor-perception-ai-23858/>
11. Payne, M., Manera, V., Robert, P., Vandersteen, C., Beauchet, O., Galery, K., Sacco, G., Fabre, R., & Gros, A. (2022). Olfactory identification disorders due to Alzheimer's disease: A new test from France to Quebec. *PLoS One*, 17(4), e0265764. <https://doi.org/10.1371/journal.pone.0265764>
12. Jackson, F. (1982). Epiphenomenal Qualia. *The Philosophical Quarterly*, 32(127), 127. <https://doi.org/10.2307/2960077>

IMAGE REFERENCES

1. *Digitizing Smell: Using Molecular Maps to Understand Odor*. (n.d.). Retrieved November 2, 2024, from <http://research.google/blog/digitizing-smell-using-molecular-maps-to-understand-odor/>
2. *Olfaction* | BioNinja. (n.d.). Retrieved October 30, 2024, from <https://old-ib.bioninja.com.au/options/option-a-neurobiology-and/a3-perception-of-stimuli/olfaction.html>
3. Lee, B. K., Mayhew, E. J., Sanchez-Lengeling, B., Wei, J. N., Qian, W. W., Little, K. A., Andres, M., Nguyen, B. B., Moloy, T., Yasonik, J., Parker, J. K., Gerkin, R. C., Mainland, J. D., & Wiltschko, A. B. (2023). A principal odor map unifies diverse tasks in olfactory perception. *Science*, 381(6661), 999–1006. <https://doi.org/10.1126/science.ade4401>
4. Lee, B. K., Mayhew, E. J., Sanchez-Lengeling, B., Wei, J. N., Qian, W. W., Little, K. A., Andres, M., Nguyen, B. B., Moloy, T., Yasonik, J., Parker, J. K., Gerkin, R. C., Mainland, J. D., & Wiltschko, A. B. (2023). A principal odor map unifies diverse tasks in olfactory perception. *Science*, 381(6661), 999–1006. <https://doi.org/10.1126/science.ade4401>
5. Lee, B. K., Mayhew, E. J., Sanchez-Lengeling, B., Wei, J. N., Qian, W. W., Little, K. A., Andres, M., Nguyen, B. B., Moloy, T., Yasonik, J., Parker, J. K., Gerkin, R. C., Mainland, J. D., & Wiltschko, A. B. (2023). A principal odor map unifies diverse tasks in olfactory perception. *Science*, 381(6661), 999–1006. <https://doi.org/10.1126/science.ade4401>