Chemical sensing with an olfaction analogue:
high-dimensional, bio-inspired sensing and computation

NSF Convergence Accelerator Virtual Workshop

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Final Report

1 THE WORKSHOP

1.1 Organization

The workshop was organized by a cross-disciplinary team of scientists and engineers from academic, industrial and non-profit organizations in the United States and Europe. It covered a range of expertise, including olfaction (perception and reception), neuroscience, chemical sensors, instrumentation, and machine learning. The team was split into two sub-committees, a Steering Committee that would provide oversight, and an Organizing Committee that would work in close collaboration with Know Innovation. The list of committee members, their affiliation and expertise is shown in **Table 1**.

Table 1. Composition of the Organizing and Steering Committees

Name	Affiliation	Expertise
Thomas Cleland*	Cornell University	Computational neuroscience
James Covington	Warwick University	Chemical sensors/instrumentation
Cristina Davis*	University of California at Davis	Chemical sensors (MEMS)
Ricardo Gutierrez-Osuna*[1]	Texas A&M University	Machine learning
Christopher Hanson	Aromyx Corp.	Machine olfaction
William Harris*	Aromyx Corp.	Biochemistry and biophysics
Santiago Marco	Universitat de Barcelona	Chemometrics
Joel Mainland	Monell Chemical Senses Center	Structure-odor relationships
Troy Nagle	North Carolina State University	Biomedical sensors
Krishna Persaud	University of Manchester	Machine olfaction
Radislav Potyrailo*	General Electric (GE) Research	Sensors and sensing applications
Nancy Rawson*	Monell Chemical Senses Center	Chemosensory reception
Susan Schiffman*	North Carolina State University	Chemosensory perception

**Organizing Committee, [1]Workshop Chair*

1.2 Agenda

The agenda and activities for the workshop were designed by the Organizing Committee in partnership with Know Innovation between July and October 2022. Activities included tutorial lectures by experts in the field, short presentations of potential applications of the technology ("provocations"), group discussions, and plenary sessions during which the most relevant ideas were identified collectively. The workshop took place online over four days: (1) Microlab, Friday, October 7, 11am - 1pm ET; (2) Session 1, Tuesday, October 11, 11am - 3pm ET; (3) Session 2, Thursday, October 13, 11am - 3pm ET; and (4) Session 3, Friday, October 14, 11am - 3pm ET.

1.2.1 Microlab

The purpose of the Microlab was to explain the Convergence Accelerator process and the desired outcome of the workshop, ensure that the audience had a shared understanding of the field, and capture some initial Big Questions from the audience. The agenda included a keynote and five tutorials:

- Keynote: Alex Wiltschko (osmo.ai): *Giving Computers a Sense of Smell*
- Tutorials
  - Introduction to the Olfactory System, Thomas A. Cleland (Cornell U., US)
  - Human Olfactory Perception, Joel Mainland (Monell Chemical Senses Center, US)
  - Electronic Nose Technology, Krishna Persaud (U. Manchester, UK)
  - Signal Processing and Machine Learning in Chemical Sensing, Santiago Marco (U. Barcelona, Spain)
  - Bioinspired Approaches to Chemosensory Data Analysis, Thomas Cleland (Cornell U., US)

1.2.2 Session 1

The purpose of Session 1 was to identify the ambitious questions that should be explored during the workshop. To facilitate this process, the session included a number of "provocation" talks that introduced the needs of various application areas:

- Bridging the Gap, James Covington (U. Warwick, UK)
- Health applications, Cristina Davis (UC Davis, US)
- Quality Control applications, Sandrine Isz (Alpha MOS, France)
- Defense applications, Heather Meeks (DTRA, US)
- Environmental applications, Saverio De Vito (ENEA, Italy)
- Olfactory Perception applications, Joel Mainland (Monell Chemical Senses Center, US)
- Legal/Ethical issues, Dimitrios Ioannidis (Roach, Ioannidis & Megaloudis, LLC., US)

At two points during this session, participants were assigned into breakout groups, in which they discussed their views and perspectives on the challenges of chemical sensing. Outcomes from these discussions were captured in a virtual whiteboard, on which participants were able to create "Post-It" notes with big questions to be addressed in later sessions.

1.2.3 Session 2

The purpose of Session 2 was to develop ideas that would address the questions raised in the previous two sessions. For this purpose, questions/ideas were organized into nine different topics: (1) sensor dimensionality, (2) machine learning, (3) bio-inspired models, (4) sensors based on olfactory receptors, (5) other sensor technologies, (6) development of databases and standards, and (7) ethical and legal considerations. Participants were allowed to select a breakout group of their choice, with the suggestion that they select the topic to which they could contribute the most (rather than a topic they were interested in but knew less about). Two breakout sessions took place; one in the morning, and another in the afternoon. At the end of the first breakout sessions, a speaker for each of the topics reported findings to the entire audience.

1.2.4 Session 3

The initial purpose of Session 3 was to describe the societal applications of the ideas developed in Session 2. Due to the large number of ideas that were generated in Session 2, however, we devoted part of this session to prioritizing ideas based on their readiness for acceleration. For this purpose, participants were asked to vote for those ideas in the virtual whiteboard that they considered to be the most suitable. The organizing committee then clustered those ideas into themes, and participants were again asked to vote on those themes.

1.3 Participants

The workshop attracted participants from a variety of disciplines and the four stakeholder sectors (industrial, academic, non-profits, and government organization). An initial list of 146 participants was generated by the organizing committee, with help from NSF program managers who provided additional contacts from government and military organizations. Each person in the list was contacted individually by one of the members of the committee. Participants were invited to submit an online registration form, which asked for their area of expertise, sector, availability on the dates of the workshop as well as their needs for accommodations. Each of the committee members voted on each of the registrations received, the votes were combined, and a subset of the participants were officially invited a few weeks prior to the workshop.

A total of 78 participants attended the workshop, following the distributions shown in **Table 2**. When participants submitted the initial application, they were asked to describe their area of specialization and how they expected to contribute to (and benefit from) the workshop. Results of the analysis of this text data are summarized in the word cloud shown in **Figure 1**. From these results, we estimate that 70% of participants came from engineering fields, and 30% from science.

Table 2. Distribution of workshop attendees

Expertise*	%	Sector	%	Sex	%	Career level	%
Applications		Academia		Male		Middle	
Chemosensors	54	Industry	23	Female	27	Late	41
Instrumentation		Government		Other		Early	
Data analysis	46	Non-profit	6				
Olfactory reception							
Olfactory perception	23						
Computational neuroscience							

**Participants rated their expertise for each area in a 1-5 scale. Ratings >3 were considered as expertise*

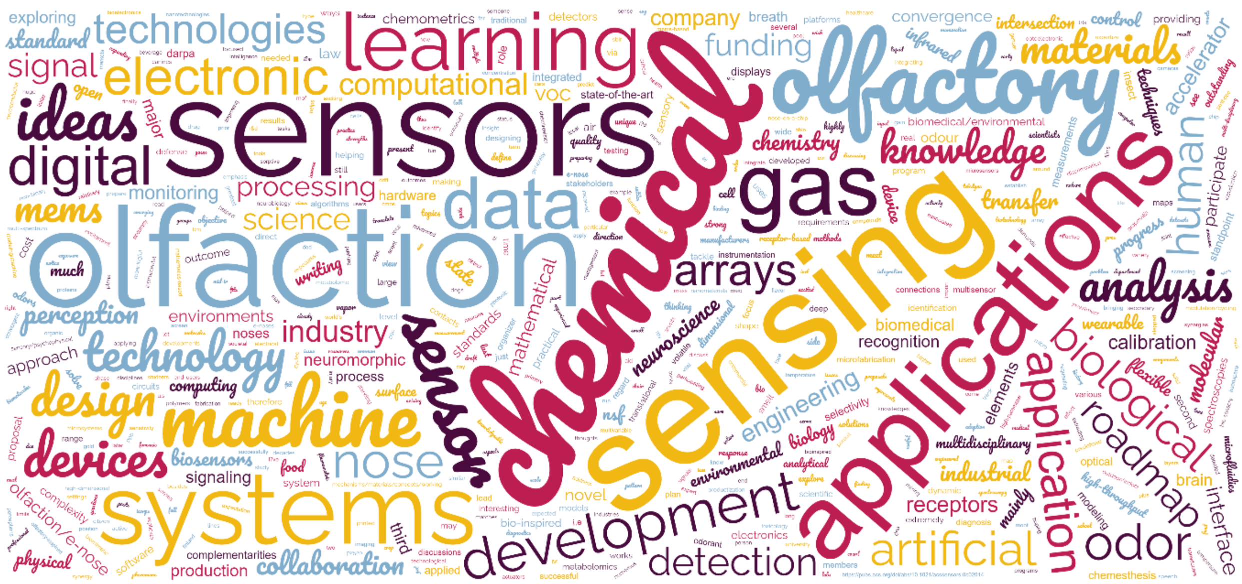

Figure 1. Word cloud of participants' self-reported expertise

2 BIG QUESTIONS AND EMERGING THEMES

Over the course of the four-day workshop, participants contributed over 100 "post-it" notes to the Big Questions wall. Qualitative analysis and manual coding of these questions revealed seven general themes (potential solutions, olfaction, machine learning, urgent needs, sensor limitations, dimensionality, and ethics/legal issues) and twenty cross-cutting sub-themes. The distributions of questions per theme and subtheme are shown in Error! Reference source not found..

The most dominant sub-theme was the development of mappings from chemical sensors (and/or olfactory receptors) to perceptual odor characteristics as critical to furthering our understanding of biological olfaction and the development of machine-olfaction instruments. Participants also highlighted the importance of prioritizing applications, starting with "easy" ones (e.g., outlier detection, controlled environments) to gain momentum, before tackling the more challenging ones (e.g., odor mixtures, field studies). The topic of seeking bio-inspiration to develop new sensors and computational techniques was also highlighted early in the process, as was the need for standards and benchmarks. Highlights of each subthemes are shown in **Table 3.**

Table 3. Description of the themes and sub-themes identified within the Big Questions

Theme (outer bar)	Theme (inner bar)	Sub-theme
	Potential solutions	**New sensing technologies**. Sensors with multiple transduction principles, sharing information between sensors in a network to improve accuracy, using ultra-violet energy to facilitate desorption.
	Potential solutions	**Adaptation techniques**. Make instruments/models adaptive, so they can identify if they are operating outside of the training set, regenerate, adapt and tune to the environmental conditions and the types of analytes present.
	Potential solutions	**Sample preparation**. Separation techniques (e.g., gas chromatography) should be standard in machine olfaction, as well as amplification techniques (e.g., pre-concentration). Active sniffing techniques mimicking the biological olfactory system should be explored.
Olfaction	Potential solutions	**Bio-inspired techniques**. Mimicking capabilities of the biological olfactory system, such as active sniffing, or the ability to deal with changes in humidity, temperature or backgrounds, and receptor turnover.
Olfaction	Potential solutions	**Olfactory receptor (OR) neurons/sensors**. Using OR-based sensors, or synthetic sensors based on the 3D structure of OR binding sites. Are OR-based sensors the only option if the goal is to predict olfactory perception from sensor data?
Olfaction		**Odor perception**. Olfaction differs from vision and hearing: Individual/genetic differences; smell is subjective; culture, context and experience shape the perception of pleasantness of various odors.
Olfaction	Machine learning	**Sensor-odor mappings.** How can we develop "maps" (mathematical functions) between sensor responses and olfactory percepts or outcome variables, such as disease states. Analogies were made to vision and hearing, where the mappings are well known (e.g., RGB space, Fourier analysis.)
Olfaction	Machine learning	**Structure-odor relationships (SOR)**. Closely connected to the development of sensor-odor mappings is the problem of predicting odor perception from the molecular structure of odorant molecules. Can these SORs lead to the development of new sensors?
	Machine learning	**Calibration transfer**. There is a need for techniques that allow ML models trained on data from one instrument to be adapted to other instruments, or use pre-trained models, as opposed to training each new model from scratch. The ability to used pre-trained models is a key component of the success of deep learning models in vision and speech.
	Machine learning	**Big data techniques**. "Cracking" machine and biological olfaction will require massive datasets, as has been the case in other sensing applications. For example, massive datasets are needed to account for variations in field conditions.
Urgent needs	Machine learning	**Dataset generation**. There is a need to collect and publicly release datasets to advance research in machine olfaction. This includes datasets containing instrumental and human psychophysiological responses to odors, and sensitivity matrices (OR responses to different odorants), collected using validated, standardized methods.
Urgent needs		**Standards/benchmarks**. There is a need to develop standards for odors and sensors, as well as benchmarks so that different instruments and sensor arrays can be compared objectively against each other.
Urgent needs		**Prioritizing applications**. Before tacking the larger problem of predicting odor perception from sensor data, there is a need to identify "easy" applications, such as those with limited variability in the analytes that make up the odor.
	Sensor limitations	**Mixture recognition**. Most natural odors are complex mixtures, and arrays based on single transduction principles cannot reliable analyze mixtures with more than two components, regardless of the number of sensors, sorptive interface or transducer.
	Sensor limitations	**Drift/poisoning/backgrounds**. Current gas/chemical sensors suffer from drift, aging and poisoning, and interferences from backgrounds (other odors, humidity, etc.)
	Sensor limitations	**Sensitivity/selectivity**. Current gas/chemical sensors have low sensitivity, broad selectivity, and poor dynamic range.
Dimensionality	Sensor limitations	**Intrinsic dimensionality**. Current gas/chemical sensors have low diversity because they rely mostly on physisorption. As a result, sensor responses in an array are highly correlated, to where a large sensor array is intrinsically low-dimensional.
Dimensionality		**Dimensionality of olfaction**. On one hand, olfactory reception relies on a large number of ORs (~ 400). On the other hand, sensory analysis suggests that the true dimensionality of olfaction is very low (primarily pleasantness). However, is this "low-dimensionality" the result of language/vocabulary limitations to describing odor perceptions.
Dimensionality		**High-dimensional arrays**. How can we generate sensor arrays that are intrinsically high-dimensional? Suggested techniques included using bio-recognition elements or separation techniques.
		Ethical/legal issues. There are potential issues concerning misuse/abuse of odor measurements (e.g., to identify individuals or predict their disease state). These issues need to be addressed in advance.

For instance, should odor identity information be classified similarly to genetic information?

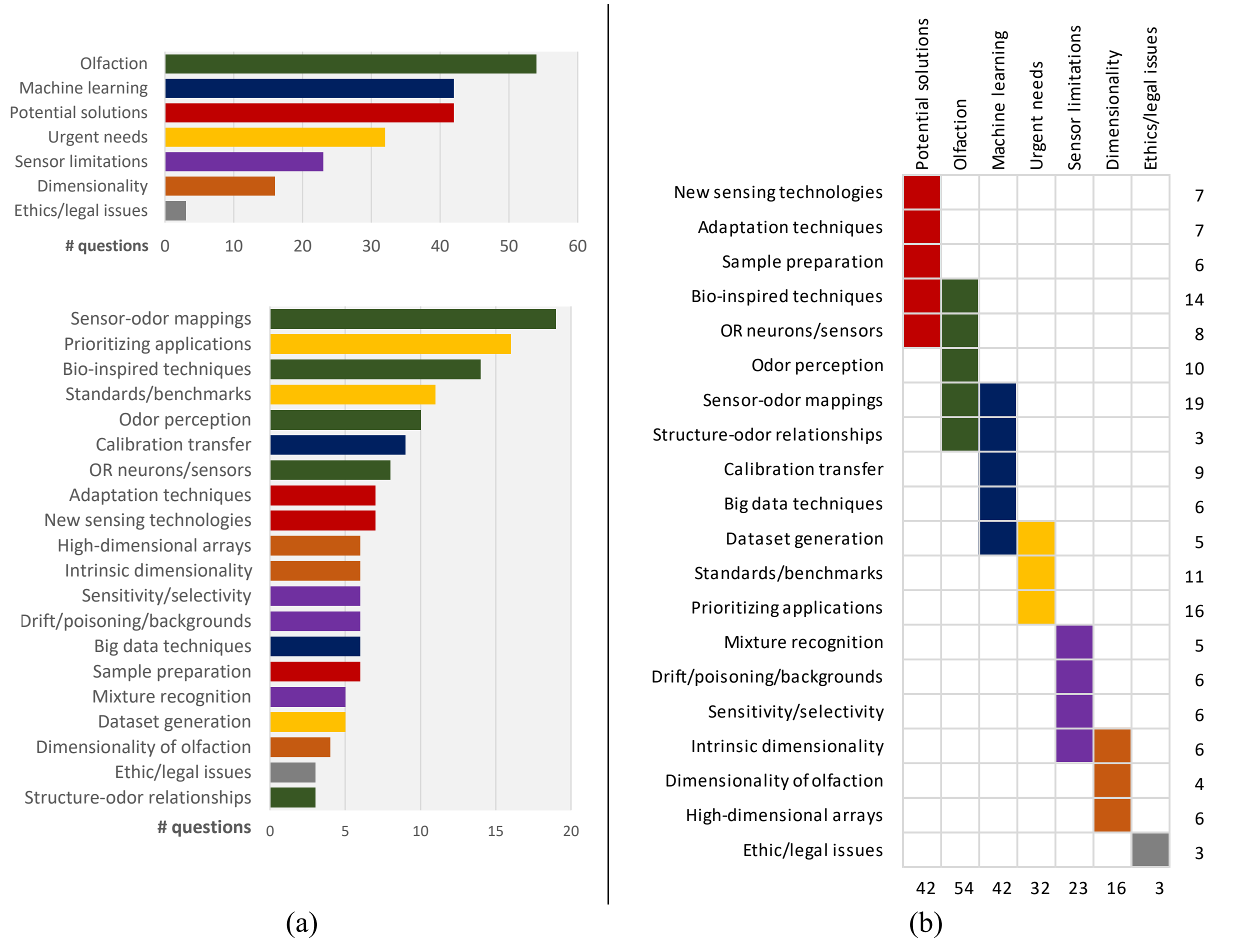

Figure 2. (a) Distribution of questions across themes (top) and sub-themes (bottom). (b) Relationships between themes and sub-themes.

3 BREAKOUT DISCUSSIONS

To further explore these questions and themes, participants were divided into 9 breakout groups, with participants being able to join any of the groups, while the organizing committee monitored progress and nudged the discussions as needed. Three of the breakout groups (analytical approaches[1], ethical/legal issues, 10-year plan) were unattended. A summary of the discussions in the remaining six breakout groups is provided in the following subsections.

3.1 Dimensionality

This group was asked to discuss issues pertaining to the dimensionality of the olfactory system, and whether that was an essential element to mimic in an artificial counterpart. This discussion was somewhat polarized between two camps. The first camp argued that, despite the high number of olfactory receptors in the biological system (~400 in humans), the perceptual dimensionality of olfaction was actually very low, of about 6 dimensions, with the first dimension being "pleasantness," as Susan Schiffman had originally proposed in the 1970s. The second camp argued that the olfactory system was truly high dimensional

[1] As it turns out, the use of analytical techniques emerged naturally in the breakout group on "new sensing technologies," and was its primary focus.

because of evolutionary pressure, and that the acuity of the system increased with the number of dimensions (i.e., olfactory receptors). To add more nuance, some participants argued that the perceptual dimensionality of olfaction was low because of limitations in human language –describing an odor accurately is difficult and naïve "noses" often rely on the use of analogies ("*this smells like…, reminds me of…*"). This might explain why, according to one of the participants, people tend to rate odorants as similar if they have similar pleasantness.

Regardless of whether olfaction is low- or high-dimensional (a surprisingly contentious subject), there was agreement in the group that first we should mimic the olfactory system of simpler animals. As an example, it was convincingly argued that mimicking the olfactory system of the fly (~50 receptor types) would be a major scientific/engineering achievement facilitating the development of artificial olfactory systems.

3.2 Machine learning

This group focused on aspects pertaining to data acquisition and analytics. Several promising ideas emerged from this group:

- Generate massive amounts of annotated olfactory/sensor data. Some participants suggested that the current status of machine olfaction is constrained by the volume of training data, and that a 10-100-fold increase in data might "crack" the problem. Such data-collection campaign would require the use of participatory science with low-cost devices of intrinsically high dimensionality, with the goal of collecting 1 million olfactory scenes, opportunistic sensing in massive geographically distributed sensor nodes or mobile technologies, or the use of data perturbation (based on solid principles) for the purposes of data augmentation.
- Improve calibration techniques. Rather than rely on traditional calibration techniques (i.e., factorial designs), adaptive approaches should be explored, as in the sub-field of interactive machine learning, where an ML algorithm and a human work together to annotate unlabeled data, or using active-sensing strategies, where the ML algorithm controls a gas delivery system to generate various gas mixtures on the fly or introduce interferences (e.g., moisture), as needed to reduce uncertainty in the model.
- Adopt transfer learning techniques. One of the major limitations of current sensing arrays is the need to build a new calibration model for each instrument. However, progress in computer vision and speech processing over the past decade would not have been possible if it were not for the ability to use pretrained models built to solve a similar problem (e.g., the *VGG16* model trained on ImageNet, or speaker-independent acoustic models for speech recognition, such as the *wav2vec* model trained on Librispeech). Similar ML techniques may be used to transfer models developed on high-fidelity data (e.g., measuring human breath with analytical instruments) to low-fidelity devices such as point-of-care consumer devices (e.g., breath monitors for exercise and metabolic analysis).
- Use computational materials science for sensor design. Machine learning techniques could also be used to design sensing elements, based on molecular models and simulations to predict the response of sensing elements. ML techniques have been used for decades to optimize sensor arrays (e.g., feature subset selection), but this work is limited by the lack of diversity in chemical sensors.

3.3 Olfactory signal processing

Biologically-inspired design principles have been used in machine olfaction since at least 1982, when Persaud and Dodd constructed an "electronic nose" based on the mammalian olfactory system. The central principle of this innovative approach was to use an array of broadly-tuned chemosensors (rather than a single specialized sensor), with analyte selectivity arising from the pattern of sensor responses to each odorant across the array. This group focused the discussion on post-sampling processing and analysis mechanisms incorporating biomimetic principles that would contribute to the success of artificial chemosensory systems.

A number of ideas were proposed, such as feedback-dependent, representation-specific adaptation mechanisms to sort out multiple knowns, top-down adjustments per task (e.g., add priors, alter contrast), or algorithms based on timing of sensory information processing. Goals would include, for example, biasing towards Type I vs Type II errors, "what is present?" versus "is this specific odorant present?", adaptation to "noisiness" of environments, on multiple timescales.

Advances in this area, however, would require datasets from large-scale sensor arrays that incorporate hard problems, such as mixtures and unpredictable backgrounds. Collecting such data is limited in part by current sensing technology, which typically relies on limited numbers of sensors. So, the overarching question was: What kinds of sensors can be used to replicate the biological tactic of increasing the number of receptors, and what types of sensors can support the biomimetic use of statistics to improve systemwide sensitivity? The latter problem, in particular, would require detailed characterization of sensor properties (binding/signaling properties, timescales, molecular receptive ranges) to optimize postprocessing and help with sensor selection for particular goals.

3.4 Olfactory-based instruments

This group discussed the development and use of sensors and instruments based on olfactory receptors, arguably the most promising approach to mimic olfaction.

The current state of the art of using mammalian ORs as the biological basis of assay systems has been in use for about a decade and has resulted in approximately 100 functional ORs from the human repertoire of approximately 400 ORs. From these studies about 1000 OR-odorant interactions have been published. While this progress is admirable, understanding the combinatorial nature of olfaction requires orders of magnitude more data. However, this assay-based system is not amenable to the development of a ubiquitous sensor or instrument. These assay methods require a sterile, 37^{o} C, 5% CO_2 cell culture environment which is much too restrictive for wide, easy use.

The greatest impediment to progress is due to inadequate expression of OR proteins. Olfactory receptors are natively expressed in neuronal cells of the nasal epithelium and these cells are very difficult to grow in culture in sufficient quantities to be of much practical use. Currently, ORs are typically expressed in other cell types such as HEK or CHO cells that have been engineered to express exogeneous proteins using transient transfection methods. These methods still don't always result in adequate expression for downstream uses and, in many cases, don't result in any measurable expression. Progress in this area requires funding to develop robust immortalized cell lines that express as many human ORs as possible and in adequate amounts for subsequent work. In addition, funding for using protein engineering techniques to increase OR protein stability would also be of great value since removal of the ORs from the cellular environment for use in *in vitro* instrumentation would require significantly greater stability than they current exhibit. In addition, being able to express ORs that contain single nucleotide polymorphisms (SNPs) that are unique to specific social, geographic, or genetic groups would allow the customization of sensor arrays for each of these groups. This would allow better understanding of how olfaction varies in different groups and better understand how these differences influence olfaction on societal or cultural biases.

Obtaining an atomic level resolution structure of one or more ORs to be able to study the structure-function relationships of the OR-odorant selectivity, binding, and signal transduction mechanisms is key to understanding OR function. These structures could be obtained by X-ray crystallography, electron diffraction, single particle reconstruction methods as well as *in silico* methods such as using data provided by the AlphaFold program and database. Knowledge of the OR structure at an atomic level could also provide the architecture for synthetic sensors that would not require amino acids as the building blocks of the sensor.

Developing techniques that take functional ORs and their signal transduction pathways out of live cells and into other forms such as nano-discs, nano-bodies, styrene malic acid anhydride lipid particles (SMALPs), carbon nanotubes, or other materials that permit coupling ORs to electrical circuits.

3.5 New sensor technologies

This group was the most heavily attended, and the one that produced the most detailed set of ideas and plans. The overarching goal was "*sensing anything, anywhere, anytime*," and achieve second-order analytical instrumentation in a ubiquitous form factor. This goal would lead to a major change in how society understands the benefits of exploiting olfaction. It would require massive convergence, including materials science, packaging, instrumentation, system integration, application engineering, and regulatory and certification authorities.

Though we intended for participants to discuss this topic in a separate breakout group, the development of micro-analytical systems was a major topic in this group. Three techniques in particular emerged as the most promising to pursue, alone or preferably in combination (hyphenated systems).

- Mid-infrared (IR) spectroscopy to measure characteristic (functional group) and fingerprint (molecular) absorption. IR sensors are reliable and inexpensive, and IR sources are improving (quantum cascade lasers, nonlinear optical materials). The limitation of interaction pathlength can be addressed through the use of convoluted waveguides, and nano-photonic circuits (e.g., micro-ring resonators) can achieve high selectivity.
- Micro gas chromatography (μ-GC) is a proven concept that is ready for acceleration. Wearable μ-GCs have been developed in the past 4 years, and further refinement and miniaturization appears feasible and worthwhile to pursue.
- Sample pre-concentration using multifunctional materials and surface enhancement techniques.

Other analytical techniques were considered, but the discussion appeared to focus on their limitations:

- Ion mobility spectroscopy (IMS). This technology is available but is high-cost, has poor selectivity and requires an ionization source and clean gases.
- Surface-enhanced Raman spectroscopy (SERS). Portable Raman spectrometers have progressed significantly, but are still high-cost and the stability of the substrates can be problematic.

The development of new chemical sensors was also discussed but, with one exception (see next paragraph), the main focus was on the plethora of limitations (poor sensitivity, specificity, stability, cross-selectivity to interferences, etc.), with some participants voicing strong concerns about continuing to promote single-transducer arrays with reversible interfaces and single outputs: "*These will never work. We know this. Let's move on.*"

The exception was the use of colorimetric sensors based on analyte chemical reactivity. These sensors are inexpensive (paper-based), easy to produce (ink-jet printing technology), disposable (thus, no drift issues), robust to interference (e.g., humidity), can achieve higher diversity and dimensionality than conventional sensing technologies (e.g., metal-oxide sensors), and are prime for acceleration.

3.6 Benchmarks/standards

This group discussed past and current efforts in developing standards for olfaction, and the need for standards and benchmarks to be able to objectively evaluate different technologies against each other and against the "gold standard": human perception.

Several types of benchmarks were discussed, including limits of detection and sensitivity, and intensity and discrimination/quality tasks. Developing these benchmarks would require identification of standard sets of individual odors and mixtures, and standard methods of odor delivery. These benchmarks and standards could then be used to train the instruments (or potentially animals) for various applications. Given the variety of applications and the size of the "odor space", a one-size-fits-all approach would not be appropriate or necessary. As an example, the barriers for medical diagnosis differ from those in food and environmental applications.

The group also discussed ongoing standardization efforts for odor measurements. One example is the IEEE P2520 series of standards for testing methods and conformance processes to ensure that machine olfaction devices and systems achieve reliable and reproducible results that are comparable to human odor panels. Another example is the CEN/TC264/WG41 effort by Technical Committee 264 'Air Quality" of the Committee Européen de Normalisation (CEN) to establish a preliminary work item "*Air quality – Continuous instrumental odorant monitoring in air to assess risks of odour (nuisance) and safety*" which was entrusted to working group WG41 "Electronic sensors for odorant monitoring" for a period of 6 years starting May 2015. After 20 meetings over 6 years, however, WG41 came to the end of the time assigned without presenting a final draft standard for voting to TC 264. Other efforts have been successful, though, such as the European Standard for Olfactometry EN13725 (initially published in 2003), which has since been developed by CEN/TC264 Working Group 2 (WG2) into a new standard (March 2022).

A concrete plan with short and long-term milestones was developed in this breakout group:

- 6 months: Calibration set design
    - Agree on a set of 20 single molecules that can be used in gas canisters as standard odors.
    - Criteria: molecule stability, span perceptual and chemical spaces.
    - Define methods for
        - Collecting perceptual data for these 20 molecules (profiling, similarity, etc.)
        - Delivering odorant, including lab conditions, humidity, etc.
- 1.5 years: Calibration set POC
    - Establish manufacturing and distribution and demonstrate success.
    - Establish a set of 20 single-molecule odors with known concentrations to be used as standards in the field.
    - Ask journals to require specific tests before publication of e-nose performance metrics.
- 3 year: Run Grand Challenge
    - Develop benchmarking tests: limit of detection, limit of recognition, triangle tests for discrimination, etc.
    - Define performance metrics that are independent of sensor type
- 5 year: Evolve the standard to generate standardized datasets
    - This would enable comparison and data transfer across instruments
    - Develop methods for using standard odors in standardized mixture discrimination or figure/ground separation tests
- 10 year: Develop single pantone of odors

Finally, several milestones were proposed to compare instrumental against human performance:

- Discrimination benchmarks: matching human level of discrimination for single molecules and odor mixtures in the lab and in field conditions
- Multidimensional scaling benchmarks: compare the similarities between odors in sensor outputs against their similarities in perceptual space.
- Instrument benchmark: calibration procedures to demonstrate consistent performance over time

4 PRIORITIES FOR ACCELERATION

After two full days of idea generation, clustering and refinement in breakout groups, the last day of the workshop was entirely devoted to selecting those individual technologies and/or applications that, with funding from the NSF Convergence Accelerator program, would be more likely to yield societal impact in three years.

4.1 Sensing technologies

The process started with participants being allowed to suggest individual sensing technologies as "post-it" notes a virtual whiteboard. The Organizing Committee would then review these to eliminate duplicates, and submit them back to participants for voting through the Kistorm interface. This cycle was repeated several times, with participants being allowed to vote in different ways (number of votes, assigning multiple votes to a single idea) following guidance by Know Innovation. After removing duplicates, 66 technology ideas were proposed. Six technologies emerged atop:

- Micro-GC + detectors
- OR-based arrays
- Heterogeneous & multi-parameter sensors
- Mid-IR and photonics sensors
- New sensing materials
- Disposable colorimetric arrays

In a closed session, the organizing committee discussed these sensing technology ideas. Two of them were discarded: (1) new sensing materials, as it was not fully developed and therefore not ready for acceleration, and (2) heterogeneous & multi-parameter sensors, since they relied on traditional transduction techniques that have been investigated for decades. The four remaining sensing technologies ideas were combined with two additional themes that had emerged as priorities in the workshop (but were not sensing technologies per-se): bio-inspired models, and datasets.

4.2 Applications per technology

In a final round of idea generation and voting, the six themes selected from the previous session were turned into separate virtual whiteboards: (1) micro-GC + detectors, (2) biology-based sensor arrays, (3) mid-infrared micro spectrometers, (4) public datasets, (5) disposable colorimetric arrays, and (6) neuromorphic analysis methods. Participants were then asked to generate potential application areas for each of these themes, which the Organizing Committee reviewed to eliminate duplicates, and submitted back to participants for voting. The emerging application areas for each of the whiteboards are shown in Table 4. We found significant agreement on priority application areas across multiple disciplines, such as food quality/safety/waste applications, disease diagnosis and monitoring, environmental applications, and chemical threat detection, which suggest potential federal agencies with which to partner for joint funding.

Table 4. Application areas per technology

Micro-GC + detector	Food quality control and spoilage Large-scale data collection for disease diagnosis In-field detection of chemical threats Medical diagnosis (breath, urine, wounds) Real-time environmental odor monitoring
Biology-based sensor arrays	Odor-based disease diagnosis Food quality assurance and spoilage detection Malodor detection Agricultural pest management Chemical threat detection
Mid-IR micro spectrometers	Food safety and quality Fast screening of bacterial biofilms Waste disposal odors Compliance of greenhouse gas emissions

	Air quality testing
Public datasets	Calibration datasets for deep learning Dataset of ORN-ligand affinity Large-scale geographical datasets of odor pollution Citizen-science datasets with colorimetric devices Datasets with analytical references as ground truth
Disposable colorimetric arrays	Food waste/safety detection Smart labels for traceability of food products Analysis of bodily fluids (sweat, saliva, tears, breath) Aids for patients with anosmia (e.g., COVID related) Disposable arrays for citizen science
Neuromorphic analysis methods	Models for drift and interference compensation Odor plume detection (drones) Real-time online learning Architectural priors for high-dim datasets Comparison against statistical ML techniques

5 DISCUSSION

The objective of this workshop was to identify emerging odor and chemical sensing technologies that are ready for acceleration. This objective was ambitious, as myriad chemical sensing technologies are available, from low-cost chemical sensors to high-fidelity analytical instruments. For this reason, the workshop emphasized sensing techniques that would yield high-dimensional data and highly-diverse responses, as those appeared to be the key characteristics to borrow from the biological olfactory system. Underlying this focus was the concern that most of the chemical sensor arrays (electronic noses) that have been studied over the past 40 years offer limited performance *because* they lack both types of characteristics.

5.1 Smelling or sensing?

An additional challenge for the workshop was to consider two types of applications: those that require prediction of human perceptual responses (let's call it machine olfaction), and those that do not (chemical sensing). The main challenge in machine olfaction comes down to developing "mappings" between sensor responses and odor percepts. This could be viewed as a computational problem, except there such mappings are not possible unless the input (sensor) space and the output (perceptual) space overlap. Let us leave aside the fact that odor perception (e.g., pleasantness) is influenced by culture, context and experience, and therefore difficult to predict from sensor responses alone. The main "technical" issue in machine olfaction is to find sensors that measure physico-chemical characteristics of molecules that somehow (sort of?) relate to those captured by olfactory receptors. This would suggest focusing exclusively on bio-mimetic approaches (e.g., use OR-based sensors, neuromorphic models). A strong case can be made for using actual olfactory receptors (ORs) as the basis for many sensors, since we know they work exquisitely well. Millions of years of evolution have resulted in sensors that have an extremely wide dynamic range of sensitivity and tuned to molecules that are important to human survival.

At the same time, most of the success in other machine perception problems (visual and auditory) have been largely bio-agnostic. Thus, it seems unwise to disregard bio-agnostic approaches to machine olfaction (e.g., based on analytical instruments and chemometrics/statistical machine learning), and for two reasons. First, bio-mimetic approaches require an understanding of olfactory reception and perception that we currently do not have; this was clear from multiple discussions. As an example, there is no universal agreement about whether olfaction is high-dimensional; it appears to be so at the reception level, but not at the perception level, perhaps because of language? A second reason to continue to explore bio-agnostic approaches is that the majority of chemical sensing applications do not require correlation with human perception. These applications could still benefit from bio-mimetic sensors (e.g., disease detection based on odors), but bio-agnostic approaches (e.g., molecular recognition from mass or optical spectra) also seem suitable.

5.2 We need data (!)

A strong message echoed throughout the workshop: the need for data. At the risk of oversimplification, the success of deep-learning in vision and speech applications can be attributed to three factors: access to compute power, advances in machine-learning algorithms, and access to massive amounts of data. While the fields of machine olfaction and chemical sensing can already benefit from the availability of computational power and fast machine-learning algorithms, it is the lack of large datasets that prevents the exponential progress seen in other domains. As one of the workshop participants eloquently wrote: "*Some problems appear to be uncrackable without massive amounts of training data (e.g. human-level image segmentation and classification), where massive is >>1M data points. There does not appear to be any way around this*."

What kinds of data are needed? At the basic-science level, there is a need to build a "sensitivity matrix" that relates olfactory receptor responses to odorants and their physico-chemical properties. This matrix would significantly improve our understanding of the olfactory code and inform the development of new sensors, whether natural (OR-based) or synthetic sensors. Data is also needed on the 3D structure of mammalian and/or insect olfactory receptors to learn about odorant-receptor binding site architecture and how it influences odorant molecule-receptor interactions. This information could be used to develop inorganic sensors.

Data is also needed at the engineering/application side. At present, developing a new instrument requires training the calibration model from scratch. Publicly available large datasets containing the response of instruments based on different sensing technologies (along with analytical ground-truth) to multiple gases/odorants and their mixtures would enable the development of "pre-trained" models that can be later tuned to specific applications (as is commonly done in vision and speech), and transfer-learning techniques that allow a calibration model from one instrument to be adapted to another instrument using only limited adaptation data. For example, in the domain of speech synthesis, so-called "zero-shot" machine learning techniques have been available for several years that allow a generic synthesizer to be adapted to a new speaker using only a few seconds their speech. Building these datasets (whether olfactory or instrumental) will also require the development of standards and benchmarks.

6 FINAL RECOMMENDATIONS

Clearly, "cracking" olfaction will require an effort that goes beyond the 2-3 year timeframe of the NSF Convergence Accelerator program. But several technologies and approaches were identified in the workshop that ready for acceleration. These are:

- **Olfactory receptor-based sensors**. Assay systems that use mammalian ORs have been available for over a decade, with approximately 100 functional ORs from the human repertoire of approximately 400 OR having been extracted. However, this assay-based system is not amenable to the development of a ubiquitous sensor or instrument. We recommend that funding be devoted to developing techniques that take functional ORs and their signal transduction pathways out of live cells and into other forms such as nano-discs, nano-bodies, styrene malic acid anhydride lipid particles (SMALPs), carbon nanotubes, or other materials that permit coupling ORs to electrical circuits.
- **Micro-analytical systems**. For many chemical sensing applications, odor perception is not necessary. For these applications, analytical techniques are the gold standard, but these instruments are expensive, hard to operate and not portable. We recommend that funding be devoted to miniaturization efforts of three technologies: chromatographic separation, pre-concentration, and infrared spectroscopy. Micro gas chromatographs can enable rapid and sensitive analysis of

complex mixtures. Integrated pre-concentrators can increase device sensitivity by up two orders of magnitude. Finally, integrated mid-IR spectrometers (e.g., MEMS, nano-photonic) can provide information that can be related to ground truth (functional groups, molecular fingerprints).

- **Colorimetric sensor arrays**. Optical arrays based on colorimetric techniques (dyes, nano-porous pigments) have been available for two decades. These arrays are inexpensive (paper-based), easy to produce (ink-jet printing technology) and instrument (web/mobile cameras). Compared to traditional chemical sensors, these arrays don't suffer from drift issues (the are disposable), are robust to interference (e.g., humidity), and can achieve high sensitivity, specificity, as well as diversity and dimensionality. It is also uniquely suited to enable massive data collection through citizen science. We recommend that funding be devoted to manufacturing and distribution of this technology at scale, to make it broadly available to the olfaction and chemical sensing community and to the public. Funding initiatives could be coordinated with other federal agencies, such as NIH to enable rapid and point-of-care monitoring of biomarkers in non-invasive bodily fluids (e.g., sweat, saliva, breath), as well as defense agencies to enable threat detection and exposure (dosimetry). As an example, the DARPA Biological Technologies Office (BTO) has expressed interest in olfaction for chemical sensing of environmental toxicants and chemical warfare agents and is in conversations with the NSF to explore they can further engage.
- **Data-collection methodologies**. Exponential progress in olfaction-related applications is not possible without access to massive amounts of data. There does not appear to be any way around this. Large datasets are needed to "crack" the olfactory code (OR-ligand matrices), develop pre-trained calibration models that can be fine-tuned for specific applications and instruments, and transfer learning techniques that allow models developed on high-fidelity instruments to be transferred to low-fidelity devices. We recommend that funding be devoted to developing methodologies to enable collection of massive datasets through engagement with the general public. This includes providing access to low-cost sensors (see above), defining standards and benchmarks, developing mobile- and cloud-based platforms for data collection, upload, annotation and management, and developing public engagement strategies (e.g., gamification, micro-incentives, community initiatives).