Constructing an olfactory perceptual space and predicting percepts from molecular structure

Daniel R. Keppel and Alexei Koulakov
1Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Abstract

Given the structure of a novel molecule, there is still no one who can reliably predict what odor percept that molecule will evoke. The challenge comes both from the difficulty in quantitatively characterizing molecular structure, and the inadequacy of language to fully characterize olfactory perception. Here, we present a novel approach to both problems. First, we avoid explicit characterization of molecular structure by using a similarity score for each molecular pair, derived from comparing the molecular structures directly. We show that this method improves on conventional predictions and need not rely on preexisting knowledge of chemical descriptors. Second, we generate a perceptual space, in which a molecule’s location defines its percept. We show that from a molecule’s neighbors in this space alone, we are able to reproduce all perceptual descriptors of that molecule. We propose that predicting olfactory percept from structure can be rethought of as predicting a molecule’s location in this perceptual space. This suggestion provides a framework for understanding and predicting human smell percepts.

1 Introduction

The relationship between a molecule’s chemical structure and the human olfactory percept that molecule will evoke has long remained mysterious. This is despite many years of experiment and analysis [1]. A fundamental challenge in this endeavor is to understand variation in molecular structure [2]. Using intuition or knowledge from chemistry to categorize and relate molecules, such as with functional group counts, has proved insufficient to reproduce percepts [3]-[4].

From recent research to visualize olfactory receptor responses to an ensemble of molecules [5], we now appreciate the promiscuity and complexity of the olfactory receptor. Molecules that look similar to a researcher may elicit very different responses in a receptor, and vice versa. For this reason, modern attempts to characterize molecular structure have focused on machine learning approaches, hoping that a systematic analysis will capture what our intuition misses [6]-[10].

Any algorithm’s success, however, still hinges upon what information it is provided. Therefore, researchers have used every possible physicochemical measure imagined by chemists, collected into a software called Dragon 6 [11]. These quantitative descriptors vary from simple functional group counts to normalized eigenvalue sums of the powers of connectivity matrices. It is often unclear how a particular property might be recognized by a receptor, or if the full structure of a molecule is truly encapsulated in these properties. What is clear, however, is that predictions made using these properties leave room for improvement [6][7][10].

Similarly, machine learning methods are limited by the ability of perceptual descriptors to characterize human olfactory perception. The perception of a smell is usually presented as a group of words such as “flowery,” “sweet,” or “rotten” [12]. The relationship or higher order organization between these coarse descriptors is unknown. Then, to make any percept prediction, a separate predictor must be built for each percept. These individual percept predictors necessarily use less data and ignore information about other percepts that could be critical in determining which molecular features are selected by olfaction.
There is good reason to believe some higher order perceptual organization exists. For example, we know “flowery” and “sweet” are both pleasant, but “rotten” is not. Previous research has used “pleasantness” to aggregate data and improve statistical techniques [7]-[10]. Unfortunately, information about individual perceptual features is lost in this transformation.

We present a novel approach for characterizing the olfactory molecular input space, as well as a new framework for understanding the space of human olfactory perception. We characterize molecules by direct comparison of their structure, requiring no prior knowledge of physicochemical properties. We stitch together a perceptual space from local relationships between percepts, finding a low dimensional perceptual space while still retaining resolution of the full single-percept set. We show that our alignment based predictor makes more reliable predictions than Dragon-based methods.

2 Olfactory Perceptual Space

2.1 Constructing a Perceptual Space

We used the Flavornet odorant database to construct a human olfactory perceptual space [12]. This database contains 738 naturally existing monomolecular odorants described by 197 olfactory percepts. A single molecule is described by from one to five perceptual descriptors, but on average 1.72.

We connected all molecules of the Flavornet database into a graph. In this graph, each node is a molecule and each weighted edge between two molecules is calculated based on the overlap between those two molecules’ percepts. Using this graph, we used ISOMAP to approximate human olfactory perceptual space (Figure 1A) [13]. We found this perceptual space to be low dimensional. Using only six dimensions, we can explain ~80% of the variation in the Flavornet database (Figure 1B).

2.2 Dimensions of Perceptual Space

To understand what higher order relationships are captured by the dimensions of this olfactory perceptual space, we gave each percept a score along each axis. The score of a percept on any given axis was the mean position of molecules described by that percept. For the first five dimensions, the high ranking percepts are shown in Figure 1D-H. The first dimension seems to recover the “pleasantness” dimension that has been utilized in previous work [7]-[10]. The second appears to be related to whether something has been cooked. For other dimensions, these scores do not provide clear insight (Figure 1F-H). For that reason, we also looked at unique, high-scoring percepts in each dimension (Table 1). Interestingly, only one side of each of the first five axes provided unique descriptors. While dimension three remains unclear, unique descriptors in dimensions four and five seem to relate to anise and sweetness respectively.

2.3 Flavornet perceptual space features are robust to subsampling

After randomly subsampling the Flavornet database to sets of 300 molecules, we found that the number of dimensions had already saturated. The average variance explained using six dimensions on 10,000 subsets of 300 molecules is 85% +/- 2%. Using six dimensions with the full set, which is more than twice the number of molecules, explains 78%. This suggests that the dimensionality of perceptual space is not strongly limited by the number of data points in Flavornet.

Further, we found that the percept scores of those six dimensions in each of the subsampled datasets correlate strongly with the dimensions of the full database (Figure 2). Although the amount of variance explained by each dimension varied, the six principal dimensions of the full percept space were still present in the subsets. This indicates that the underlying perceptual space generated from each subset’s embedding might be the same. To confirm this, we randomly split the Flavornet database into half, with only two random molecules shared between each half. For 10,000 iterations,
Figure 1: Human Olfactory Perceptual Space. Two dimensional ISOMAP embedding of Flavornet odorant database (A). Each node in the graph is molecule and each edge represents a shared percept between two molecules (B). Residual variance of the ISOMAP embedding in higher dimensions (C). Word clouds of the percepts on dimensions one to five (D-H). Color indicates which side of the axis the word is on, and size indicates its valence. Word clouds were generated with wordclouds.com.

Table 1: Unique, high scoring percepts in each dimension of perceptual space

| Dimension 1  | Dimension 2       | Dimension 3 | Dimension 4 | Dimension 5       |
|--------------|-------------------|-------------|-------------|-------------------|
| sulfur       | fried             | plastic     | apple peel  | caramel           |
| burnt        | cooked meat       | hot milk    | anise       | mint              |
| garlic       | meat broth        | lemon       | cinnamon    | brown sugar       |
|              | smoke             |             |             | cotton candy      |
we calculated the distance between these two points. We found a correlation of ~.55, compared to .01 in an Erdos-Renyi random graph with the same edges and number of nodes.

### 2.4 Location in Percept Space is Sufficient to Recover Individual Percepts

Next, we tested if a molecule's position in this six dimensional perceptual space could be used to recover which of the 197 percepts it evokes. We scored each percept for a given molecule based on the percepts of neighboring molecules in perceptual space. Specifically, for each percept, we sum the distance of all molecules containing that percept from the test molecule, with exponential decay controlled by a parameter lambda (Figure 3A). Then, from these scores, we predict both the number of percepts describing a molecule and the identity of those percepts (Figure 3B).

Remarkably, using this simple method, we could predict all percepts for the majority of molecules. For more than 80% of the molecules, our predictions were off by one percept or fewer. Therefore, we propose that predicting a molecule’s olfactory percept from its structure can be rethought of as predicting that molecule’s location in this perceptual space.

![Figure 3A](image1.png)

**Figure 3A:** Percepts can be recovered from location in perceptual space. Example of ranked scores for individual percepts for a single test molecule. Percentage of molecules for which all percepts are predicted correctly (blue) and those with one or fewer (red) errors using increasing numbers of perceptual dimensions.

![Figure 3B](image2.png)

**Figure 3B:** Cumulative percent variance of subset perceptual spaces in the principal components (PC) of the full set (red). The cumulative percent variance of the full set is shown in blue.

### 3 Alignment Kernel Regression

#### 3.1 Predicting a Molecules Location in Perceptual Space

Molecular structures are not directly compatible as input for standard machine learning algorithms. In the past, researchers have used chemical descriptors, such as the 4885 Dragon descriptors, to make a machine-learning-compatible input [6][7][10]. This descriptor set is an attempt to aggregate everything chemists have been interested in for hundreds of years. None of these descriptors, however, were designed to holistically capture molecular structure, but instead some feature of it.
While numerous, these descriptors are highly redundant and are not guaranteed to capture features of structure pertinent for olfactory percept.

Therefore, we use a novel approach to holistically characterize molecular structure for machine learning approaches. To achieve this, we directly score similarity for each pair of molecules, availing ourselves of the entire structure. Using this score to define an inner product space, we create a machine learning compatible input for predictions based on molecular structure, rather than potentially subjective descriptors. Similar methods have been used in assigning protein function based on amino acid sequence [14].

### 3.2 Molecular Alignment Scoring

We computed similarity between two molecules as the maximum overlap across all orientations and rotations. This overlap is calculated to emphasize alignment of similar atom types and partial charge. To find this optimal alignment, we use simulated annealing (Figure 4A). In Figure 4B we show an embedding of the Flavornet molecules with distances calculated from our alignment score, where nearby molecules have high alignment scores. From inspection, clusters of molecules in this space indicate that our alignment algorithm is correctly finding optimal alignments (Figure 4B).

![A](image1.png) ![B](image2.png)

**Figure 4:** Molecular Alignment Results. Sample alignments with one molecule in black and the aligned molecule in green (A). Neighboring molecules in alignment space share structural features (B).

### 3.3 Support Vector Regression with Alignment Kernel

Using support vector regression (SVR), one can make predictions of a continuous variable using only the inner product between data points [15]. Here we used the alignment scores as the inner product for support vector regression. We can then avail ourselves of the full structure of the molecules for percept prediction without ever having to explicitly represent the molecular structures with quantitative descriptors.

We compared our molecular alignment kernel support vector regression method to other machine learning methods which rely on Dragon physicochemical descriptors (Figure 5). For the first comparison, we used LASSO to build linear predictors using small subsets of Dragon descriptor. For the second comparison, we used support vector regression with a radial basis function kernel of the distances between molecules’ Dragon descriptors.

We tested these three methods on predicting molecules’ location in perceptual space. Using a leave-one-out procedure, we made predictions on only untrained molecules. Our method outperformed both methods on predicting pleasantness. For other dimensions, our method performed similarly or better.

### 3.4 Relationship between Dragon Properties and Alignment Space
To understand the relationship between the Dragon properties and our alignment scores, we used our alignment kernel support vector regression method to predict the 4885 physicochemical descriptors of the Dragon software. We found that the vast majority of Dragon properties could be reliably predicted (Figure 6A). Similarly, using LASSO and the Dragon properties, we could predict the 9 dimensions of alignment space (Figure 6B). In order to predict these alignment space dimensions reliably, we needed about 200 Dragon properties per dimension. This suggests that the structural features selected by our alignment algorithm are difficult to represent in terms of chemical properties. Additionally, using the Dragon properties to reconstruct the entire alignment kernel produces a kernel with .74 R value correlation with the original alignment kernel. Percept predictions using this reconstructed kernel score lower than predictions made with the actual alignment kernel. For example, predictions using the Dragon property reconstructed alignment kernel have a correlation R of .58 with pleasantness, whereas the actual alignment kernel has a correlation R of .63. This suggests that the structural features missed by the Dragon properties are indeed relevant to olfactory perception.

4 Discussion

Here we have developed a method for predicting olfactory percepts based on molecular structure. Olfactory percepts are described by semantic profiles of molecules. At the basis of our method is representing olfactory percepts by a point in a low-dimensional semantic space. We find that this representation is capable of accounting for over 80% of dataset variance with only 6 higher order perceptual dimensions. We find that if one can determine location of a molecule in this low
dimensional perceptual space, one can reliably reconstruct 197 individual semantic descriptors. We then attempted to predict molecules’ location in this perceptual space given their molecular structure. We tested two approaches. First we used an array of physicochemical molecular properties computed using available software. Second, we developed a novel method for representing molecular structures by pairwise alignment of their 3D structures. The latter method bypasses computing physicochemical properties, and allows us to build alignment kernels by comparing molecular structures directly. Using support vector regression with the alignment kernel, we obtain predictors that outperform the physicochemical property based predictors. Thus, our novel method opens the possibility to incorporate molecular structure into a regression for molecular properties directly.

Recently, there has been an increase in interest in molecular structure based prediction of olfactory percepts. This is in part due to the DREAM challenge, which aimed to use Dragon properties to predict olfactory percepts [7]. In this challenge, it was was not possible to make individual perceptual predictions. We have shown our prediction method can produce comparable results to those published on different datasets. Using similar Dragon based methods on the same dataset, we found our alignment based method performs better. As we have shown, this is because the alignment kernel is able to capture whole-structure features that escape the Dragon properties. In addition, we make our predictions in a perceptual space which is capable of recovering individual percepts, which is lost in all previous work.

References

[1] Sell, C. (2006) Structure-odor relationships: On the unpredictability of odor. Angew. Chem. Int. Ed. 45:6254–6261.

[2] Koulakov, A.A., Koltermann, B.E., Enikolopov A.G. & Rinberg D. (2011) In search of the structure of human olfactory space. Front. Syst. Neurosci. 5:65.

[3] Laska, M. & Teubner, P. (1999) Olfactory discrimination ability for homologous series of aliphatic alcohols and aldehydes. Chem. Senses 24:263–270.

[4] Boesveldt, S. M., Olsson, J. & Lundström, J.N. (2010) Carbon chain length and the stimulus problem in olfaction. Behav. Brain Res. 215:110–113.

[5] Mainland, J.D., Li, Y.R., Zhou, T., Liu, W.L.L. & Matsunami, H. (2015) Human olfactory receptor responses to odorants. Sci. Data 2:150002

[6] Snitz, K., Yablonska, A., Weiss, T., Frumin, I., Khan, R.M. & Sobel, N. (2013) Predicting odor perceptual similarity from odor structure. PLOS Comput. Biol. 9:e1003184.

[7] Keller, A., Gerkin, R.C., Guan Y., Dhurandhar, A., Turu, G., Szalai, B., Mainland, J.D., Ihara, Y., Yu. C.W., Wolfinger, R., Vens, C., Schietgat, L., De Grave, K., Norel, R., DREAM Olfaction Prediction Consortium, Stolovitzky, G., Cecchi, G.A., Vosshall, L.B., Meyer, P. (2017) Predicting human olfactory perception from chemical features of odor molecules. Science 355(6327):820-826.

[8] Zarzo, M. (2011) Hedonic judgments of chemical compounds are correlated with molecular size. Sensors (Basel) 11:3667–3686.

[9] Kermen, F., Chakirian, A., Sezille, C., Joussain, P., Le Goff, G., Ziessel, A., Chastrette, M., Mandairon, N., Didier, A., Rouby, C. & Bensafi, M. (2011) Molecular complexity determines the number of olfactory notes and the pleasantness of smells. Sci. Rep. 1:206.

[10] Khan, R.M., Luk, C.H., Flinker, A., Aggarwal, A., Lapid, H., Haddad, R. & Sobel, N. (2007) Predicting odor pleasantness from odorant structure: Pleasantness as a reflection of the physical world. J. Neurosci. 27:10015–10023.

[11] Todeschini, R., Consonni, V., Pavan, M. (2000) Dragon Software for the Calculation of Molecular Descriptors. http://www.talete.mi.it/

[12] Acree, T. & Arn, H. (1998) Flavornet: a database of aroma compounds based on odor potency in natural products. Food Flavors: Formation, Analysis and Packaging Influences 40:27.

[13] Tenenbaum, J., de Silva, V. & Langford, J. (2000). A global geometric framework for nonlinear dimensionality reduction. Science 290(5500):2319–2323.
[14] Qiu J, Hue, M., Ben-Hur, A., Vert, J.P. & Noble, W.S. (2007) A structural alignment kernel for protein structures, *Bioinformatics* **23**:1090-1098.

[15] Cortes, C. & Vapnik, V. (1995) Support vector networks. *Machine Learning* **20**:273–297.