Integrated Analytical Systems

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Computational Methods for Sensor Material Selection
Series Preface

In my career I’ve found that “thinking outside the box” works better if I know what’s “inside the box.”

Dave Grusin, composer and jazz musician

Different people think in different time frames: scientists think in decades, engineers think in years, and investors think in quarters.

Stan Williams, Director of Quantum Science Research, Hewlett Packard Laboratories

Everything can be made smaller, never mind physics;
Everything can be made more efficient, never mind thermodynamics;
Everything will be more expensive, never mind common sense.

Tomas Hirschfeld, pioneer of industrial spectroscopy

Integrated Analytical Systems

Series Editor: Dr. Radislav A. Potyrailo, GE Global Research, Niskayuna, NY

The book series Integrated Analytical Systems offers the most recent advances in all key aspects of development and applications of modern instrumentation for chemical and biological analysis. The key development aspects include (i) innovations in sample introduction through micro- and nanofluidic designs, (ii) new types and methods of fabrication of physical transducers and ion detectors, (iii) materials for sensors that became available due to the breakthroughs in biology, combinatorial materials science, and nanotechnology, and (iv) innovative data processing and mining methodologies that provide dramatically reduced rates of false alarms.

A multidisciplinary effort is required to design and build instruments with previously unavailable capabilities for demanding new applications. Instruments with more sensitivity are required today to analyze ultra-trace levels of environmental pollutants, pathogens in water, and low vapor pressure energetic materials in air. Sensor systems with faster response times are desired to monitor transient
in vivo events and bedside patients. More selective instruments are sought to analyze specific proteins in vitro and analyze ambient urban or battlefield air. For these and many other applications, new analytical instrumentation is urgently needed. This book series is intended to be a primary source on both fundamental and practical information of where analytical instrumentation technologies are now and where they are headed in the future.

Looking back over peer-reviewed technical articles from several decades ago, one notices that the overwhelming majority of publications on chemical analysis has been related to chemical and biological sensors and has originated from Departments of Chemistry in universities and Divisions of Life Sciences of governmental laboratories. Since then, the number of disciplines has dramatically increased because of the ever-expanding needs for miniaturization (e.g., for in vivo cell analysis, embedding into soldier uniforms), lower power consumption (e.g., harvested power), and the ability to operate in complex environments (e.g., whole blood, industrial water, or battlefield air) for more selective, sensitive, and rapid determination of chemical and biological species. Compact analytical systems that have a sensor as one of the system components are becoming more important than individual sensors. Thus, in addition to traditional sensor approaches, a variety of new themes have been introduced to achieve an attractive goal of analyzing chemical and biological species on the micro- and nanoscale.
Sensor arrays for chemical vapor sensing, frequently known as electronic noses, have grown in popularity over the last two decades. The relative simplicity of design and small size, leading to ease of use, make electronic noses very appealing for applications such as process control monitoring, environmental monitoring and medical diagnosis. Since the introduction of the concept of an electronic nose in the 1980s, starting with work on arrays of metal-oxide vapor sensors, there has been a significant increase in research into sensing materials and the use of arrays. Today, there are several journal articles a month discussing evaluation and selection of sensing materials as well as associated work such as transduction methods, measurement circuitry, data analysis, and sampling methods.

As approaches to designing and using sensing arrays have become more mature, and as applications of the technology have grown, it has become increasingly important to tailor the sensor materials in an array to the selected application. From the early days of research and demonstration, work has moved to focused applications, which require attention to selection of types of sensing materials as well as to selection of specific sensors within a type. Empirically derived models and first-principles computer simulations are playing an increasingly important role in our understanding of the interactions between sensing material and analytes, where the sensing materials may be polymers, metal oxides, self-assembled monolayers (SAMs), or biologically based materials.

In general, selection of sensors for a sensing array is a three-step process. First, a transduction method and a class of sensing material appropriate to that method are selected. Second, specific sensing materials within the selected class are evaluated as candidates for inclusion in the array. Third the sensing materials which will make up the array are selected. We have focused this volume on the second and third steps, selecting and evaluating specific sensing materials in order to select the elements in an array. This volume covers methods which have been used successfully in the construction of full sensing devices as well as emerging methods which show promise, with a particular emphasis on computational and statistical approaches to materials and array evaluation and selection.
We begin this volume with an introductory chapter focused on experimental methods for evaluation and development of chemical sensors and sensor arrays. Chapter 1 begins with a discussion of the mammalian model of olfaction and how it has inspired the array-based approach to chemical sensing. It goes on to establish the issues that must be considered in developing sensing materials and sensing arrays, such as sensor feature space, sensor orthogonality, geometries, and transducers. Chapter 1 also discusses the issues underlying the design of experiments and sensor evaluation, and finally, the use of experimental data in arriving at an endpoint in the evaluation process. This introductory chapter lays the groundwork for all the approaches discussed in this volume; that is, it establishes an approach to planning what to do once we have determined which sensors to test.

These computational approaches to sensor and array evaluation and selections are divided into three parts (1) First-Principles Methods of Materials Evaluation and Selection, (2) Multivariate and Statistical Methods of Materials Evaluation and Selection, and (3) Methods for Array Selection and Optimization.

Part One, Chaps. 2–6, discusses First-Principles Methods of Materials Evaluation and Selection. The general goal of developing a model of sensor performance based on first principles is not to replace existing experimental methods or knowledge-based methods of sensing material selection, but to complement these by providing quantitative approaches which can be used to prioritize the selection of new materials. First-principles design methods are being developed which can be used to plan rational modifications in the structure and function of a sensing material. This design methodology allows us to develop a theoretical understanding of the sensing material and analyte system and to predict their interactions. The predictions can then be put to an experimental test.

First-principles calculations include quantum mechanical, molecular dynamic, and structural approaches. These methods have focused primarily on developing fundamental electronic and atomic level descriptions of materials to provide insight into chemical interactions of materials with target analyte(s). Quantum mechanical techniques are discussed in Chaps. 2, 3, and 6. Molecular dynamics or atomistic techniques and statistical mechanical and multiscale approaches are discussed in Chaps. 3, 4, and 6. Chapters 3 and 6 describe a method which relies on both quantum mechanical and molecular dynamics approaches for screening sensors for their response to specific analytes. De novo structure-based design of receptors for selective chemical sensors as described in Chap. 5 applies fundamental information about structure and bonding as a basis to search for host architectures that are highly organized to form a complex with a guest molecule.

Chapter 2 uses application examples to illustrate the use of Density Functional Theory and electronic transport modeling based on nonequilibrium Green’s Function in modeling carbon nanotube-based nano-electromechanical sensors and the gas-sensing properties of carbon nanotubes and metal-oxide nanowires.

Chapters 3 and 6 show that a combination of quantum mechanics with first-principles molecular dynamics can afford a great deal of information that is useful in designing and selecting materials for specific analytes.
Chapter 4 investigates the predictions of sensor responses using Grand Canonical Monte Carlo simulations. This method is used to predict the degree of sorption of analyte into polymers by calculating partition coefficients of alcohols, aromatics, ketones, esters, alkanes, and perfumes for typical gas chromatography films and compares predicted values with experimental values.

Chapter 5 presents an overview of a computer program, HostDesigner, that has been created to allow the de novo structure-based design of receptors that are structurally organized for complexation of small ionic and molecular guests. The methodology applies fundamental information about structure and bonding as a basis to search for host architectures that are highly organized for guest complexation.

Part Two, Chaps. 7–9, discusses Statistical and Multivariate Methods for Materials Evaluation. In this section, the work of various laboratories that have taken a combined theoretical and experimental approach to problems in vapor sensing and identification is discussed. Statistical and multivariate methods include semiempirical approaches, such as combinatorial approaches, Quantitative Structural Activity Relationships and Quantitative Structure Property Relationships, and calculation of solvation energy relationships. Many of these approaches have been developed to elucidate mechanistic aspects of sensing material activity. These approaches can, however, also be used to guide selection of materials. As array-based chemical sensing is still a relatively young field, many of the computational methods for sensor selection are still in a developmental phase.

Chapter 7 covers the experimental technique of high throughput (HT) screening, which applies combinatorial strategies to screen large sets (tens and hundreds) of sensing materials. This topic is discussed in greater detail in a companion volume in this series.

Chapter 8 discusses a statistical and multivariate method for correlating sensor response with molecular descriptors using a combination of Quantitative Structural Activity Relationships and Quantitative Structure Property Relationships. This approach develops statistically validated models of sensor response based on experimentally developed data.

Chapter 9 shows how an understanding of solubility interactions informs the selection of polymers to obtain chemical diversity in sensor arrays and obtain the maximum amount of chemical information, using principle components analysis to analyze array data. This chapter also discusses new chemometric methods which have been developed to extract chemical information from array responses in terms of solvation parameters serving as descriptors of the detected vapor.

Part Three, Chaps. 10–12, Designing Sensing Arrays, considers the computational and experimental methods that have been used together to select the components of an array designed to detect a particular analyte set.

Statistical methods based on experimental data have been used successfully to optimize an array; statistical methods may also be used with data simulated in the computational approaches discussed in Part I or with sensing data analyzed by methods discussed in Part II. The process of selecting the components of an array considers both type and identity of sensing materials, the optimum number of
sensors to be used in an array for a particular set of analytes, and how the responses of sensors will be treated in data analysis.

Chapter 10 presents a generic approach for designing sensor arrays for a given chemical sensing task. This chapter describes a correlation-based metric used to assess the analytical information obtained from chemiresistors as a function of operating temperatures and material composition combined with a statistical dimensionality-reduction algorithm to visualize the multivariate sensor response obtained from sensor arrays.

Chapter 11 discusses an iterative approach to statistical evaluation of experimental responses of candidate materials for a sensing array by developing parameters which are used to evaluate sensor performance. These three parameters are used to compute a measure of sensor suitability for inclusion in an array designed to detect a given set of analytes.

Chapter 12 discusses a hybrid sensor array, a multimodal system that incorporates several sensing elements and thus produces data that are multivariate in nature and may be significantly increased in complexity compared with data provided by single-sensor-type systems. In this chapter, various techniques for data preprocessing, feature extraction, feature selection, and modeling of sensor data are introduced and illustrated with data fusion approaches that have been implemented in applications involving data from hybrid arrays.

Finally, we close with some thoughts on future directions for work in developing computational approaches to sensor evaluation. There are several computational approaches, which have been used to design and evaluate select materials for chemical sensors. Computational methods also include use of statistical and computational approaches to characterize measured and experimentally observed analyte-sensing material interactions and sensing material responses to the presence of analyte. With the increasing use of sensing arrays, computational approaches offer complementary information to that developed through experimental approaches.
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Part I

First Principles Methods For Materials Evaluation
Chapter 1
Introduction: Experimental Methods in Chemical Sensor and Sensor Array Evaluation and Development

Joseph R. Stetter

Abstract Sensors are devices, sensor arrays are collections of sensors, and it is through experimentation and computation that we obtain the knowledge we need to make useful analytical measurements. Gas and liquid chemical sensor arrays provide a new multidimensional analytical technique not unlike Gas Chromatography, Liquid chromatography, or GC/MS [gas chromatography mass spectrometry]. Exciting possibilities for advanced analytical measurements are emerging with the development and use of chemical sensor arrays. The multidisciplinary nature of sensor development and the diversity of the types of sensors, analytes, and applications provide a rich venue for research and development as well as the complex issues that lead to lively debates. Progress in developing arrays for analytical purposes is coming from applying new knowledge about biosystems that use sensor arrays, advanced predictive chemical computational capabilities, and significant increases in experimental materials and methods. The protocols for the experimental understanding of sensor arrays provides the foundation for present strategies and future models that will enable realization of the contributions of sensor arrays to analytical measurement science and technology.

Acronyms and Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Analyte</td>
<td>Substance or chemical constituent whose identity or quantity is determined by conducting the analytical procedure</td>
</tr>
<tr>
<td>ANN</td>
<td>Artificial neural network</td>
</tr>
<tr>
<td>Ar</td>
<td>Argon</td>
</tr>
<tr>
<td>atm</td>
<td>Atmosphere (pressure)</td>
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e-mail: jrstetter@kwjengineering.com
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Term</th>
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<tbody>
<tr>
<td>$A_s$</td>
<td>Analytical sensitivity</td>
</tr>
<tr>
<td>BAW</td>
<td>Bulk acoustic wave</td>
</tr>
<tr>
<td>C</td>
<td>Capacitance</td>
</tr>
<tr>
<td>CGS</td>
<td>Combustible gas sensor</td>
</tr>
<tr>
<td>Chembio</td>
<td>Chemical–biological</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical interface</td>
</tr>
<tr>
<td>Cl₂</td>
<td>Molecular chlorine</td>
</tr>
<tr>
<td>cm³</td>
<td>Cubic centimeter</td>
</tr>
<tr>
<td>CO</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPS-100</td>
<td>Chemical Parameter Spectrometer – 100</td>
</tr>
<tr>
<td>E</td>
<td>Electromotive Force or Voltage</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>H₂</td>
<td>Hydrogen</td>
</tr>
<tr>
<td>HCN</td>
<td>Hydrogen cyanide</td>
</tr>
<tr>
<td>H₂S</td>
<td>Hydrogen sulfide</td>
</tr>
<tr>
<td>I</td>
<td>Current – charge per unit time</td>
</tr>
<tr>
<td>IMCS2</td>
<td>International Meeting on Chemical Sensors 2</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>$K$ or $k$</td>
<td>Sensitivity – signal per unit concentration</td>
</tr>
<tr>
<td>KNN or $k$-NN</td>
<td>$k$-nearest neighbor</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit of detection</td>
</tr>
<tr>
<td>M</td>
<td>Mass</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MOSES II</td>
<td>Laboratory electronic nose by Lennertz</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>mV</td>
<td>Millivolt</td>
</tr>
<tr>
<td>nA</td>
<td>Nanoampere</td>
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<tr>
<td>N₂</td>
<td>Nitrogen</td>
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<tr>
<td>Ne</td>
<td>Neon</td>
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<tr>
<td>NH₃</td>
<td>Ammonia</td>
</tr>
<tr>
<td>NO₂</td>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
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<tr>
<td>OR</td>
<td>Olfactory Receptor – a G-receptor protein used in olfaction</td>
</tr>
<tr>
<td>pA</td>
<td>Picoampere</td>
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<tr>
<td>ppb</td>
<td>Parts per billion – by volume</td>
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<tr>
<td>ppq</td>
<td>Parts per quadrillion</td>
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<tr>
<td>ppt</td>
<td>Parts per trillion</td>
</tr>
<tr>
<td>R</td>
<td>Resistance – ohms</td>
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<tr>
<td>$S$</td>
<td>Sensor signal</td>
</tr>
<tr>
<td>SAW</td>
<td>Surface acoustic wave</td>
</tr>
<tr>
<td>SPME</td>
<td>Solid-phase microextraction</td>
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<tr>
<td>SSTUF</td>
<td>Shared sensor testing user facility</td>
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1.1 Introduction

At the turn of the nineteenth century, Lord Kelvin (Sir William Thompson) said, "To measure is to know," and "If you can not measure it, you can not improve it." These thoughts are timeless. For those of us developing sensors and sensor arrays and applying them to new and increasingly difficult and complex analytical problems, these quotations exemplify the two reasons we make experimental measurements with sensors and arrays. First, measurements allow us to understand the sensor principles of operation and the mechanisms of their response to analytes so that we can develop new sensors and improve the old ones. Second, experimental measurements allow us to calibrate sensors, evaluate their performance, use them effectively, and rely on them for quantitative results even in life-threatening and critical health-monitoring situations. Sensors, arrays, and the measurements they enable, help us work and improve our quality of life.

Every sensor array consists of individual sensor elements, either discreet or integrated, and all the analytical information we obtain comes from the sensors’ signals. Therefore, all the information that characterizes either the concentration and/or the molecular identity of the analyte, a situation, or a simple or complex chemical environment is created by the experiment that generates the sensor data. Sensory experiments thus demand stringent control and the specific experimental setup and procedure are intricately tied to the data quality and hence the precision, accuracy, and validity of the outcome or analysis.

The first law of analytical measurement is: “a measurement is useless without a report of the error.” That is, every experimental result should be reported with a quantitative statement of the uncertainty. To be fair, uncertainty boundaries are frequently implied in experimental reports, but for the most precise work or for accurate comparisons of sensors, specific error analysis is critical.

Constructing a workable sensor array and applying it with confidence are extremely difficult if the sensors that make up the array have not been fully characterized and understood. Not characterizing the sensors and yet building an array is akin to an architect’s building a bridge without knowing the strength of his materials. It is thus crucial that a sensor’s performance under probable use conditions be known or anticipated. Understanding the signal(s) from the sensing system, especially their error sources, drift characteristics, and failure modes is essential for accurately interpreting the signals over short- and long-time intervals.
In developing a focused analytical method, therefore, three issues need to be addressed (1) the invention and development of new sensors, (2) the invention and development of new sensor arrays, and (3) the application of the arrays. These three issues are best addressed from three perspectives, each of which can constitute a separate project (or a separate phase of a larger project). Integrating sensor technology, a sensor array, and an analytical method, constitutes both a challenging and a complex systems problem.

What data are needed about sensors and arrays for a given problem? How should the data be gathered and used experimentally in each case? Where does the most critical information come from, and how is it created in the first place? These questions are the topic of this chapter. In this regard, the “Edisonian” or experimental approach to R&D will complement theory vis-à-vis chemical sensors. Experiments are required to obtain the chemical sensor array data to improve on theory, create models, and to guide the design of the experiments themselves.

1.2 Chemical Sensing: Inspiration from Biomimetics and Biology

Natural sensing processes provide biology-inspired and biomimetic examples of the use of sensor arrays and, of course, computation in chemical sensor array research. In mammals, gas sensor arrays in the nose, liquid sensor arrays in the tongue, light sensors in the eye, and mechanical sensors in the ear involve chemical transduction processes that are part of a larger, intricate sensory system. Artificial sensors and arrays, today often called electronic noses (e-noses), e-tongues, etc., mimic biological organs, often relying on the actual biological molecules and the biological processes of sensing. Understanding the mammalian sense of smell (Fig. 1.1) provides a useful backdrop for chemical sensor array research – research that is increasingly amalgamating knowledge and techniques derived from physics, math, chemistry, biology, and engineering.

Our understanding of mammalian olfaction is expanding rapidly. Recent publications [1–3] illustrate this merging of the realms of biological and physical sciences and indicate that creating the bionic or at least the cybernetic nose is not very far away off. Additional research using authentic olfactory receptors or other bio-derived molecules as elements in sensors for target analytes is also being conducted [4, 5]. Such work parallels the extensive R&D in immunosensors, where biological molecules or fragments thereof are being used as molecular recognition elements [6, 7].

1.2.1 Understanding the Mammalian Model

Inspiration from biology has led to experimental models for sensing structures, processes, and components, including those for gas sensor arrays. Studies of the
characteristics of mammalian olfaction have provided background information for experimental aspects of sensing with arrays. For example, the human nose contains as many as 350 types of olfactory receptors (ORs), and dog, rat, and mouse noses contain more than a 1,000 ORs. In this regard, throughout this chapter, we often use the dog olfaction model in exemplifying various sensor aspects. Thousands of each type of receptor are spatially dispersed over the olfactory epithelium in an intermixed, albeit not random, fashion. However, signals from each type of OR all meet at the same location in the olfactory bulb and from there, a “movie” of impulses (more study is needed to resolve the temporal/spatial aspects of this signal) is sent to the brain for interpretation. The nasal sampling system preconditions the temperature, humidity, and particulate matter in the gas sample.

A dog’s initial sniff brings the gas sample into the nose in about 0.2 seconds through a channel to the back of the throat where it meets a larger chamber and wafts slowly over the olfactory epithelium containing the ORs. The flow of the sniffed sample over the mucus depletes mucus-soluble odorant molecules from the sample and concentrates odorants using odorant-binding proteins. The binding event of an odorant to an OR triggers a signal in the ON (olfactory neuron); these neurons provide a nonlinear array of signals to the glomeruli (a cluster of nerve fibers in the olfactory bulb) that has the spatial and temporal qualities to encode the signals’ variations, representative of the original sample’s interactions. The working of the dog’s mammalian olfactory system [8, 9] helps illustrate each of three complex components in a sensor array: sampling (preparation/separation), sensing (transport/binding/detection), and subsequent pattern analysis.

Fig. 1.1 Dog olfactory system
In a bionic-, cybernetic-, or electronic-nose, the sampling component allows for the separation, conditioning, and presentation of the sample to the detection layer either in a constant or a variable manner. The detection process and equipment can include filtration materials, such as is provided by the mucus in the mammalian nose, and can be configured so as to geometrically and chemically bias the detection system for individual molecular or supramolecular target analytes. We do not yet understand the entire role of the mucus layer in mammalian olfaction, but we do know it is a complex mixture containing molecules like the odorant-binding proteins that help in trapping, concentrating, or otherwise facilitating transport or binding of the target odor molecules. We also know that signal conditioning and chemical amplification occur in the detector layer of a mammal’s nose and that the nose also contains multiple detectors or a sensor array. The olfactory analysis in mammals includes the collection of the sensory outputs into an odor record and the use of that record to identify and quantify the currently sniffed molecular presentation or odor. The analysis of sensor array patterns is performed by computers in an artificial nose but is, as yet, a poor mimic of the mammalian brain.

Systems engineering aspects to the analysis of an odor with a “nose” is revealed by consideration of the synergistic operation of the parts. Mammalian sensors apparently have “off,” “on,” and “partially on” qualities in their levels of response for a given molecular stimulus. “Off” is a particularly important experimental state, and one that is often ignored in the construction of artificial sensor arrays [10]. Artificial sensors can also have several partially “on” states including “on positive” and “on negative” states [11]. Sensory transmission to the brain is complex and considered largely digital with temporal and spatial qualities [8]. Mechanically, the nose contains a complex gas sampling system [11], and the sample changes composition and temperature as it enters the nose and passes over the olfactory epithelium (sensor array). In interpreting olfactory signals as odors, memory and connections to other brain areas such as the limbic system are used. For example, one way of training a dog to respond to a target odor entails using a reward to link the target directly to a response from the limbic system. Moreover, results from zoology experiments show that training a dog in odor recognition can result in a sensitivity increase that is an order of magnitude greater [12] than that of an untrained dog.

Where does this increase in sensitivity come from, given the sensor array is thought to be similar and of the same sensitivity in both trained and untrained animals? Possible answers include improved sensory feedback from the brain or a more trained and efficient cerebral algorithm resulting from something akin to weighting vectors. Alternatively, the number or activity of a certain specific OR may change, or signals from certain types of samples may be suppressed. Thus, whether the sensitivity increase from training is due to improvements in computational capability or to physical changes, or to both is still debated.

We can cite examples of physical and neuronal changes that affect odor perception in mammals. Bodily influence on mammalian olfactory performance is exemplified in the well-known heightened sense of smell for some odorants in
pregnancy and the depressed sense of smell in people undergoing chemotherapy. Accident victims with brain trauma can temporarily or permanently lose all or some of their sense of smell. In any case, the sensory capability in the physical hardware of the sensory system can be affected in many ways, and the brain’s plastic computational capability can be changed to enhance or destroy the effective sensory experience. Hence, using the mammalian model affords us with parallel choices in constructing artificial sensory arrays, and we should make full use of our knowledge of these systems to create increased experimental possibilities.

### 1.2.2 Extrapolating from the Mammalian Model

We can make experimental progress in sensory problems by examining biology in two ways. First, we can create a hypothesis about the manner in which the biological system works and then emulate it in engineered hardware and software, with the resulting system evaluated and studied experimentally. If we achieve the expected result, we may be on the way both to understanding the biological system as well as to improving our own sensor array performance. Second, we can continue to unravel the mechanism of cellular signaling and interconnections at the molecular level. This second task is daunting, but progress has been and is being made at a rapid pace in using receptors and cloning receptors for use in artificial sensing.

We live in an odor-rich world in which an initial analog sensory interaction is converted to a digital code both in mammals and artificial noses. Each sample is characterized by a high degree of chemical or molecular variation, interactions of different molecules with the sensors are often unique, and the signal information created by the sensor(s) has the ability for extremely high and diverse information content. We need to better understand each of these issues from the experimental perspective. This issue of “richness” in sample and signal can be called the experimental diversity, and we address it in Sect. 1.3.

### 1.3 Experimental Diversity in Chemical Sensors and Sensor Arrays

In this section we examine the diversity or dimensionality of the problem and experimental hardware and methodology. The sample has diversity and the array of different signals create the dimensionality. Experimental sensor arrays are not yet able to gather and use all available data, data features, and available signal dimensions. However it is good to consider chemical sensor array experiments as “imaging” in the various dimensions that are available: space \((x, y, z)\), time,
chemical and biochemical composition, and concentration dimensions. Feature space for imaging purposes is an abstract space wherein each dimension can be considered a coordinate and \( n \)-dimensions result in an \( n \)-dimensional feature space. Thus, any property of an odor/molecule can be used as a dimension or feature in \( n \)-dimensional feature space. A molecule can be sorted on the basis of molecular weight, polarity or dipole moment, electrochemical activity, or other chemical property in chemical feature space. Therefore, \textit{feature space}; that is, an abstract space where each sample or molecule (or “pattern/element” or “feature”) is considered a point in \( n \)-dimensional space, with its dimension determined by the number and value of “the patterns” or “the features” used to describe the sample or molecule.” The importance of the chemical and biochemical dimensions of sensors becomes more apparent when we consider that each molecule in a sample that is different from another molecule contributes to the sample’s molecular diversity and that each molecular property being measured by the sensor–molecule interaction is considered a dimension – whether it is electrochemical activity, partitioning into a polymer matrix, or the molecular mass of the analyte.

\subsection{1.3.1 Sample Diversity}

Let us consider sample diversity first (see Table \ref{table:1.1}). Although perfect analysis of a gas sample is not yet possible, consideration of the molecular diversity of

\begin{table}[h]
\centering
\caption{Molecular diversity in a single breath}
\begin{tabular}{lll}
\hline
Breath constituents & Molecules & Total molecules		\\
\hline
78\% N\textsubscript{2} & 1.05E + 22 & 1.04813E + 22 \\
20\% O\textsubscript{2} & 2.69E + 21 & 1.31688E + 22 \\
1.9\% H\textsubscript{2}O at about 80\% relative humidity & 2.55E + 20 & 1.34241E + 22 \\
400 ppm CO (0.04\%) & 5.37500E + 18 & 1.34294E + 22 \\
5 ppm CO (0.0005\%) & 6.71875E + 16 & 1.34295E + 22 \\
500 ppb for 150 VOCs each & 6.71875E + 15 & 1.34295E + 22 \\
600 ppt for 100 unknowns & 6.71875E + 12 & 1.34295E + 22 \\
500 at femtomolar (10e\textsuperscript{-15}) & 6.71875E + 09 & 1.34295E + 22 \\
X at attomolar (10e\textsuperscript{-18}) & 10,000 ? & 10 ? \\
X at zeptomolar (10e\textsuperscript{-21}) & & \\
\hline
\end{tabular}
\end{table}

Avogadro’s number is the number of molecules in a gram-mole of any chemical substance. In the table entries \( E = 10 \), and “\( + \) number” value following \( E = \) the exponent of 10. That is, for Molecules in a breath, \( 1.34375E + 22 = 1.34375 \times 10^{22} \).
A single breath sample is instructive in order to consider analytical complexities. In one normal human breath about 500 mL of air is exhaled from the lung, which has about a 4.8-L capacity. If we knew the exact chemical composition of this 500 mL sample at 1 atm and room temperature, we would need to specify the number, identity, and position of about $10^{22}$ molecules in the 500 cm$^3$ space. Even though most of the molecules are oxygen and nitrogen, there are a dozen other gases present at the ppm level, including CO$_2$, Ar, and CO; and at least 150–1,200 common organic materials, which have been measured by gas chromatography and mass spectrometry (GC/MS) on breath samples at the ppm and ppb level [13, 14]; plus possibly many more such as ammonia (NH$_3$), hydrogen cyanide (HCN), or hydrogen (H$_2$) that are not easily chromatographed along with breath volatile organic compounds (VOCs). A few techniques are able to peer into the window below ppb levels, but literally thousands and thousands of different compounds could be present at the ppt, femtomolar, and attomolar levels, including those produced by human metabolic processes or from the environment (e.g., some explosives have a vapor pressure of $10^{-14}$ atm and such compounds could be present if the solid particles and their vapors are present and inhaled and exhaled by humans). In Table 1.1, as we sum the molecules, when we get to the attomolar level, there are only 10,000 molecules in our sample of each type, and so even 10,000 types will only add $10^8$ molecules to our total of more than $10^{22}$ and so we would need $10^{11}$ types to bring our cumulative total to account for each molecule in the breath. It is clear, current analysis of human breath can still have many unreported compounds at the ppm, ppb, and lower levels.

In fact, the true chemical diversity in one breath could easily be $10^{17}$ different types of molecules illustrating the immense composition and concentration diversity in a single breath. And $10^5$ molecules or more of each of billions of different chemicals are likely to be present. Even 10,000 molecules are clearly sufficient concentration to measure with today’s best analytical techniques and with some sensors. When analysis of a complex mixture, e.g., human breath, reports only a few hundred analytes present, we are most assuredly missing much information! Sample diversity is a daunting problem and immense opportunity for today’s sensor experimenters. How will we achieve our “gedanken” experiment of perfect analysis, i.e., to specify the location and identity of each molecule even in a single cc of sample?

### 1.3.2 Experimental Diversity in Sensor Arrays

From a statistical perspective, we need at least as many dimensions in our experiment as we have in our real sample, otherwise the method may not have the statistical capacity to perform an analysis. We now know how many dimensions we might expect from our sample. The next question is how many dimensions can we create with a sensor array experiment?
The dimensionality or features of a sensor array experiment can be estimated by considering its constituent parts of the sensor array and their function, according to (1.1) [15]:

\[
\text{Materials} \times \text{transducers} \times \text{structures} \times \text{methods} = \text{features/dimensions} \\
10^8 \times 10^2 \times 10^3 \times 10^8 = 10^{21} \quad (1.1)
\]

### 1.3.2.1 Types of Sensor Feature Space

Equation (1.1) is a bit like the Drake equation from astrophysics (an equation that allows quantification of the factors that determine the number of extraterrestrial civilizations in our galaxy with which we might come into contact) in which we can only estimate each term to provide a gross indication of the dimensionality of the imaging space that can be created by sensor arrays [15]. In (1.1), we estimate that there are about \(10^{21}\) features in sensor array space due to the four different properties of materials, transducers, structures, and methods that produce differentiating molecular interactions/signals in sensors. Material space includes the elements from the periodic table that can be applied singularly or combined in many organic, inorganic, and/or biochemical compounds and composites to make sensors. Transducer space is divided into the different forms of energy used to transduce each sensor signal, with each providing a different class of sensor (see Fig. 1.2) for which there are many types. The classes of sensors are based on transducers for light (radiant), heat (thermal), charge (electronic), chemical (electrochemical), mechanical (mass and force), and magnetic energy. Combinations of these classes provide for, conservatively, 100 types of sensor responses. The structure and geometry of the sensor materials also profoundly influence the sensory response of those materials (e.g., the material can consist of a thin or thick film on a mechanical or optical transducer). Finally, the richest source of diversity, limited only by the creative mind of the developer, is that created by operational method. For example, a sensor can be heated to constant or variable temperatures and with a high or low sample flow rate yielding differentiating chemical responses. In addition, there are many electronic influences on sensor signals. It is the interplay of all these diverse possibilities that results in the immense number of features that exist in chemical or biochemical space and any given sensor array can contain a large number of these features. The examples shown in Fig. 1.2 summarize these aspects of sensor diversity organized by the structure and the process used to create the dimension.

### 1.3.2.2 Orthogonal and Nonorthogonal Features

Not all features are “orthogonal” (i.e., not correlated with one another, strictly in mathematics two vectors must be perpendicular to be orthogonal, but here we will use
the term non-rigorously to infer a degree of non-relatedness). For example, electronic conductivity and mass loading could have the same concentration dependence on a given sensor and hence be correlated and thus not be orthogonal. If responses are not correlated (i.e., if conductivity is exponential in concentration and mass loading is linear in concentration), they would have at least some degree of orthogonality.

In an array experiment, the orthogonality of the sensory responses is important because it implies a higher information content for the array of signals. Creating orthogonal parameter space with sensors can be challenging, but is necessary for effective analytical results. Experimentally, more often than not, a one-to-one relationship does not exist between the number of sensors in an array and dimensionality in the sense of independent noncorrelated or partly correlated responses of the data. A single sensor can be operated by many methods, including cyclic heating, cyclic voltage application, and pulsed current, and these combinations can produce multidimensional data rapidly. Sensors can also combine transducer platforms as is done in spectroelectrochemistry to produce multidimensional data from a single sensor/method.

An early heterogeneous gas sensor array [16, 17] used four sensors and a heated catalytic combustible gas sensor (CGS) in a synergistic operation to detect virtually all gaseous compounds at ppm to percent levels. The chemical parameter spectrometer (CPS-100) instrument that implemented this early pre-electronic nose sensor array era gathered 16 channels of data from four sensors operated in four modes. These 16 channels were not totally independent (orthogonal) for all analytes as
shown by statistical analysis [17]. Later, a modulated concentration sensor was used to provide added features in the data that reflected the chemical composition [18]. This example of forming multidimensional data by using different sensors and processes is presented in more detail later to illustrate the impacts of experimental work on sensor array research.

A classic GC/MS experiment illustrates another form of the sensor array experiment. The GC separates hundreds of compounds in time, and the MS detects them in sequence. In this case, one MS detector provides a multidimensional mass spectrum of data for each compound, often doing so multiple times each second. Collection of the entire data set can take more than an hour for each GC sample, producing extremely large multidimensional data bases. Such data has been used to derive structure-activity relationships for, among many other things, drugs and to differentiate killer bees from European honey bees. Modern arrays, sensors, and sensing systems use many dimensions as well as scientific and engineering methods/techniques [19].

1.3.2.3 The Experimental Matrix Surrounding a Single Sensor

To understand “sensor-created” feature space, we need to look at the experimental matrix that can be obtained from a single sensor. A single sensor exposed to a step change or pulse of gas produces signal-vs.-time data. These data, in turn, are characterized by several features, including signal height, the area under the signal–time curve, the response and decay times, and the ratios of the several features. The many dimensions possible by combining just the material and transducer platforms and modes of operation are estimated at more than $10^8$ combinations, which, in fact, appear to be a conservative estimate.

1.3.2.4 Transducers

Transducers can manifest any of the six types of energy exchange – thermal, mechanical, chemical, electronic, magnetic, and optical. Each transducer category can be considered a sensor class; each class can consist of many sensor types, with each type based on the parameter measured. Electronic transducers can measure resistance ($R$), capacitance ($C$), or impedance ($Z$). Mechanical transducers may respond to and their signal may reflect change in mass ($M$) or elastic properties or a combination thereof. Optical transducers measure a change in optical properties (e.g., absorption or emission of a specific wavelength of specific energy or the change in the refractive index). A conservative estimate of transducer parameter space is $10^2$ dimensions because transducers can operate alone or in combinations.
1.3.2.5 Sensor Geometries and Structures

To produce differing responses, sensors can also be made with many geometries and structures. On a mechanical platform, thick sensors may produce slower but more sensitive responses per unit of analyte than do thin sensors. In addition, an observed sensor response may be due to more than one effect (e.g., simultaneous mass change and elasticity change in a polymer with increasing analyte concentration). Each of these effects can be the dominant response under a different set of conditions (e.g., sensor thickness, geometry, or formulation, or at a different analyte concentration). Such effects produce multidimensional data from sensor responses and allow “imaging” in chemical space when combined with the other dimensions of the structure.

1.3.2.6 Methods of Sensor Operation

By far the largest contribution to diversity in sensor response is the method of operation. Methods include internal and external modulation of sensor responses, combination of sensors into homogenous or heterogeneous arrays, and the production of hyphenated, multidimensional sensor responses from sensor systems of all kinds, various qualities, and any number of sensors [19]. Examples include heterogeneous arrays [17], modulation of input concentrations [18]; modulation of sensor operational variables like electrochemical bias [16], operation in nonsteady-state modes [20]; and discontinuous, cyclic, or pulse modes of operation. The highest information content is acquired when the sensor or sensor array can obtain parameters that contain noncorrelated (orthogonal) responses to the same analyte, the concentrations, or the target matrix. For example in spectroelectrochemistry, the data from electrochemistry can relate to the reaction of one functional group in a molecule [e.g., nitrogen dioxide (NO₂) reduction] and the spectroscopic information can relate to another part of that molecule (e.g., light absorption of the aromatic side chain). Both signals provide information about the molecular identity, and signal intensity relates to concentration. Differing concentration dependence of the two responses can add significant data dimensionality for example, if one parameter measurement functionality is linear and the other logarithmic and the method involves changes in concentration.

Experimental parameter space for sensors is extremely large and difficult to navigate, but can yield an enormous number of features in an array’s sensory responses. The prospect of working in such a space experimentally with so many possibilities is daunting but also leads to the richness of this research and the possibility of significant analytical power from sensors. The important role of experimentation is thus to quickly screen choices and select promising practical approaches from the many possibilities. Combining experimentation with theory helps narrow choices for achieving different sensor responses by forming hypotheses about those responses. These hypotheses can guide and simplify experimental
work. In sensor array development, a powerful paradigm for analytical advances is created when theory and experiment work together.

1.4 Experimentation to Create New Sensors

1.4.1 New Tasks for Sensors

Today, chemical and biochemical sensors are being tasked with providing information about more and more analytically-complex endpoints. We not only ask of the sensor/instrument how much substance in general is present (quantitative analysis), but also ask how much of a particular substance A is present (qualitative analysis). Instruments that contain sensor arrays are also tasked with answering other complex questions about product quality and environmental situations: Has this coffee been roasted? Has this cheese been adequately aged? Does this plastic have an off odor? Where does this toxic spill come from? Is this situation hazardous or toxic? What “type” of fire is beginning and in what “stage” is it? The endpoints desired are often chemically or biochemically complex, and demand a great deal, analytically from the sensory system.

We assume that the answers to these questions are contained in a sample’s molecular diversity. The complex endpoint analyses needed are often analogous to finding a needle in a haystack (e.g., a ppb-level of benzene in air or does this package contain TNT?). Can a chemical sensor array conduct these analyses? We know that the analytical task is possible because a dog can do it, often astounding us by performing such experimental feats in only a few seconds with a sniffer, a biosensor array, and just a few ounces of gray-matter as its “computer.” We know that the airborne information is transmitted in the molecular diversity of the sample and all we need is a suitable sampler, sensor array, and computational capability to answer such complex analytical questions. However, the performance of all sensor array systems is not equal and artificial noses have not been able to duplicate the feats of mother nature yet, although the gap is closing today between artificial and natural approaches.

Clearly, we have much more to learn from natural systems, particularly vertebrate and invertebrate, and even from insect olfactory organs. We can find the answers only through experiment. This last statement may be controversial. For example, what can we learn from theory and what can we learn from experiment? In many cases, doing the experiment and creating a device is the only way to understand something. In the early days of electricity, Michael Faraday sent a copy of his electric motor to his colleagues, not a paper about it, because the action of the device transmitted more information than could be written at the time. There is knowledge and information in the experiment itself. We shall not further argue here the merits of experiment vs. theory. As we know, they are complementary and
valuable. However, experiment is the final arbiter and herein, we are emphasizing the role of experimentation.

1.4.2 Defining the Approach for Creating Sensors and Arrays

Chemical sensor array instruments (like the e-nose or e-tongue) have been created primarily to perform experiments. To understand these devices, we must break them down into their components, just as the experimental process itself can be divided into instructional steps. We need to follow specific steps to progress toward achieving a goal and, whether they are formal or informal, building an effective sensor array instrument that needs to include several distinct steps.

1.4.2.1 Step 1: Seek to Understand, from a Fundamental Viewpoint, the Problem/Goal

For any sensor array experiment, it is important to articulate as clearly as possible its specific goal or objective; otherwise, we cannot tell when we have achieved that which is wanted. Conducting a comprehensive literature search about the topic is typically required, and clearly stated goals with a specific and focused application in mind will narrow the often vast possibilities.

1.4.2.2 Step 2: Isolate and Identify Major Issues in Reaching the Goal

All available information on the topic needs to be distilled to isolate and identify relevant gaps in knowledge or technology. The major issues/problems that prevent the immediate design and implementation of a complete solution to the problem at hand should be listed. Step 2 can be conducted concurrently with Step 1, with the ongoing literature search and theoretical analysis used to identify and quantify the major issues as they are defined. Those issues will most likely consist of which of the materials, structures, components, processes, and algorithms need to be chosen, as well as a list of systems and interface problems.

1.4.2.3 Step 3: Develop a Strategy

A strategy consists of creative thought and conclusions about the possible approaches that will be required to reach the goal and overcome the major problems. A strategy should seek to bring typically disparate or often conflicting requirements into harmony. Sometimes, for instance, a solution may require both a fast sensor and an extremely sensitive sensor; if so, compromises will be required in which more sensitivity will require more time for sample collection. In this case,