Literature Review for CA685 Practicum

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Abstract: Previous Structure-Odor-Relationship (SOR) studies have involved the collection and modelling of a structure-percept data set. This data set maps the physical descriptors of a molecule (e.g. molecular weight) to a single, or set, of perceptual descriptors (linguistic description of smell e.g. "fish"). Using this data as a training set, machine learning (ML) programs have been shown to achieve high predictive accuracy for the classification of novel/unseen odorant molecules. I propose to extend a machine learning program to improve its interpretability for the purposes of elucidating the underlying mechanics of Olfaction. Explainable AI is a concept that places a requirement on a ML program to describe/justify its output; In the context of the SOR problem, this approach would help in the statistical analysis of the multivariate interactions between chemical compounds and human olfactory systems by providing a generalized solution for studying any structure-dependant chemical interaction with a complex system.

KEYWORDS

Multivariate Statistical Analysis, Olfaction Processing, Structure-Odor-Relationship (SOR), Machine Learning (ML), Principle Component Analysis (PCA), Explainable AI (XAI), Interpretability, Pattern Recognition, Classification, Dimensionality Reduction, Semantic Analysis, Non-Negative Matrix Factorisation (NMF)

1 INTRODUCTION

Structure in this context refers to the shape, size and characteristics of an odorant molecule. An 'odorant' is a molecule which has been shown to produce a perception of smell when it interacts with our odorant receptors (OR); In other words, humans can smell and identify this molecule in isolation. Since the work of Axel & Buck in 1991 the prevailing theory of Olfaction has been that the structure of an odorant has significant bearing on the type of smell we perceive – referred to since in the literature as the shape theory of olfaction [1]. There are some inconsistencies which allude to shape not being the only relevant factor, but still perhaps the most influential on our final perception; Although two molecules may have similar shapes, they may have different sets of weak intermolecular forces available to them, and thus they may activate different combinations of ORs [2].

We currently understand how light is encoded in the human brain; The perceptual space for human colour vision has three dimensions and every colour sensation can be fully characterized by three numbers, namely the intensity of the primaries that match it. We now know that colour-vision is based on three kinds of cone photoreceptors in the retina that differ in their sensitivity to the wavelength spectrum of light [3]. This understanding enables us to encode this as digital information and package it as images and videos in the form of 1's and 0's; No such understanding exists for olfactory information. Understanding how our brains processes olfaction information is extremely difficult due to the number and variation of odorants, the number of receptor neurons, the nature by which they react with odorant molecules, the non-linear mappings of receptors to glomeruli, and the consequent flow of information to higher areas of the brain such as the amygdala and the hippocampus [4]. I propose to put a black box around the neural processing component of the problem and apply a general approach to classifying odorants by their chemical structure based on labelled training data. Using this method, I intend to analyse the structure-odor mapping of odorants from a relevant combined dataset.

As olfaction processing is difficult to study biologically I propose instead studying the output of a configurable & explainable AI which has been trained to identify odorants in the same manner as a

human. Highly predictive models have been trained on such data - most recently an organisation held a competition to see which team could produce the most accurate model; They subsequently wrote up their findings and released the underlying perceptual data needed to perform this analysis [5].

A highly predictive model could be configured to consider and explain certain subsets of the total set of physical descriptors, which can be vast e.g. the most recent 2017 experiment considered 4,884 chemical descriptors. It has been shown that the multivariate dimensionality of this problem can be reduced down to principle components while retaining most of the salient information of the data set [6]. Components can be extracted and multiple experiments have repeatedly shown pleasantness or the hedonistic measurement to be the primary or secondary principle component [7] [8]. Odor categories have been extracted using similar methods of dimensionality reduction followed by subsequent projection and clustering [6]. A machine learning program, which can accurately predict unseen molecules could tell us how it arrives at its conclusion. I believe that extracting rules and reconfiguring the input variables to be explained/considered would be a very useful iterative process for the elucidation of the underlying olfactory system mapping – consider a fictitious example output such as:

"Ethanol: Alcohol => Ox > 2, MW <156

This molecule smells like Alcohol because it has more than 2 oxygens AND a molecular weight of less than 156."

This type of information can often be inferred from the weights and values of the resulting trained model but this usually requires a familiarity with the data, the algorithm and machine learning principles i.e. someone with a computer science background. Understanding the meaning of these connections and their significance to the underlying process at hand requires knowledge of the full olfaction processing chain, all other processes involved, and a firm understanding of biology and chemistry i.e. someone with a scientific background. I intend to use my own domain knowledge of this problem in conjunction with the analytic techniques taught in this course to attempt to add to the current body of knowledge relating to olfaction processing.

My contribution to this problem is to compare statistical methods for reducing the dimensionality of this problem and use these results as a guideline for interpreting our machine learning models. It is necessary to use a comparable dataset to those used in previous analytic efforts; As such data collection, combination and validation will be of utmost importance and will occupy a large portion of my efforts.

In Section 2, I will outline the current academic knowledge in the main research areas involved, namely: Olfaction Processing & Multivariate Statistical Analysis. In Section 3, I will outline my initial Research Plan which is only representative of my current thinking and not a rigid project schedule. Finally, in Section 4, I will discuss the conclusions reached so far in my investigation including what such a system can and cannot accomplish.

2 LITERATURE REVIEW

To address this problem there were two main areas of literature to be investigated. First, to understand the problem at hand an investigation into the full chain of olfaction processing was necessary to identify key areas for original contribution. My approach to solving the problem was inspired by a combination of the methods of two separate experimental studies conducted with entirely separate datasets [5] [6]. Multivariate statistical analysis techniques were used in these papers, including machine learning models, to classify unseen molecules by their smell with high receiver operating characteristic and prediction scores. This type of multivariate analysis and modelling makes up the other major area of my background literature review.

2.1 Olfaction Processing

Axel & Buck discovered that ORs in mammals are a large subfamily of G-protein-coupled receptors (GPCRs) [1]. These types of receptors are seven-transmembrane receptors which have been studied and shown to activate through ligand/receptor binding. This interaction involves a lock and key mechanism where the shape of the molecule determines the receptor it binds with. Most odorant molecules also undergo protein-ligand binding in the nose for the purpose of becoming water soluble before entering the mucus [4] where they can bind with our odorant receptors. These bindings are only but the start to a long, convoluted chain of neural processing where eventually a perception is formed; perhaps only after context, acquired knowledge, and other senses are considered [9]. Currently the literature has no answer for where and how our final conscious perception of smell is derived.

Although the ligand/receptor binding seems to explain and give a basis for the mapping of this relationship there are some edge cases and inconsistencies that cannot seemingly be explained by shape alone. Some molecules are structurally similar and have different percept [10]. Some odorant molecules are structurally very different but have a similar perceived scent. These quandaries sparked debate for decades and the matter is still unsettled. Recent work from the biological side has shifted to gene expression experiments, new imaging techniques for in-vivo experimentation [11], gene sequencing and in-silica modelling of olfactory systems [12].

2.2 Multivariate Statistical Analysis

Many Structure-Odor studies have attempted to reduce the dimensionality of this problem through various methods. One study attempted to identify categories of smell using non-negative matrix factorization [9]. The author of this paper mention concerns that constraining perceptual judgments to a fixed and possibly limited lexicon (i.e. the descriptors) may obscure the true complexity of odor space. Subsequent studies have performed semantic analysis on the perceptual descriptors to ensure that categories of smell are not just formed based on the semantic relatedness of the perceptual descriptors themselves [6].

The identification of latent variables and principle components has been used to identify classes of smells as shown here. In multiple studies the primary component extracted is usually representative of a scale of pleasantness [8] – with one explanation asserting that early olfactory processing only resolves odor

quality to a degree sufficient to rank relative pleasantness, with further parsing of this percept into discrete categories occurring through mechanisms involving learning and context [9].

3 RESEARCH PLAN

3.1 Constructing Dataset

First, we need to collect the perceptual data; I have already scraped the molecule-percept mapping for 750 molecules from a single source [13]. I have also obtained a rigorous dataset containing molecule-percept results for 55 subjects across almost 400 molecules [5]. I intend to combine and consolidate this data with other similar data sources to form a robust dataset for my modelling purposes. Second, we need to combine the physical data (set of physical molecule descriptors) with our combined percept dataset. At present I have 507 mappings of perceptual to physical data. After some initial statistical analysis, we may decide to augment this dataset with other data sources.

3.2 Statistical Analysis & Dataset Validation

I intend to apply techniques and methods employed previously by other authors to test the validity, completeness and robustness of my collected dataset before it shall be used for the training of a machine learning models. Certain measurements, metrics, and features of the multivariate data can be used to test and compare the results of my machine learning program. PCA, non-negative matrix factorisation, stochastic modelling, analysis of the co-variance and variance matrices could all be useful in this regard. Perceptual data can be analysed semantically using a co-occurrence network via analysis of its structure and, in particular, its difference from a random network [6].

3.3 Data Pre-Processing

Quite a substantial portion of data processing will have been done by the time we reach this stage. Data has already been processed and transformed in the constructing of a final combined dataset, but also some processing was necessary to make a co-occurrence network. This pre-processing phase is focussed on preparing our data for machine learning. We will need to consolidate the perceptual data (one data source has many descriptors (100+) while another has only 19. We will also need to normalise the physical data to a range between 0 – 1.

3.4 Machine Learning

For training some molecules will be kept from the ML program to be used as testing data after training has taken place. The training and testing sets will be mutually exclusive samples of the overall combined dataset. Random-Forrest decision trees, linear models and perhaps types of neural networks can be trained on this dataset and later tested. While training our models it may be useful to perform k-fold cross validation to ensure our models don't over-fit to a certain subset of the data.

We can compare our results with those of previous experiments to ensure we have a model that is worth interpreting. A prediction rate of ~80% for unseen molecules should be sufficient for our purposes and

while it may not capture the full nuance of the underlying interaction it should give us an indication of which molecular features to study in further detail. It is important that we can sufficiently train our model to predict human response otherwise there is not much point in analysing the output as it will not correlate to the mechanisms of human olfactory processing.

3.5 Integrate Interpretability to Model

LIME is the library that I intend to use to extend a ML model so that it obeys the requirements of Explainable AI. LIME stands for Local Interpretable Model-agnostic Explanations and is written in python and released as open source. It integrates with ski-kit learn models seamlessly and I intend to achieve my goal of interpretability using these tools.

3.6 Hypothesis Testing

As I have previously studied the domain of olfaction processing I will attempt to do some analysis on the output of my ML program and use this information to inform our previous multi-variate statistical analysis. Hopefully I may be able to extract some reasoning for the machine's classifications that has some implications for formulating a viable theory of Olfaction. I would ideally like to identify some of the molecular features which influence the primary principle components of our dataset. PC1, which appears to correlate to pleasantness, has previously been linked to molecular size and subsequent studies have affirmed these results. Secondary principle components are less understood in the literature and this is where I believe our explainable machine learning program will be of most use.

4 CONCLUSIONS

This system can produce meaningful predictions but importantly it does not account for relative quantities of the molecules or the combinatorial effects of multiple odorant compounds in the air both of which have an effect on the final perception of smell in real world scenarios. This system can study a large or small subset of the total physical descriptors available for each molecule as both approaches have seen success. It has been shown that odorants densely sample a two-dimensional curved surface embedded in the multidimensional sensory space. This surface can account for more than half of the variance of the psychophysical data. This paper shows also that only 12 percent of experimental variance cannot be explained by curved surfaces of substantially small dimensionality (i.e. <10) [14].

Other structure-dependant interactions of molecules with complicated systems (biological/ mechanical/ computer systems) could be elucidated using an Explainable AI approach. For instance, if we trained our Explainable AI on a training set of mappings of 'structure-drug effects' we could use our model to predict the effects of new, unseen (or yet to be developed) drugs on the human body. This type of modelling could drive the creation of new fragrances, drugs and other compounds which interact with complex systems including but not limited to the human body.

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