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Combinatorial and High-Throughput Development of Sensing Materials: The First 10 Years

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Contents

1. Introduction

Chemical and biological sensors have found their niche among modern analytical instruments when real-time determination of the concentration of specific sample constituents is required. Development of sensors with new capabilities is driven by the ever-expanding monitoring needs of a wide variety of species in gases and liquids. On the basis of a variety of definitions of sensors,[1−3] here we will accept that a chemical or biological sensor is an analytical device that utilizes a chemically or biologically responsive sensing layer to recognize a change in a single or multiple chemical or biological parameters of a measured environment and to convert this information into an analytically useful signal.

In a sensor device, a sensing material is applied onto a suitable physical transducer to convert a change in a property of a sensing material into a suitable physical signal. The obtained signal from a single transducer or an array of transducers is further processed to provide useful information about the identity and concentration of species in the sample. The energy transduction principles that have been employed for chemical and biological sensing involve radiant, electrical, mechanical, and thermal types of energy.[4,5] Specific sensing concepts are further implemented with each energy transduction. Sensors based on radiant energy of transduction can employ intensity, wavelength, polarization, phase, or time resolution detection. Sensors based on electrical energy of transduction can employ conductometric, potentiometric, or amperometric detection. Sensors based on mechanical energy of transduction can employ gravimetric or viscoelastic detection. Sensors based on thermal energy of transduction can employ calorimetric or pyroelectric detection. Hyphenated techniques in sensing are of significant importance and combine several transduction techniques in one sensor.[6,7] In addition to a sensing material layer and a transducer, a modern sensor system often incorporates other important components such as sample introduction and data processing components.

In contrast to sensing based on intrinsic analyte properties (e.g., spectroscopic, dielectric, thermal), indirect sensing utilizes a responsive sensing material.[2,5,8−13] This approach dramatically expands the range of detected species, improves sensor performance (e.g., analyte detection limits), and is more straightforwardly adaptable for miniaturization.[6,14−33] These attractive features can be offset by some limitations of indirect sensors, for example, insufficient selectivity, poisoning, poor long-term stability, and slow response and recovery times. Nevertheless, indirect sensors constitute the most active research area in developing sensing approaches that cannot be addressed with direct sensing.

1.1. Requirements for an Ideal Sensor

The exact configuration of a sensor for a particular application may be dictated by the nature and requirements of that application. Nevertheless, it is useful to set the features that one would wish in an ideal sensor for chemical and biochemical species. Requirements for an ideal sensor system

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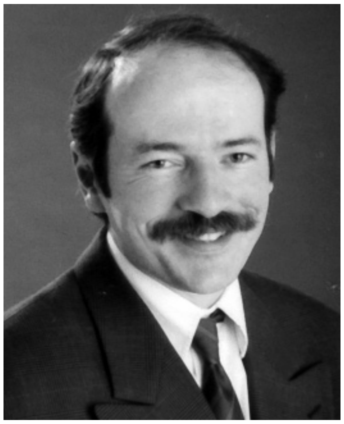

Vladimir M. Mirsky received a M.D. in Biophysics from Moscow Medical University in 1981. Then he studied physical chemistry and electrochemistry, completed a postgraduate course in electrochemistry and physical chemistry at the Frumkin Institute of Electrochemistry of the USSR Academy of Sciences and obtained a Ph.D. in electrochemistry in 1986. In 1991 he was awarded the Alexander-von-Humboldt Research Fellowship and moved to Germany. In 1993–1994 he worked for the CNRS Centre of Molecular Biology in France. Since 1995, Dr. Mirsky has been working at the Institute of Analytical Chemistry, Chemo- and Biosensors, University of Regensburg (Germany), currently as professor. His research interests comprise applied biophysics and physical chemistry of interfaces and development of new chemical and biological sensors. He is/was a supervisor of 23 Master and Ph.D. works, a member of the editorial boards of three scientific journals, and an editor of a number of topic issues including the recent book *Ultrathin Electrochemical Chemo- and Biosensors* in the Springer Series on Chemical Sensors and Biosensors. The results of his work are presented in 18 patents or patent applications and in about 100 peer-reviewed scientific papers.

Table 1. Sensor Requirements[a]

system requirements and performance	sample introduction	sensing material	transduction principle	data analysis
dynamic range	X	X	X	X
ergonomic design	X			
false-positive rate	X	X	X	X
initial cost	X	X	X	X
long-term stability	X	X	X	X
maintenance simplicity	X	X	X	
multicomponent detection	X	X	X	X
multiple operation modes		X	X	X
operation cost	X		X	
operation simplicity	X			X
power consumption	X		X	
probability of detection	X	X	X	X
response speed	X	X		X
response reversibility	X	X		
robustness	X	X	X	X
selectivity	X	X	X	X
self-calibration	X			X
sensitivity	X	X	X	X
shelf life		X	X	
size	X		X	
sterilizability		X	X	

[a] Analytical definitions are provided in refs 5 and 34.

can be analyzed from the viewpoint of requirements for individual subsystems that include (1) sample introduction, (2) sensing material, (3) transduction principle and implementation, and (4) data analysis. As shown in Table 1, the proper design of each individual subsystem has a significant impact on the overall system requirements and performance. For example, a desired sensor dynamic range can be obtained with an appropriate design of sample introduction, type of sensing material, transduction principle selected for the generation of the sensor signal, and data analysis.

In real-world applications, the qualities of an ideal sensor are often weighted differently according to application. High reliability, adequate long-term stability, and resolution top the priority list for industrial sensor users, whereas often the size and maturity of the technology are the least important factors.[2,3,6] A low false-positive rate and an ergonomic design are very critical for first responders.[34] In contrast, medical users focus on cost for disposable sensors. Specific requirements for medical in vivo sensors include blood compatibility and minute size.[35] Resistance to gamma radiation during sterilization, drift-free performance, and cost are the most critical specific requirements for sensors in disposable bioprocess components.[36] The importance of continuous monitoring also differs from application to application. For instance, glucose sensing should be performed two to four times a day using home blood glucose biosensors, whereas blood-gas sensors for use in intensive care should be capable of continuous monitoring with sub-second time resolution.[37,38]

1.2. Challenges in Rational Design of Sensing Materials

As illustrated in Table 1, all subsystems, including sensing materials, are equally important for a successful sensor. Rational design of sensing materials based on prior knowledge is a very attractive approach because it avoids time-consuming synthesis and testing or numerous candidates. However, to be quantitatively successful, rational design[39−43] requires detailed knowledge regarding how the intrinsic properties of sensing materials relate to their performance properties (e.g., magnitude of response to analyte and interferences, long-term stability, shelf life, resistance to poisoning, response and recovery times, best operation temperature, adhesion stability to substrate).

Unfortunately, the multidimensional nature of the interactions between the function and the composition, preparation method, and end-use conditions of sensing materials often makes difficult the rational design of sensing materials for real-world applications.[28,44−48] Thus, in addition to rational design, a variety of sensing materials have been developed using detailed experimental observations or discovered by chance.[49−57] Such an approach in the development of sensing materials reflects a more general situation in materials design that is "still too dependent on serendipity" with only limited capability for rational materials design as recently noted by Eberhart and Clougherty.[58] Examples of significant discoveries that have been recognized with the Nobel Prize in chemistry and that are currently being explored as the foundation of new sensing technologies include discovery and development of conductive polymers by Heeger, MacDiarmid, and Shirakawa (2000), discovery of fullerenes by Curl, Jr., Kroto, and Smalley (1996), development and use of molecules with structure-specific selective interactions (crown ethers) by Cram, Lehn, and Pedersen (1987), and investigations in surface chemistry by Langmuir (1932).

Conventionally, detailed experimentation with sensing materials candidates for their screening and optimization consumes tremendous amounts of time and project cost without adding to "intellectual satisfaction". Fortunately, new synthetic and measurement principles and instrumentation significantly accelerate the development of new materials. Several of these developments that are currently routinely used in creation and characterization of sensing and other materials have been recognized with Nobel Prizes in chemistry and physics. These include design of the first electron microscope by Ruska (1986), design of the scanning tunneling microscope by Binnig and Rohrer (1986), development of methodology for chemical synthesis on a solid matrix by Merrifield (1984), construction of maser and laser systems by Townes, Basov, and Prokhorov (1964), invention of the phase contrast microscope by Zernike (1953), invention of partition chromatography by Martin and Synge (1952), discovery of new light scattering effect by Raman (1930), and invention of the method of microanalysis of organic substances by Pregl (1923). The practical challenges in rational sensor material design also provide tremendous prospects for combinatorial and high-throughput research, which is the applied use of technologies and automation for the rapid synthesis and performance screening of relatively large numbers of compounds.[59−67]

Sensing materials can be categorized into three general groups that include inorganic, organic, and biological materials. In this review, inorganic sensing materials are defined as materials that have inorganic signal generation components (e.g., metals, metal oxides, semiconductor nanocrystals) that may or may not be further incorporated into a matrix. Organic sensing materials comprise indicator dyes, polymer/reagent compositions, conjugated polymers, and molecularly imprinted polymers. The emphasis of this review is to comprehensively cover combinatorial and high-throughput development of inorganic and organic sensing materials. Development of biological receptors such as aptamers, peptides, and antibodies using combinatorial approaches has been extensively reviewed elsewhere[68−73] and is beyond the scope of this review. Other earlier reviews were focused on applications of sensors[47,74] and MEMS devices[63,75] for high-throughput materials characterization and on high-throughput development of polymer- and biopolymer-based sensing materials.[13]

This review is organized in several sections. First, it sets a stage with the general principles of combinatorial and high-throughput materials screening technologies followed by the analysis of opportunities that are provided for sensing materials from these new technologies. A section on combinatorial inorganic sensing materials provides a critical analysis of developments in catalytic metals for field-effect devices and metal oxides for conductometric and catalumінescent sensors, plasmonic, and semiconductor nanocrystal materials. A section on combinatorial organic sensing materials provides a critical analysis of developments in indicator dyes, polymeric compositions, homo- and copolymers, conjugated polymers, and molecularly imprinted polymers. Because the widespread applications of combinatorial techniques for sensing materials are quite recent, this review also serves as an introduction to this field. We demonstrate that new parallel synthesis and advanced analytical instruments and data mining tools accelerate the discovery and optimization of sensing materials and provide more fundamental knowledge on the material fabrication with tailored initial and long-term stability properties.

2. Combinatorial and High-Throughput Materials Screening

2.1. General Principles

In pharmaceutical and biotechnology industries, combinatorial synthesis and high-throughput analysis methods have found their applications in systematic searching of large parameter spaces for new candidate therapeutic agent molecules.[76] Combinatorial chemistry originated in several laboratories around the world when Frank in Germany,[77] Geysen in Australia,[78] and Houghten in the United States[79] developed methods to make more compounds in a shorter period of time.[80] In materials science, the materials properties depend not only on composition but also on morphology, microstructure, and other parameters related to the material preparation conditions. As a result of this complexity, a true combinatorial experimentation is rarely performed in materials science with a complete set of materials and process variables explored. Instead, carefully selected subsets of the parameters are often explored in an automated parallel or rapid sequential fashion using high-throughput experimentation (HTE). The terms "combinatorial chemistry" and "combinatorial materials science" are often applied for all types of automated parallel and rapid sequential materials evaluation processes. Thus, an adequate definition of combinatorial and high-throughput materials science is a process that couples the capability for parallel production of large arrays of diverse materials together with different high-throughput measurement techniques for various intrinsic and performance properties followed by the subsequent navigation in the collected data for identifying "lead" materials.[61−64,81]

Individual aspects of accelerated materials development have been known for decades. These include combinatorial and factorial experimental designs,[82] parallel synthesis of materials on a single substrate,[83,84] screening of materials for performance properties,[85] and computer data processing.[86,87] However, it took the innovative scientific vision of Joseph Hanak to suggest in 1970 an integrated materials

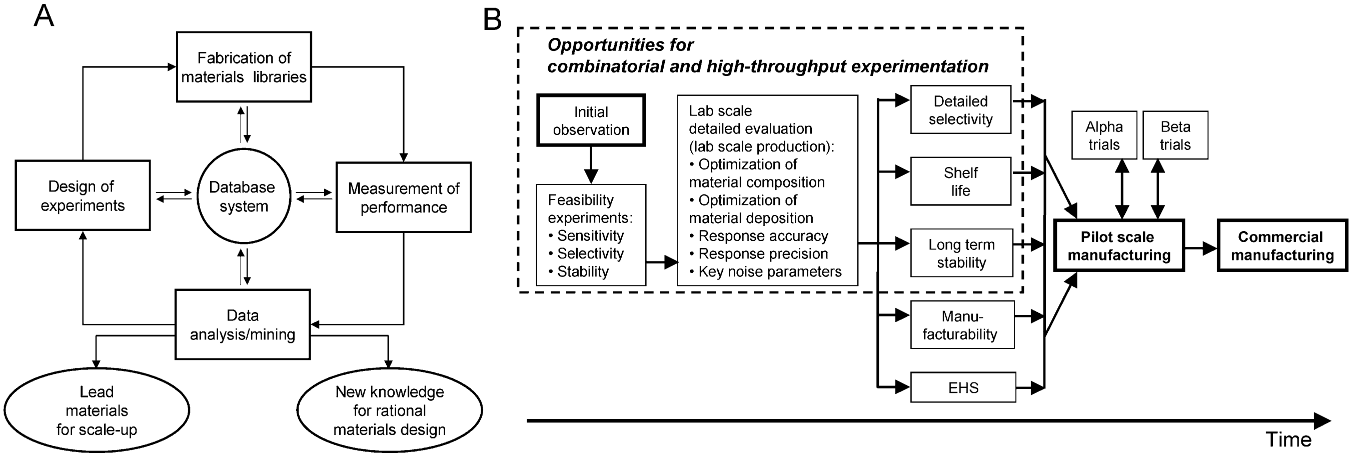

Figure 1. Combinatorial and high-throughput approach for materials development: (A) typical combinatorial materials development cycle; (B) development phases of new sensing materials in sensors and opportunities for combinatorial and high-throughput experimentation.

development workflow.[88] Its key aspects included (1) complete compositional mapping of a multicomponent system in one experiment, (2) simple, rapid, and nondestructive all-inclusive chemical analysis, (3) testing of properties by a scanning device, and (4) computer data processing. Hanak was truly ahead of his time and "it took 25 years for the world to realize his idea".[60]

In 1995, Xiang, Schultz, and co-workers initiated the avalanche of applications of combinatorial methodologies in materials science with the publication of their paper "A combinatorial approach to materials discovery".[89] Since then, combinatorial materials science has enjoyed much success, rapid progress for over a decade, and tremendous diversification into a wide variety of types of materials. Besides sensing materials, discussed in this review, examples of materials reported in conjunction with combinatorial and high-throughput screening techniques include superconductor,[89] ferroelectric,[90] magnetoresistive,[91] luminescent,[92] agricultural,[93] structural,[94] hydrogen storage,[95] and organic light-emitting[96] materials; ferromagnetic[97] and thermoelastic[98] shape-memory alloys; heterogeneous,[99] homogeneous,[100] polymerization,[101] electrochemical,[102] and hydrogen evolution[103] catalysts; polymers,[104] zeolites,[105] and metal alloys;[106] materials for methanol fuel cells,[107] solid oxide fuel cells[108] and solar cells;[109] automotive,[110] waterborne,[111] vapor-barrier,[112] marine,[113] and fouling-release[114] coatings, and others.

A typical modern combinatorial materials development cycle is outlined in Figure 1A. Compared to an initial idea, the modern workflow has several new important aspects such as planning of experiments, data mining, and scaleup. In combinatorial screening of materials, concepts originally thought of as highly automated have been recently refined to have more human input, with only an appropriate level of automation. For the throughput of 50−100 materials formulations per day, it is acceptable to perform certain aspects of the process manually.[115,116]

To address numerous materials-specific properties, a variety of high-throughput characterization tools are required. Characterization tools are used for the rapid and automated assessment of single or multiple properties of the large number of samples fabricated together as a combinatorial array or "library".[62,117,118] Typical library layouts can be discrete[82,89] and gradient.[83,88,119−121] A specific type of library layout will depend on the required density of space to be explored, available library fabrication capabilities, and capabilities of high-throughput characterization tools.

In addition to the parallel synthesis and high-throughput characterization instrumentation that significantly differs from conventional equipment, the data management approaches also differ from conventional data evaluation.[66] In an ideal combinatorial workflow, one should "analyze in a day what is made in a day",[122] which requires significant computational assistance. In an exemplary combinatorial workflow (Figure 1A), design and synthesis protocols for materials libraries are computer assisted, materials synthesis and library preparation are carried out with computer-controlled manipulators, and property screening and materials characterization are also software controlled. Furthermore, materials synthesis data as well as property and characterization data are collected into a materials database. Data in such a database are not just stored but also processed with the proper statistical analysis, visualization, modeling, and data mining tools. Table 2 illustrates important current capabilities and remaining needs for the data management system.[123]

Production of combinatorial leads on a larger scale reveals how reliable and realistic are the data obtained on the combinatorial scale. Materials developed at the combinatorial scale and validated on scale-up versions or in practical applications include catalysts, polymers, phosphors, formulated organic coatings, and sensing materials.[13,67,116,124−130]

2.2. Opportunities for Sensing Materials

Development of a sensor system with a new sensing material includes several phases such as discovery with initial observations, feasibility experimentation, and laboratory-scale detailed evaluation, followed by the transition to the pilot scale and to commercial manufacturing (see Figure 1B). At the initial stage, performance of the sensing material is matched with the appropriate transducer for the signal generation. The stage of the laboratory-scale evaluation is very labor-intensive because it involves a detailed testing of sensor performance. Some of the aspects of this evaluation include optimization of the sensing material composition and morphology, its deposition method, detailed evaluation of response accuracy, stability, precision, selectivity, shelf life, long-term stability of the response, effects of potential poisons, etc. The pilot-scale manufacturing focuses on the identification and elimination of manufacturing issues that affect the reproducible, high-yield manufacturing of the sensors. During this phase, alpha and beta tests are typically performed. The alpha tests are typically performed by the

Table 2. Functions of Data Management System[123]

function	current capabilities	remaining needs
experimental planning	composition parameters process parameters library design	iterative intelligent experimental planning based on results from virtual or experimental libraries
database	entry/search of composition/process variables operation with heterogeneous data unification of data between different instruments	storage and manipulation (search) of large amounts (terabytes and more) of data
instrument control	operation of diverse instruments	interinstrument calibration full instrument diagnostics plug'n'play multiple instrument configurations
data analysis	visualization of composition/process conditions and measured parameters of library elements univariate/multivariate processing of steady-state and kinetic data quantitative analysis outlier detection	advanced data compression processing of large amounts (terabytes and more) of data, cloud computing when required
data mining	prediction of properties of new materials virtual libraries cluster analysis molecular modeling QSAR	identification of appropriate descriptors on different levels (atomic, molecular, process, etc.)

researchers on an advanced sensor device prototype to identify issues related to sensor operation and functionality. Beta tests are typically performed on the further improved version of the sensor system by the identified group of end-users ("early adopters") to seek their feedback on sensor performance, ease of use, failure modes, etc.

The pioneering work by Xiang, Schultz, and co-workers published in 1995[89] inspired applications of combinatorial methodologies for sensing materials. In 1996, Lundström proposed to make arrays of sensing films with multiple types of metals.[131] In 1996, Natan and co-workers applied a solution-based combinatorial assembly of metal nanoparticles to create an efficient substrate for surface-enhanced Raman measurements.[132] In 1997, Walt and co-workers performed combinatorial polymerizations of sensing films and fabricated discrete and gradient film arrays.[44] Combinatorial and high-throughput experimentation provides an attractive opportunity to accelerate the development and optimization of sensing materials. These development aspects of sensing materials are highlighted in Figure 1B and include initial screening, detailed performance screening, accelerated shelf life, and long-term stability testing. In this review, we will provide critical analysis of these developments. It is quite remarkable that most of the types of sensing materials have been explored with combinatorial technologies, which demonstrates the desire of the sensing community for the accelerated development of sensing materials using newly introduced research tools. Göpel showed that a theoretical dimensionality of the hyperspace of independent chemical sensor features is $\sim 10^{21}$ (see Figure 2) and includes the permutations of various sensor materials, transducer principles, and modes of operation for each sensor/transducer combination.[133−135]

2.3. Gradient and Discrete Sensing Material Libraries

In the past, spatial gradients in functional materials were generated by varying composite and structural characteristics.[119] Gradients in polymeric materials were produced by changing the chemical nature of monomers, the molecular constitution of polymers, and their supramolecular structure or morphology.[120] Several methods for fabrication of surface molecular chemical gradients have been reported.[136−139] In sensing materials, additional parameters of gradients are also required that can include concentrations of formulation additives, thickness, temperature, extent of cross-linking, and some others. Gradient sensor libraries (or arrays) can be produced using solvent-assisted polymerization,[44] fiber drawing,[140,141] draw coating,[48,142,143] or ink jet printing.[144] Once a gradient sensor array is formed, it is important to estimate the possibilities to adequately measure the variation of properties along the gradient. These can be intrinsic (thickness, chemical composition, morphology, etc.) and performance (response magnitude, selectivity, stability, immunity to poisoning, etc.) properties. Discrete sensor arrays can be produced using ink jet printers,[145−147] liquid-dispensing

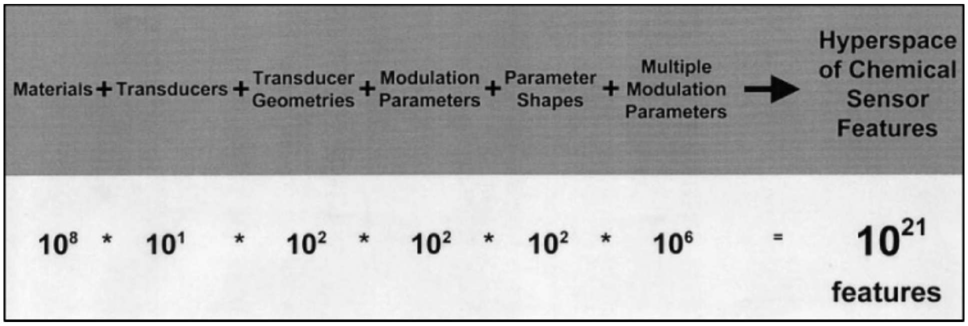

Figure 2. Hyperspace of chemical sensor features with about 10^{21} independent features. Reprinted with permission from ref 133. Copyright 1998 Elsevier.

robots,[45,148] microarrayers,[149] and automated dip-coating[150] or during in situ polymerizations.[151,152] Ink jet printing typically produces dispense volumes of around several picoliters, whereas the liquid-dispensing robots can dispense several nanoliters and up to several microliters.[149]

Once the gradient or discrete sensor film array is fabricated, it is exposed to an environment of interest and steady-state or dynamic measurements are acquired. Scanning (e.g., complex impedance, UV−vis, excitation−emission fluorescence, X-ray diffraction) systems often provide more detailed information compared to imaging systems. When a dynamic process (e.g., a response time) of sensor materials arranged in an array is monitored with a scanning system, the maximum number of elements in a sensor library that can be measured with the required temporal resolution can be limited by the data acquisition ability of the scanning system.[143]

2.4. Dynamic Combinatorial Libraries

An emerging field in combinatorial chemistry is dynamic combinatorial chemistry,[153−155] which is very attractive for the development of synthetic receptors and indicator dyes.[156] Traditional combinatorial chemistry involves the use of irreversible reactions to generate static libraries of related compounds. Dynamic combinatorial chemistry involves the use of reversible reactions to generate equilibrating mixtures of molecules, known as dynamic combinatorial libraries (DCLs). The composition of a DCL is able to respond to molecular recognition events resulting from the addition of a target of interest. The preferential binding of one member of the DCL to the target induces a shift in the equilibrium toward the formation of that particular compound. Thus, whereas in combinatorial chemistry library synthesis and screening are two separate processes that are performed sequentially, dynamic combinatorial chemistry offers in situ screening of the combinatorial library simply by comparing its composition in the absence or presence of the target and identifying library members with a high affinity for the respective target.[157]

3. Inorganic Sensing Materials

3.1. Catalytic Metals for Field-Effect Devices

In 1973, in the laboratory of Prof. Lundström, a phenomenon of hydrogen response of a thin Pd metal film that was tried as a gate of a field-effect transistor was discovered.[158,159] Later observations in the same laboratory of sensing response on defective films with cracks and holes led to the discovery of effects of discontinuous metal gates and to the development of sensors for ammonia gas.[160] Further developments of these sensors with gates of a variety of catalytic metals (Pd, Pt, Rh, Ir) demonstrated their sensitivity to numerous other gases (e.g., hydrogen sulfide, ethylene, ethanol, different amines). The mechanism of the response involves a change in the work function of the catalytic metal gate due to chemical reactions on the metal surface.

Currently, it is understood that chemical reaction mechanisms in these sensors depend on the specific gas molecules as shown in Figure 3.[161] For example, the response to hydrogen gas is due to a dipole layer, which is induced by trapping of hydrogen atoms at the metal−insulator interface of the device (see Figure 3A). The hydrogen atoms are first formed by dissociation of hydrogen molecules on the catalytic metal surface, and then they diffuse through the metal layer until a steady state is established between the concentrations of hydrogen atoms on the surface and at the metal−insulator interface. Some other hydrogen-containing molecules, such as hydrocarbons and alcohols, give rise to a response in a similar manner as hydrogen. However, the response mechanism to ammonia gas differs from the hydrogen response because of the fundamental differences in the dissociation sites. The ammonia sensitivity is related to the pores (exposed oxide) in the thin metal film (see Figure 3B).[161,162] Optimization approaches of materials for these sensors involve several degrees of freedom[163] as illustrated in Figure 4.

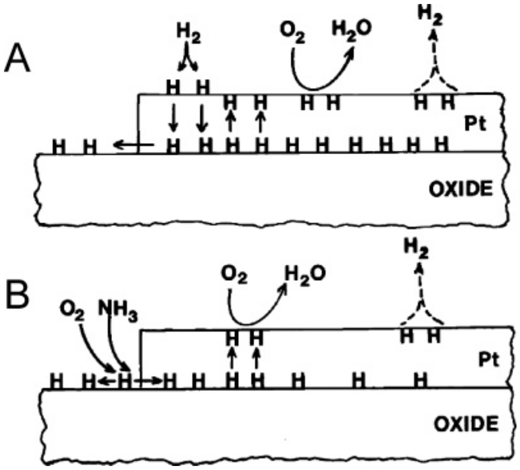

Figure 3. Mechanisms of sensing response to H_2 and NH_3 with the catalytic Pt metal gate: (A) in hydrogen gas, hydrogen atoms are mostly formed on the metal surface; (B) in ammonia gas, hydrogen atoms are produced mostly at the three phase boundaries. Reprinted with permission from ref 161. Copyright 2007 Elsevier.

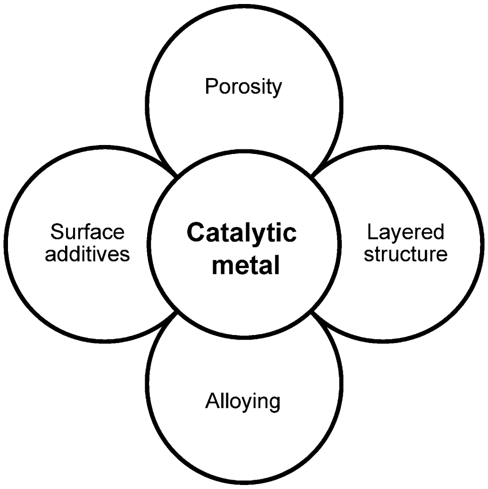

Figure 4. Diversity of optimization parameters during the preparation of catalytic metals for field-effect devices.

To simplify screening of the desired material compositions and to reduce a common problem of batch-to-batch differences of hundreds of individually made sensors for materials development, the scanning light pulse technique (SLPT) has been developed by Lundström and co-workers.[161,164,165] In these measurements, a focused light beam is scanned over a large-area semitransparent catalytic metal−insulator−semiconductor structure, and the photocurrent generated in the semiconductor depletion region is measured and creates a 2-D response pattern of the sensing film (aka “a chemical image”). An alternative method to scan such gradients utilizes a vibrating capacitor method developed by Mizsei.[166−169]

These chemical images were used to optimize properties such as chemical sensitivity, selectivity, and stability.[170] When combined with surface characterization methods, this information also has led to the increased knowledge of gas response phenomena. Early in these investigations,[164,171] it was shown how to take advantage from the ability of forming a temperature gradient along the test structure to study the temperature-dependent catalytic activity of metals. The catalytic activity of metals is related to the reactive sticking coefficient s, which. in turn, relates to the probability that an adsorbate is formed when a molecule hits an unoccupied part of the sensor surface. The sticking coefficient s and the rate constants for reactions r_1 and r_2, which remove an adsorbate from the surface, are thermally activated with activation energies E_s, E_1, and E_2, respectively. The variables s, r_1, and r_2 are the functions of position, x, along the surface due to the temperature gradient. Thus, the temperature-gradient-induced response can be described as[171]

$$\frac{\mathrm{d}}{\mathrm{d}x}\left(\frac{s(x)}{r_1(x)+r_2(x)}\right) \sim \{(E_\mathrm{s}-E_1)\exp(-E_1/kT) + r_{21}(x)\,(E_\mathrm{s}-E_2)\exp(-E_2/kT)\}\,\frac{\mathrm{d}T}{\mathrm{d}x} \quad (1)$$

where $\mathrm{d}T/\mathrm{d}x$ is determined by the variation of the operating temperature T along the surface, k is Boltzmann’s constant, and $r_{21} = c_2/c_1$ is the ratio of the frequency factors of the two reaction rates.

The use of combinatorial gradient techniques facilitated the increase of the understanding of the properties of catalytic metal gates and their influence on the selectivity and sensitivity of gas-sensitive field-effect devices. Temperature gradient experiments provided the required knowledge for selection of specific operating temperatures for detection of different gases.[161,164] By using the 1-D thickness gradients to study catalytic films, the effects of the variation of the film thickness that influence the gas response sensitivity, selectivity, and stability were discovered.[172−174]

It was suggested that a 2-D gradient made from two types of metal films as a double-layer structure should provide new capabilities for sensor materials optimization, unavailable from thickness gradients of single-metal films.[175] To make a 2-D gradient, the first metal film was evaporated on the insulator with the linear thickness variation in one dimension by moving a shutter with a constant speed in front of the substrate during evaporation. On top of the first gradient thickness film, a second metal film was evaporated with a linear thickness variation perpendicular to the first film. As the validation of the 2-D array deposition, the response of devices with 1-D thickness gradients of Pd, Pt, and Ir films to several gases has been studied with SLPT, with results similar to those of corresponding discrete components.[170]

The 2-D gradients have been used for studies and optimization of the two-metal structures[170,175] and for determination of the effects of the insulator surface properties on the magnitude of sensing response.[176] Two-dimensional gradients of Pd/Rh film compositions were also studied to identify materials compositions for the most stable performance.[170] The Pd/Rh film compositions were tested for their response stability to 1000 ppm of hydrogen upon aging for 24 h at 400 °C while exposed to 250 ppm of hydrogen (see Figure 5A,B). This accelerated aging experiment of the 2-D

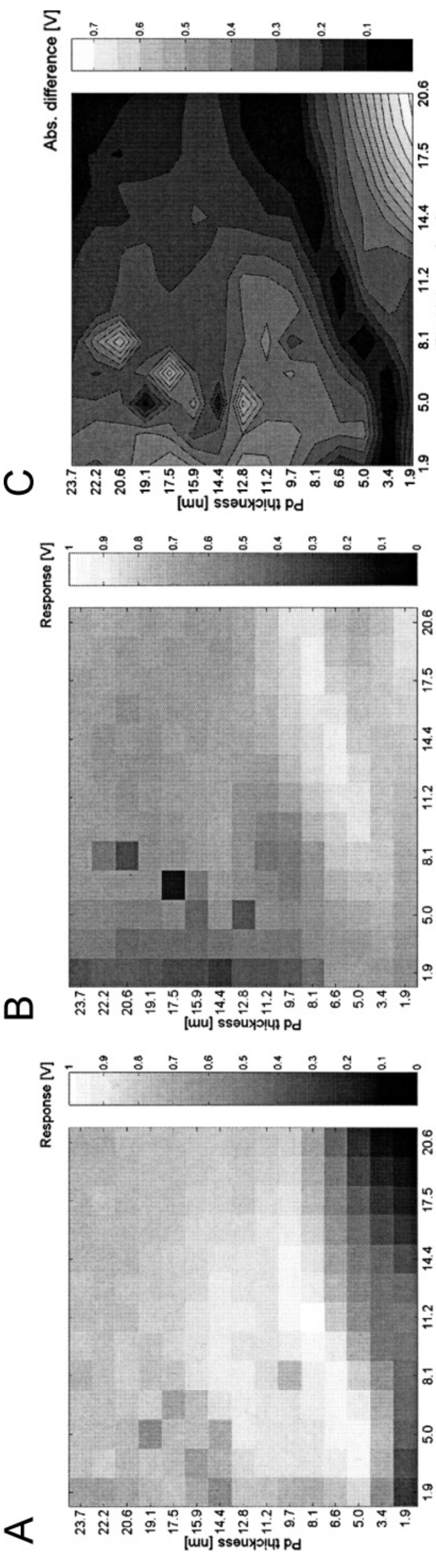

Figure 5. Results of the accelerated aging of 2-D combinatorial library of Rh/Pd film: chemical response images to 1000 ppm of hydrogen (A) before and (B) after the accelerated aging; (C) differential response after and before the accelerated aging (the most stable regions have the darkest color). Aging conditions: 24 h of exposure to 250 ppm of hydrogen at 400 °C. Reprinted with permission from ref 170. Copyright 2005 The Institute of Electrical and Electronics Engineers, Inc.

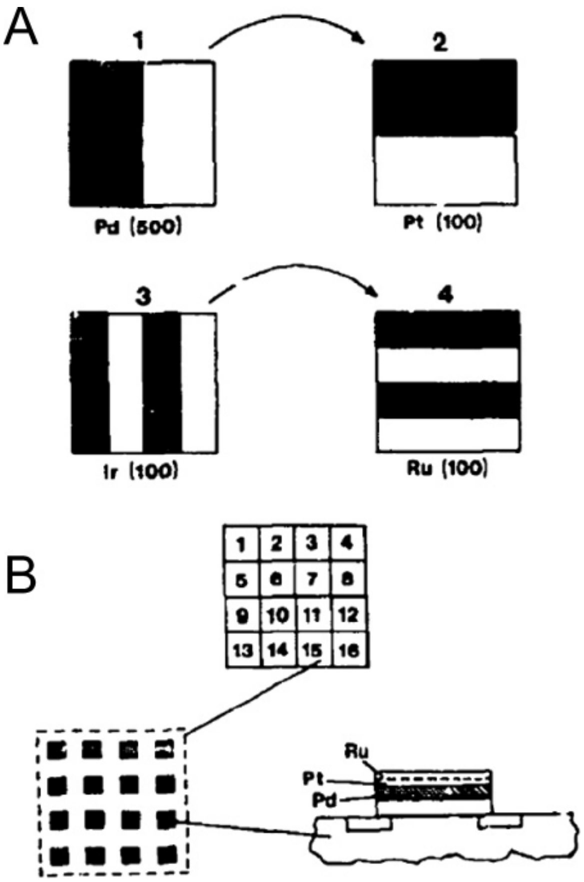

Figure 6. Use of binary masks for synthesis of a combinatorial library of catalytic metals for a gas-sensing field-effect chip to produce different selectivity patterns at different areas on the chip: (A) 16 different areas are obtained with variable metal compositions and 4 evaporation steps (1, 500 Å of Pd; 2, 100 Å of Pt; 3, 100 Å of Ir; 4, 100 Å of Ru); (B) example of the principal structure of the gate in area 15. The exact composition of the gates (alloys, mixtures, layered structures) depends on the metals used and the details of the fabrication methods. Reprinted with permission from ref 131. Copyright 1996 Elsevier.

gradient film surface demonstrated the existence of two of the most stable local regions. One region was a “valley” of a stable response shown as a dark color in Figure 5C. Another region was a thicker part of the two-component film with a ∼20 nm thick Rh film and a ∼23 nm thick Pd film. This new knowledge inspired new questions of position stability of the valley and the possibility to improve sensor stability by an initial annealing process.

In the developed SLPT methodology, the gate layers were typically electrically conducting metal films. To expand the applicability of this high-throughput screening technique to other functional materials beyond catalytic metals, a new grid gate structure has been developed.[177] This advancement made possible investigations of semiconductor or insulating materials with the possibility of studying nanometer-sized clusters of functional deposits in atmospheric conditions.

To make sensing films with multiple types of metals, Lundström[131] proposed to adapt a sensing film deposition strategy from combinatorial chemistry[178] and combinatorial materials synthesis[89] applications. In this approach, the desired pattern of sensing films can be produced using a set of binary masks and a mask that defines the gate areas on the chip. The use in sequence of only two shadow masks and four metal evaporation steps can give 16 areas with different gate metallizations (see Figure 6). These four evaporation steps ($n = 4$) through two masks will produce $2^n = 16$ different materials compositions. Such an approach should be very attractive in the future to study layered and alloyed multicomponent film compositions that are difficult or impossible to make using gradient deposition techniques.

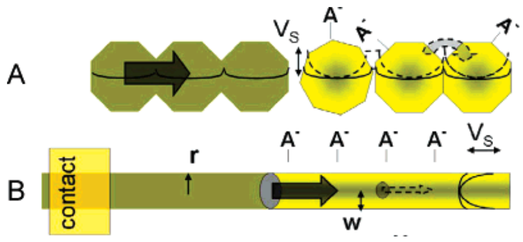

Figure 7. Key strategies for development of semiconducting metal oxide materials for conductometric sensors: (A) polycrystalline SnO_2, with two discontinuities; (B) single-crystal straight nanowire. Solid color and lines on the left correspond to vacuum or reducing conditions. Lighter areas on the right show the formation of depletion layers that reduce the effective diameter of the conducting channel (dashed arrows). A^- is adsorbed electron-acceptor species, V_S is adsorbate-induced Schottky barrier, r is the initial radius of the conducting channel in a straight nanowire, W is radius of the conducting channel upon adsorption. Reprinted with permission from ref 184. Copyright 2007 Institute of Physics Publishing.

3.2. Metal Oxides

3.2.1. Conductometric Metal Oxide Sensors

The origin of conductometric gas sensors that utilize semiconducting materials goes back to the 1950s to the discoveries of gas reaction effects with germanium by Brattein and Bardeen[179] and with semiconducting metal oxides by Heiland[180] and Bielanski and co-workers.[181] In the early 1960s, Seiyama[182] and Taguchi[183] fabricated the first such sensors.

At present, in conductometric sensors, semiconducting metal oxides are typically used as gas-sensing materials that change their electrical resistance upon exposure to oxidizing or reducing gases. While over the years significant technological advances have been made that resulted in practical and commercially available sensors, new materials are being developed that further improve the sensing performance of these sensors. Current strategies for materials development in this type of sensors are illustrated in Figure 7.[184]

The first strategy (Figure 7A) typically employs polycrystalline 2-D films in which electron transport is determined by dimensionally small interconnections between metal oxide grains. Assuming (1) a narrow size distribution of the electrically active grains in the sensing layer and hence homogeneous electrical properties, (2) percolation paths of the conductivity independent of the work function changes, and (3) constant mobility of the charge carriers in the nanoparticles, the sensor conductance G can be described as[185]

$$G = G_0 \exp\{[(E_C - E_F)_b - eV_S]/kT\} \tag{2}$$

where $(E_C - E_F)_b$ is the energy difference between the Fermi level and the conduction band in the bulk, e is the electron charge, and V_S is the band bending. In general, both $(E_C - E_F)_b$ and eV_S may change upon gas exposure.

The second strategy (Figure 7B) is based on adsorbate-induced change in the effective cross section of the conduct-

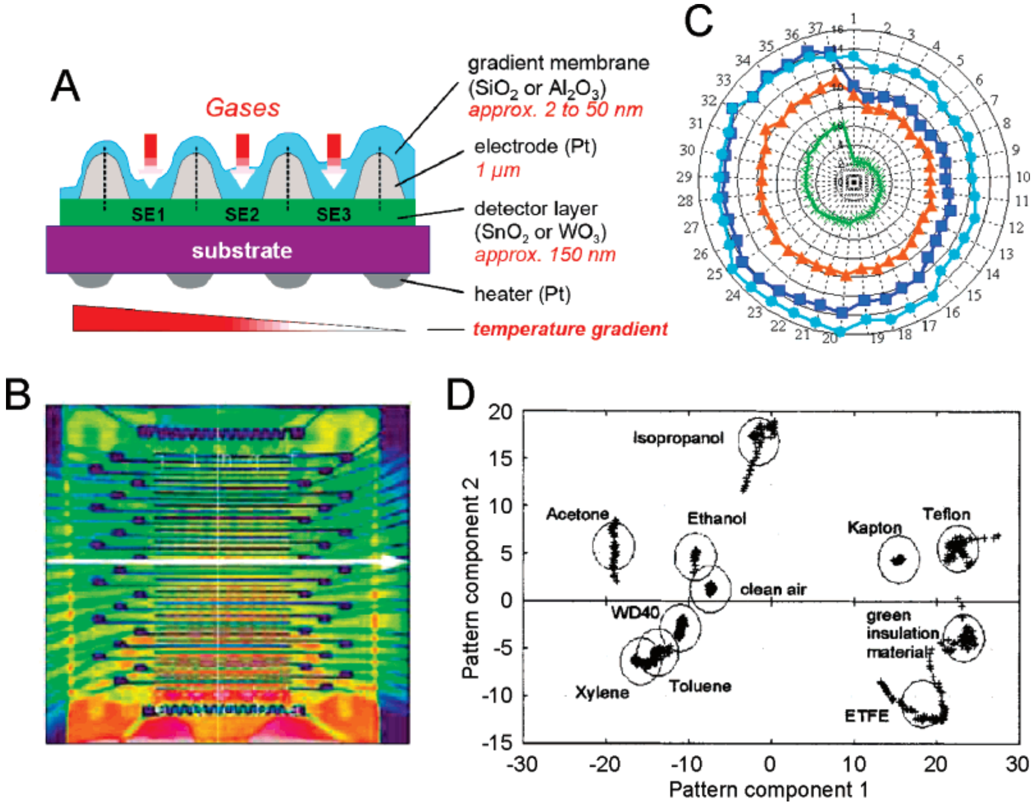

Figure 8. Double-gradient sensor microarray for selective gas detection. (A) Sensor schematic illustrating a single metal oxide thin film segmented by electrodes (SE) and arranged on a temperature gradient heater. The sensing film is further covered with a gradient thckness ceramic membrane. Used with kind permission from Goschnick. (B) False color thermal infrared image of the heated gradient sensor array with a temperature gradient of 6.7 °C/mm. The white arrow depicts the airflow direction. Reprinted with permission from ref 198. Copyright 2004 Molecular Diversity Preservation International. (C) Radar plot of resistance of 38 sensor segments operated with a temperature gradient from 310 to 360 °C (6.7 °C/mm). Resistance values (Mohm): acetone (red), ethanol (blue), ammonia (green), and propanol vapors (light blue). Reprinted with permission from ref 198. Copyright 2004 Molecular Diversity Preservation International. (D) Results of the linear discrimination analysis of the signal patterns in practical tests to detect gaseous precursors of smoldering fires induced by overheated cable insulation (ETFE: ethylene tetrafluorine ethylene). Reprinted with permission from ref 195. Copyright 2002 The Institute of Electrical and Electronics Engineers, Inc.

ing channel of a single-crystal nanowire from its initial radius r to the changed radius of the conducting channel W upon adsorption[184]

$$W \sim L_D(eV_S/kT)^{1/2} \qquad (3)$$

where L_D is the Debye length for the semiconductor metal oxide, which is a measure of the field penetration into the bulk, $L_D = (\epsilon\epsilon_0 kT/e^2 n_0)^{1/2}$, ϵ being the dielectric constant, ϵ_0 the permittivity of free space, and n_0 the carrier concentration. Details on these response mechanisms are available in several reviews.[12,186−191]

Realizing the opportunities that arise with the temperature dependence of the sensor response described by eqs 2 and 3, temperature-gradient-based sensors that utilize a single metal oxide thin film segmented by electrodes have been developed by Goschnick and co-workers.[192−198] In addition to the spatial temperature gradient heater, one of the designs of the sensor chip also had a SiO_2 or Al_2O_3 membrane with a gradient thickness from 2 to 50 nm (see Figure 8A).[199] Such a ceramic membrane provided an additional response selectivity[200] through the thickness-dependent gas transport.

To fabricate such a temperature and membrane gradient sensor, a gas-sensitive SnO_2:Pt film (Pt content of 0.8 atom %) was deposited onto a thermally oxidized Si wafer by RF magnetron sputtering using a shadow mask. Next, Pt strip electrodes and two meander-shaped thermoresistors were sputtered on the same side of the substrate as the SnO_2 film, under a shadow mask for structuring the films. The arrangement of the electrodes subdivided the monolithic SnO_2 film into 38 sensor segments on an area of 4 × 8 mm^2. Finally, Pt heaters were deposited onto the backside of the substrate to operate the chip with the 50 °C temperature gradient from 310 to 360 °C (see Figure 8B).[198] Operation of the sensor with the SnO_2:Pt film for the detection of acetone, ethanol, ammonia, and propanol vapors is illustrated in Figure 8C. The application of a temperature gradient increased the gas discrimination power of the sensor by 35%. The sensor with a SiO_2 gradient thickness membrane was employed for detection of gaseous precursors of smoldering fires induced by overheated cable insulation (see Figure 8D).[195]

The microstructure of the metal oxides deposited onto sensors depends on the deposition method (e.g., evaporation, sputtering, sol−gel techniques, aerosol methods, screen-printing) and material processing conditions.[12,201] For example, in chemical vapor deposition (CVD), one must choose suitable precursor chemistry, reagent gas concentrations, and precursor partial pressure to control the composition and microstructure of metal and metal oxide thin films.[202] Sputter deposition processes are typically sensitive to target condition, sputtering power, reactant concentrations, and substrate orientation. Nearly all deposition processes are strongly influenced by substrate temperature during and after deposition.

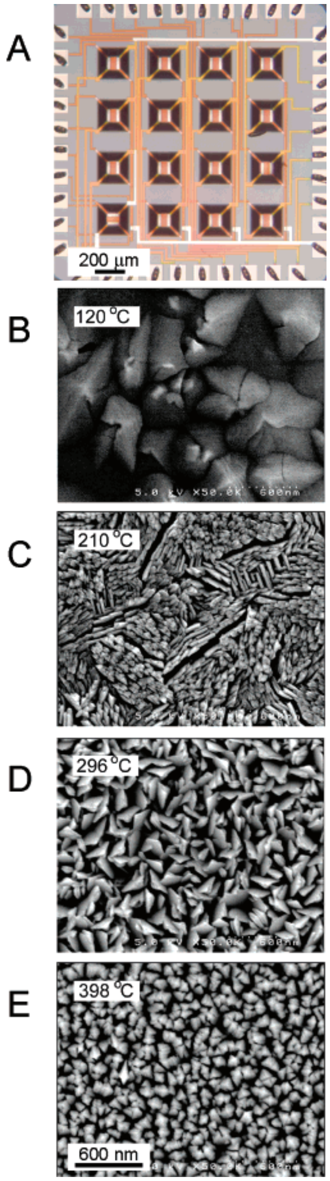

Figure 9. Results of CVD experiments with TiO_2 films performed using a single 16-element array and incremental deposition temperatures: (A) optical micrograph of a 16-element microhotplate array; (B−E) SEM microstructure images for four elements within the 16-element microarray. Dependence of microstructure on deposition temperature (^{o}C): (B) 120; (C) 210; (D) 296; (E) 398. Reprinted from ref 202.

Semancik and co-workers have applied arrays of micromachined silicon microhotplates as a platform to tailor metal oxide thin film properties for microsensors for gas detection in air[203−207] and for volatile organic compounds in water.[208] To screen materials properties, microarrays of 4, 16, 36, and 48 individually addressable elements, each element with its own independent heating and electrical probe contacts, were employed. The nominal size and mass of the suspended structure were 100×100 μm and 0.2 μg, respectively. The low thermal mass and embedded heater enabled heat rates of 10^5−10^6 °C/s and operation temperatures of >500 °C. Figure 9 depicts representative results of CVD experiments with TiO_2 films performed using a single 16-element array and incremental deposition temperatures to illustrate the microstructure's temperature dependence when $Ti(NO_3)_4$ was used as the precursor.[202] At the lowest deposition temperature, formation of large grains was observed. With the increase in deposition temperature to 250 °C, the large grains subdivided along a particular crystallographic direction and formed a plate-like microstructure. Increasing the deposition temperature further to 400 °C caused these plates to subdivide into smaller grains.

In the studies by Semancik and co-workers, the TiO_2 was in the anatase form as shown by X-ray diffraction data.[209] The anatase and rutile crystalline structures of TiO_2 have different growth kinetics, thermodynamic stabilities, surface energies, and physicochemical properties. Thus, to facilitate the understanding of the mechanisms underlying gas response, Mazza et al. developed a method for the fabrication of libraries of nanostructured TiO_2 films with a controlled gradient of the rutile/anatase ratio, film thickness, morphology, and crystalline dimensions.[210] This was obtained by using rutile <10 nm diameter clusters as seeds for crystal growth in competition with anatase nucleation from the amorphous phase. With a simple one-step postdeposition thermal treatment, a 14×15 array with individual 1×1 mm^2 chemoresistive sensing elements was formed and characterized for vapor response at 300−500 °C. Nanostructured TiO_2 films with variable anatase/rutile ratio were controlled independently from the size of the nanoparticles that allowed detailed exploration of chemical and process conditions parameters. Using a micro-Raman mapping, the relative abundance of the rutile/anatase phases in annealed samples was determined as shown in Figure 10A. These determinations were done by examining the Raman E_g mode of anatase (144 cm^{-1}) and E_g and A_{1g} modes of rutile (447 and 612 cm^{-1}); those intensities depend on abundances. Measurements of vapor response were performed using a volt amperometric technique at a constant 10 V potential and measuring the resultant current.[211] The variation of conductance ΔG can be described as $\Delta G/G = AC_g{}^B$, where A and B are empirically determined constants related to the temperature, grain size, film porosity, and gas adsorption.[211] Figure 10B shows responses to 200 ppm of methanol from three representative locations in the array. The sensitivity of the sensors was found to be correlated to the rutile/anatase ratio of the sensing layers.

To enhance the response selectivity and stability, an accepted approach is to formulate multicomponent materials that contain additives in metal oxides. Introduction of additives into base metal oxides can change a variety of materials properties including concentration of charge carriers, energetic spectra of surface states, energy of adsorption and desorption, surface potential and intercrystallite barriers, phase composition, sizes of crystallites, catalytic activity of the base oxide, stabilization of a particular valence state, formation of active phases, stabilization of the catalyst against reduction, the electron exchange rate, etc.[12,189] Dopants can be added at the preparation stage (bulk dopants) that will affect the morphology, the electronic properties of the base material, and its catalytic activity. However, the fundamental effects of volume dopants on base materials are not yet predictable.[212] Addition of dopants to the preformed base material (surface dopants) can lead to different dispersion and segregation effects depending on the mutual solubility[12] and influence of the overall oxidation state of the metal oxide surface.[12,188,189,212] The diverse optimization parameters during the preparation of metal oxide sensing films are summarized in Figure 11.

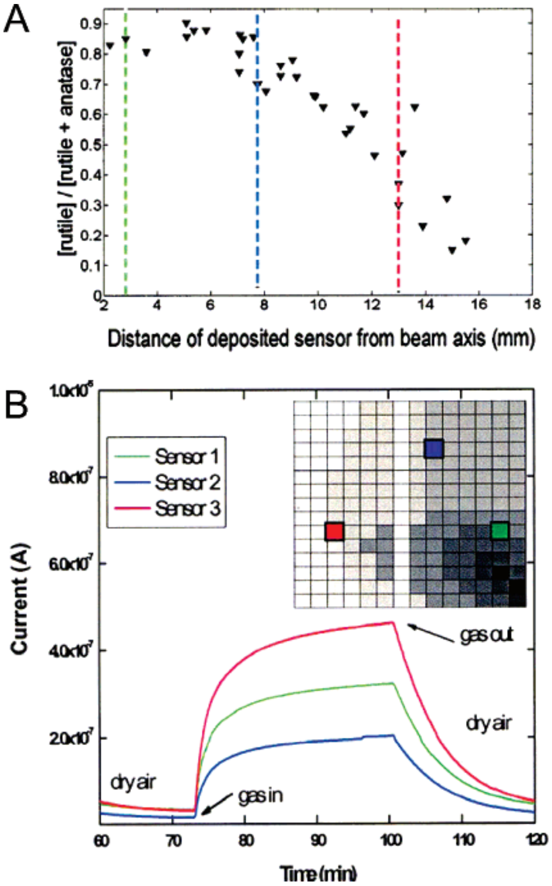

Figure 10. Screening of vapor response of cluster-assembled nanostructured TiO_2 films with a gradient in the rutile/anatase ratio: (A) quantitation of rutile/anatase ratio from ratiometric Raman analysis; (B) dynamical response of three sensors exposed to 200 ppm of methanol. (Inset) Map of the deposited sensor 14 × 15 element array; gradient in film thickness is shown as gray scale. The central white column indicates no deposition of TiO_2. Green, blue, and red dashed vertical lines in (A) indicate corresponding sensor responses in (B). Reprinted with permission from ref 210. Copyright 2005 American Institute of Physics.

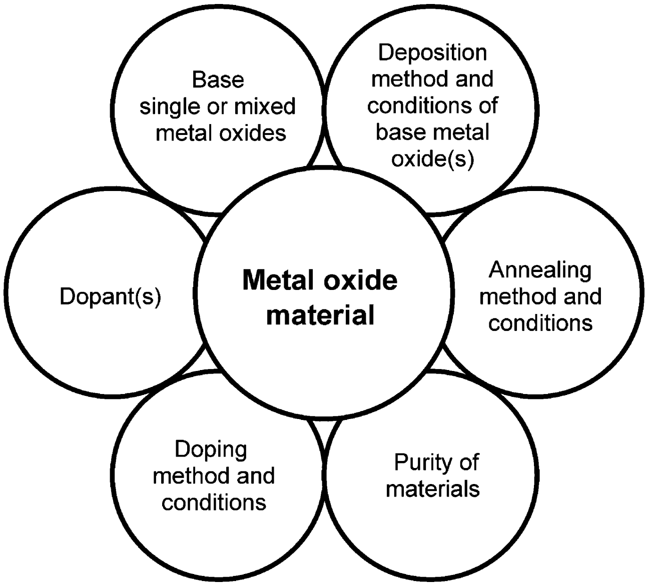

Figure 11. Diversity of optimization parameters during the preparation of metal oxide sensing materials.

To improve the productivity of materials evaluation by using combinatorial screening, Semancik and co-workers employed 36-element sensor arrays to evaluate various surface-dispersed catalytic additives on equivalent CVD SnO_2 films.[213,214] Catalysts were deposited by evaporation to nominal thicknesses of 3 nm, and then the microhotplates were heated to effect the formation of a discontinuous layer of catalyst particles on the SnO_2 surfaces. The layout of the fabricated 36-element library is shown in Figure 12A. The response characteristics of SnO_2 with different surface-dispersed catalytic additives are presented in Figure 12B. These radar plots show sensitivity results to benzene, hydrogen, methanol, and ethanol for operation at three temperatures.

Fabrication of gas sensor materials was also demonstrated using a combinatorial pulsed-laser deposition (PLD) approach that provides a spatially selective deposition of compositionally varying discrete or gradient samples with arbitrary layout designs.[215] Takeuchi and co-workers fabricated thin-film combinatorial gas sensor libraries based on doped semiconducting SnO_2 thin films.[216] Deposition of 50 nm thick sensor films of different compositions was performed at 550 °C on 2 × 2 mm Au electrode patterns (see Figure 13A). The electrode patterns were fabricated on Al_2O_3 substrates using a photolithographic lift-off process prior to the sensor film deposition. Each sensor array consisted of 16 different compositions of the SnO_2 host material and ZnO, WO_3, In_2O_3, Pt, and Pd dopants, added to modify the selectivity pattern of the sensors.[186,217] The ability of the developed materials to distinguish different gas species is depicted in Figure 13B for responses to 100 ppm of chloroform, formaldehyde, and benzene. Each gas produced a different response pattern with the five sensing materials. The response patterns for different gases were distinct with gas concentrations down to 12.5 ppm. It was suggested that this combinatorial PLD technique can be applied for not only screening of different dopants in SnO_2 and other semiconducting films but also for manufacturing of compact sensor arrays.

To expand the capabilities of screening systems, it is attractive to characterize not only the conductance of the sensing materials with DC measurements but also their complex impedance spectra.[218] The use of complex impedance spectroscopy provides the capability to test both ion- and electron-conducting materials and to study electrical properties of sensing materials that are determined by the material microstructure, such as grain boundary conductance, interfacial polarization, and polarization of the electrodes.[219,220] Simon and co-workers designed and built a 64 multielectrode array for high-throughput impedance spectroscopy ($10-10^7$ Hz) of sensing materials (see Figure 14A).[219] In this system, an array of interdigital capacitors was screen-printed onto a high-temperature-resistant Al_2O_3 substrate. To ensure the high quality of determinations, parasitic effects caused by the leads and contacts have been compensated by a software-aided calibration.[219] After the system validation with doped In_2O_3 and automation of the data evaluation,[220] the system was implemented for screening of a variety of additives and matrices with the long-term goal to develop materials with improved selectivity and long-term stability. Sensing films were applied using robotic liquid-phase deposition based on optimized sol−gel synthesis procedures. Surface doping was achieved by the addition of appropriate salt solutions followed by library calcination. Screening results at 350 °C of thick films of WO_3 and In_2O_3 base oxides surface doped with various metals are presented as bar diagrams in Figure 14B,C, respectively.[221,222] The

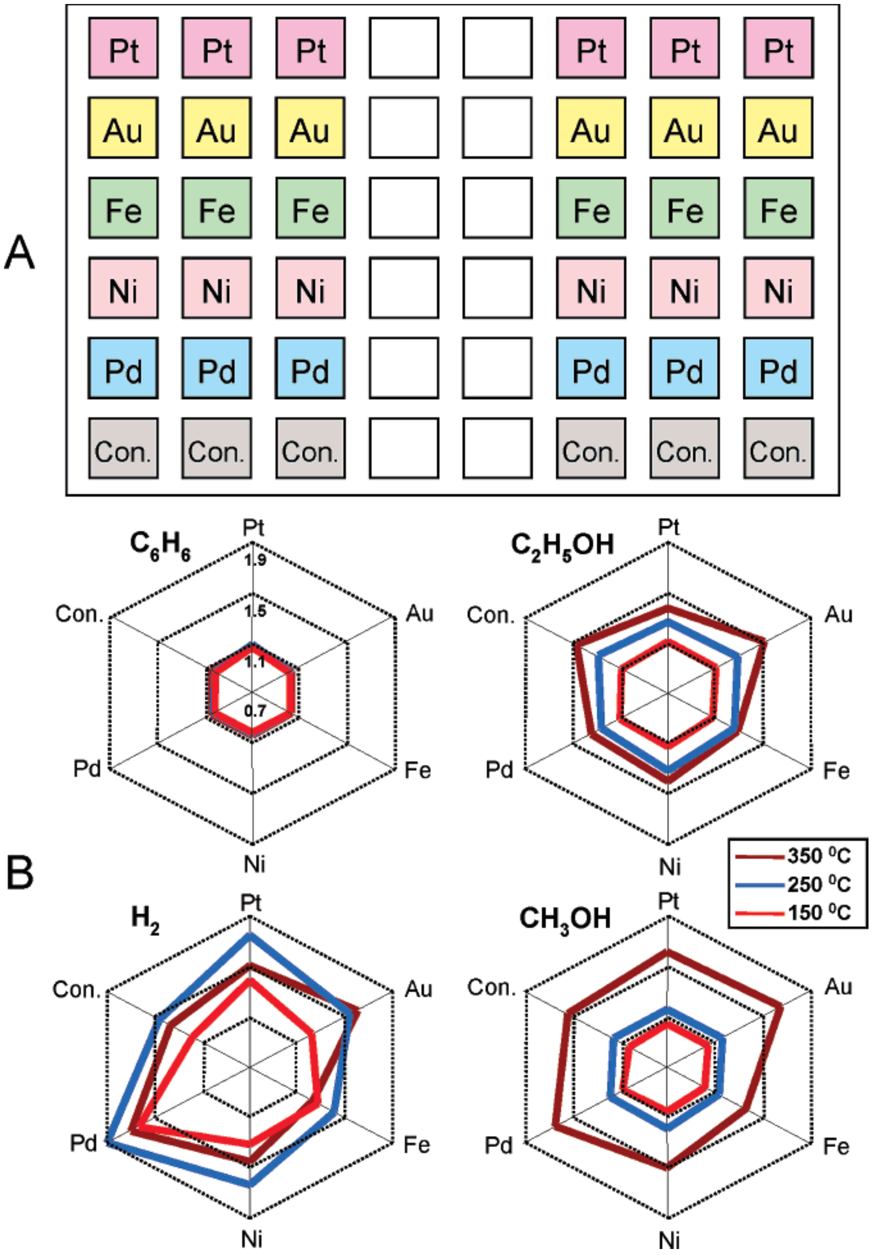

Figure 12. Combinatorial study of effects of surface dispersion of metals into CVD-deposited SnO_2 films: (A) layout of a 36-element library for study of the sensing characteristics of SnO_2 films with 3 nm of surface-dispersed Pt, Au, Fe, Ni, or Pd (Con. = control; each sample was made with six replicates); (B) radar plots of sensitivity results to benzene, hydrogen, methanol, and ethanol for operation at 150, 250, and 350 °C. Reprinted from ref 213.

effects of various surface doping elements on the gas-sensing properties of In_2O_3 thick films sensors at multiple temperatures over 250−400 °C are compared in Figure 14D.[222] It was found that some doping elements lead to changes in both the conductivity in air and gas-sensing properties toward oxidizing (NO_2, NO) and reducing (H_2, CO, propene) gases. Correlations between the sensing and the electrical properties in reference atmosphere indicated that the effect of the doping elements was due to an influence on the oxidation state of the metal oxide surface rather that to an interaction with the respective testing gases.

This accelerated approach for generating reliable systematic data was further coupled to the data mining statistical techniques that resulted in the development of (1) a model associating the sensing properties and the oxidation state of the surface layer of the metal oxide based on oxygen spillover from doping element particles to the metal oxide surface and (2) an analytical relationship for the temperature-dependent conductivity in air and nitrogen that described the oxidation state of the metal oxide surface, taking into account sorption of oxygen.[222]

Simon and co-workers further employed this high-throughput complex impedance screening system for the reliable screening of a wide variety of less explored material formulations. Polyol-mediated synthesis has been known as an attractive method for the preparation of nanoscaled metal oxide nanoparticles.[223] It requires only low annealing temperatures and provides the opportunity to tune the composition of the materials by mixing the initial components on the molecular level.[224,225] To explore previously unknown combinations of p-type semiconducting nanocrystalline $CoTiO_3$ with different volume dopants as sensing materials, the polyol-mediated synthesis method was used to synthesize nanometer-sized $CoTiO_3$ followed by the volume-doping

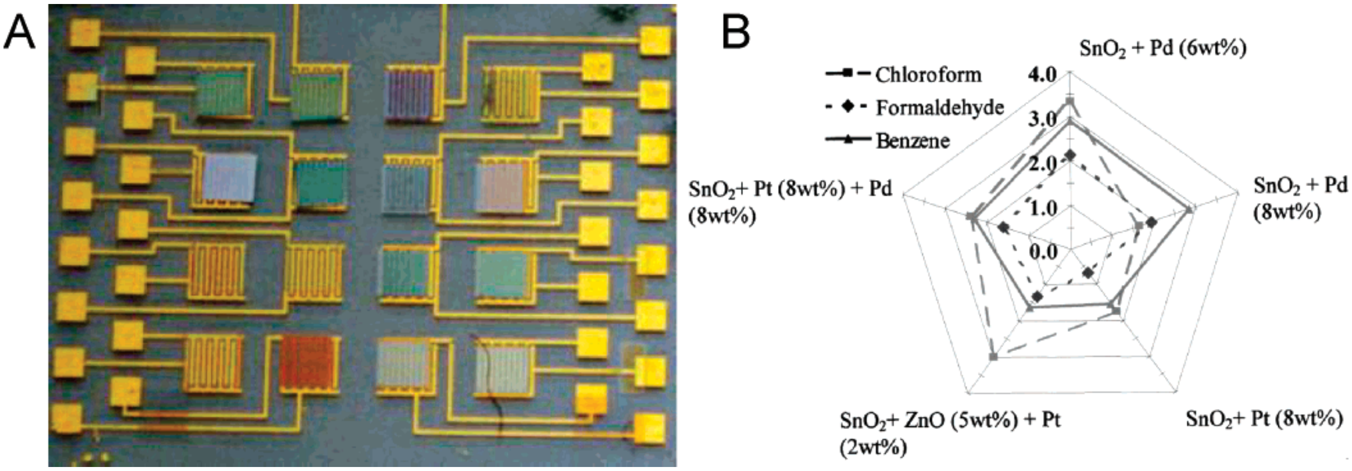

Figure 13. Application of a microfabricated electrode sensor array for evaluation of gas responses of doped semiconducting PLD-deposited SnO_2 thin films: (A) microfabricated electrode sensor array; (B) radar plot of the normalized drift-corrected resistance change of five sensors to different gases at 400 °C. Reprinted with permission from ref 216. Copyright 2003 American Institute of Physics.

with Gd, Ho, K, La, Li, Na, Pb, Sb, and Sm (all at 2 atom %). The SEM-estimated primary particle size of the volume doped $CoTiO_3$ materials was in the range from 30 to 140 nm, with the smallest particle size for $CoTiO_3$:La and the largest for $CoTiO_3$:K.

From the temperature-dependent responses to propylene and ethanol, it was discovered that the $CoTiO_3$:La [with a precursor of 0.730 mmol of $Ti[OCH(CH_3)_2]_4$ and 0.715 mmol of $Co(CH_3COO)_2 \cdot 4H_2O$] had an outstanding ethanol response compared to all other materials and insensitivity to air humidity [0−90 % relative humidity (RH)]. Evaluation of response selectivity was tested for all materials in the library. The selectivity of the volume-doped materials toward ethanol is shown in Figure 15A, demonstrating that highest selectivity (at 425 °C) was found for $CoTiO_3$:Pb and $CoTiO_3$:K. Because of the highest ethanol sensitivity, the new promising $CoTiO_3$:La material was further used for the long-term stability testing in 45% RH air for 200 h to examine the baseline stability and reproducibility of the signal change to a given analyte concentration. The stability test for $CoTiO_3$:La was done by periodic measurements of the sample resistance in air and the response and recovery behavior toward propylene (20 ppm) every 12 h as shown in Figure 15B. Doping strategy for this $CoTiO_3$:La material has been also expanded with its surface doping with various metals (Au, Ce, Ir, Pd, Pt, Rh, Ru) in different concentrations (0.2−0.6 atom %).[224] The enormous productivity of this high-quality, high-throughput experimentation approach has been further demonstrated in the fabrication and testing of p-type semiconducting perovskite-type $LnMO_3$ (Ln = La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu; M = Cr, Fe) oxides. It was found that these materials exhibited a correlation between the (Ln−O) binding energy and the gas-sensing properties.[226]

It is known that there are some similarities between chemical sensing and heterogeneous catalysis, making catalytic activity of materials an important (but not a determining) parameter for sensing materials selection.[189,190] Because of the possibility of similarity between the sensing and catalytic activity of materials, Maier and co-workers prepared libraries of sensing materials with different base oxides (WO_3, SnO_2, TiO_2, ZrO_2, In_2O_3, Bi_2O_3, Ce_2O_3) and bulk and/or surface dopants (Ag, Au, Ce, Co, Cu, Er, Fe, Gd, Lu, Mn, Pr, Ru, Sc, Sm, Tb, Th, Ti, V, Y, Yb)[227] and evaluated their catalytic activity by the emissivity corrected IR-thermography, as previously applied to heterogeneous catalysis.[99] The motivation for the use of the IR-thermography was to use it as a rapid primary screening tool, capable of discovering new compositions with sensor properties. As a control, response of these materials at 250−400 °C was evaluated concurrently by resistance measurements. It was found that emissivity-corrected IR-thermography, although providing rapid imaging capability, ranked tested materials with deviations from the ranking obtained using automated resistive measurements.[227] In particular, it was found that most materials (except the noble metal dopants) did not show the thermography/resistivity correlation (see Figure 16).[228] The thermography/resistivity correlation for doped WO_3 was slightly better than that for doped In_2O_3.[228] Possibly, the materials-ranking ability of the IR-thermography could be improved when applied for screening of more diverse types of sensing materials including those operating at relatively low, even room, temperatures.[190]

The enormous amount of data collected during these experiments facilitated the successful efforts of Maier, Simon, and co-workers to develop data mining techniques[229,230] and a database system.[231] The developed data mining tools (see Figure 17) have been successfully applied to identify from resistance measurements several promising materials candidates such as $In_{99.5}Co_{0.5}O_x$, $W_{99}Co_{0.5}Y_{0.5}O_x$, $W_{98.3}Ta_{0.2}Y_1Mg_{0.5}O_x$, $W_{99.5}Ta_{0.5}O_x$, and $W_{99.5}Rh_{0.5}O_x$ with different gas-selectivity patterns.[232]

The formation of mixed oxides has an enormous potential for sensing materials originating from the opportunities for tailoring of chemical composition, microstructure, porosity, and surface properties.[232−234] In contrast to crystalline materials, these amorphous mixed oxides are prepared under mild reaction conditions in ambient atmosphere, making available a variety of precursors, additives, modifiers, solvents, catalysts, and post-treatment conditions to provide numerous fine-tuning options. The functional properties of such solids are largely unexplored[234] and provide a tremendous opportunity for the development of new sensing materials. The facile preparation and accessibility of these materials make them ideally suited for the application of high-throughput technologies to allow investigators for the first time to access and optimize mixed oxides on a realistic time scale.[234] Initial results include the works by Maier and co-workers[232] on In_2O_3/WO_3 libraries and by Lee and co-workers[233] on SnO_2/ZnO libraries.

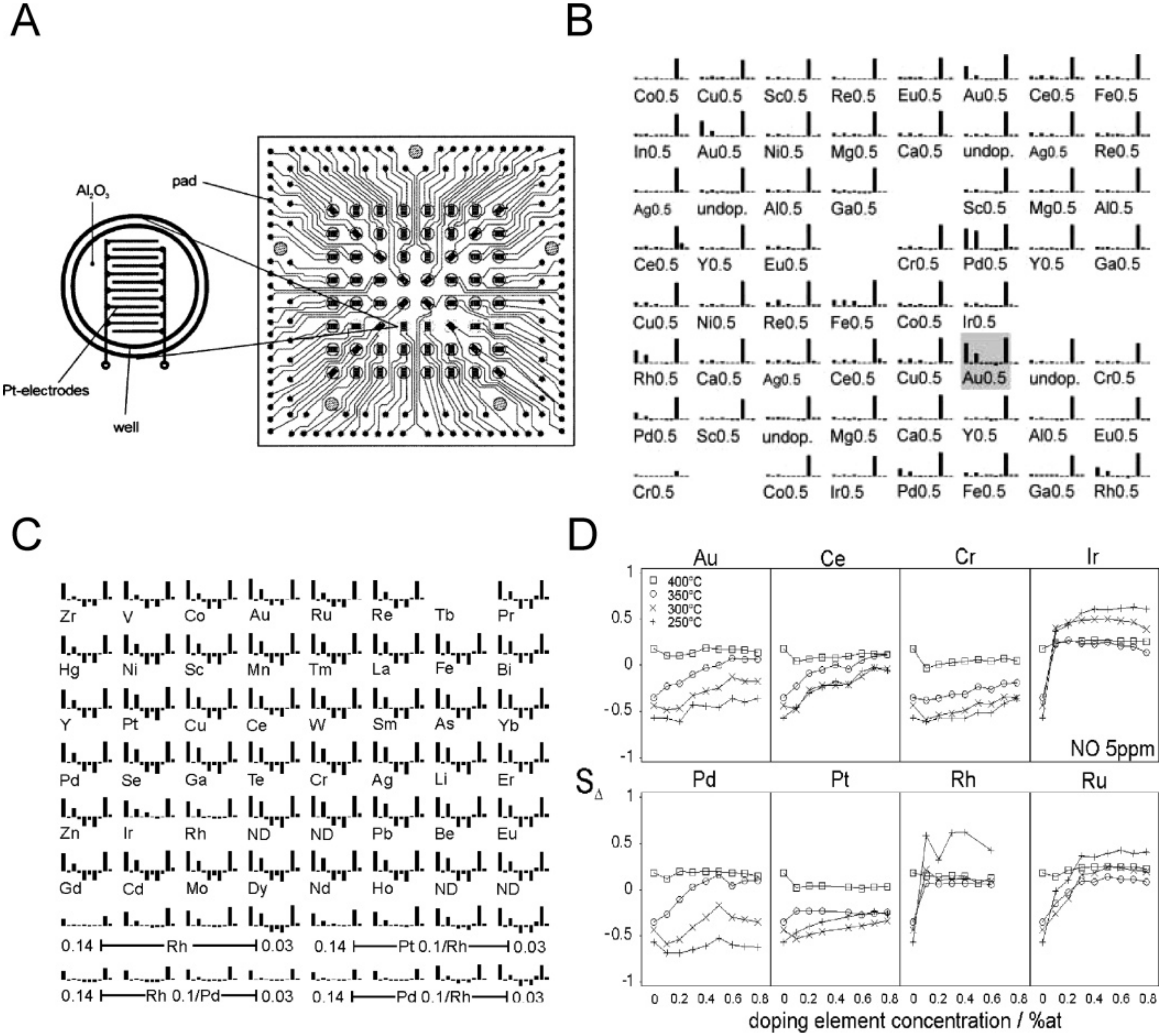

Figure 14. Screening of sensor metal oxide materials using complex impedance spectroscopy and a multielectrode 64-sensor array. (A) Layout of 64-sensor array. Reprinted with permission from ref 219. Copyright 2002 American Chemical Society. (B) Relative gas sensitivities at 350 °C of the WO_3 base oxide materials library surface-doped with multiple salt solutions, all at 0.5 atom % (bulk dopant, 0.5 atom % Ta). Sequence of test gases and their concentrations (with air between) was H_2 (50 ppm), CO (50 ppm), NO (5 ppm), NO_2 (5 ppm), and propene (50 ppm). Reprinted with permission from ref 221. Copyright 2004 Wiley-VCH Publishers. (C) Relative gas sensitivities at 350 °C of the In_2O_3 base oxide materials library surface-doped with multiple salt solutions; concentration 0.1 atom % if not denoted otherwise; ND = undoped. Sequence of test gases and their concentrations (with air between) was H_2 (25 ppm), CO (50 ppm), NO (5 ppm), NO_2 (5 ppm), and propene (25 ppm). Reprinted with permission from ref 222. Copyright 2007 American Chemical Society. (D) Dependence of the relative gas sensitivities on the concentration of doping elements of a library type shown in (C). Reprinted with permission from ref 222. Copyright 2007 American Chemical Society.

In the area of metal oxide sensing materials, combinatorial techniques will tackle very challenging and rewarding directions in the development of conceptually new materials that will provide new applications for practical metal oxide sensors. One significant application area could be to develop metal oxide materials that will be sensitive, selective, stable and free from water interferences when operating at low (80−150 °C) and room temperatures.[235−240] Such materials will become a foundation for a new generation of low-power sensors. The second significant application area is sensors for exhaust monitoring in diesel engines and other harsh environment applications.[241,242] Although diesel engines are one of the greener technologies, the operation temperatures of these engines are too high for conventional metal oxide sensors. Thus, development of new sensing materials that will in situ selectively detect pollutants at high temperatures (500−700 °C) could be another focus area for combinatorial experimentation.

3.2.2. Cataluminescent Metal Oxide Sensors

In 1976, Breysse and co-workers[243] observed a chemiluminescence emission during a catalytic oxidation of carbon monoxide on thoria. Because this emission was due to the catalytic effect, it was named cataluminescence (CTL). Oxidation of gas molecules at the surface of the solid catalyst is the heterogeneous catalytic reaction. The mechanism of the CTL emission involves recombinant radiation and radiation from excited species.[244] The reaction process is

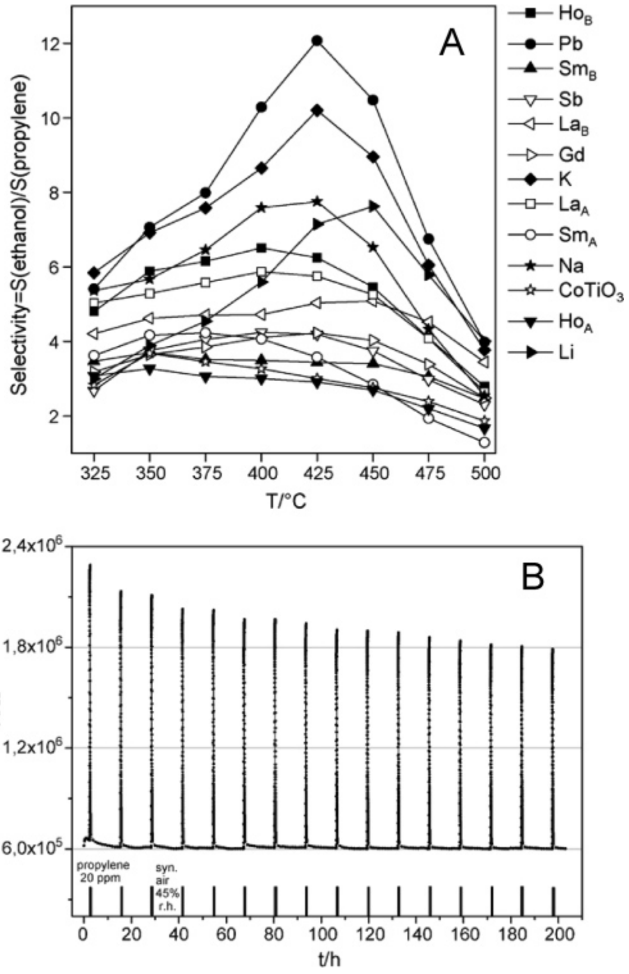

Figure 15. Performance of nanometer-sized $CoTiO_3$ synthesized via the polyol method with different volume dopants: (A) results of high-throughput screening of response selectivity to ethanol; (B) evaluation of long-term stability of CoTiO3:La at 400 °C. Reprinted with permission from ref 225. Copyright 2007 Elsevier.

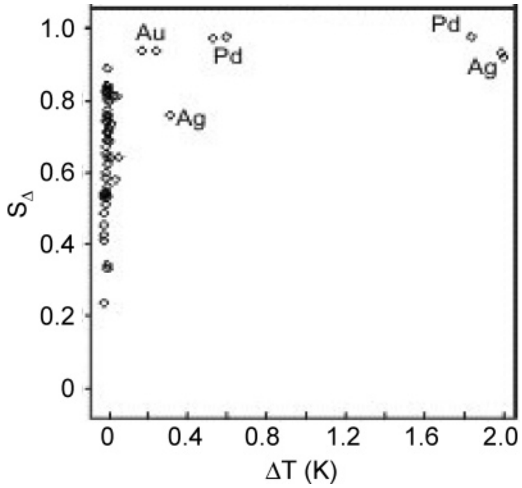

Figure 16. Correlation between temperature change and relative gas sensitivity of a library of In_2O_3 sensing films doped with a wide variety of surface dopants including different concentrations of noble metal (Au, Ag, Pd) dopants upon exposure to H_2 at 350 °C. Used with kind permission of Maier and Simon.[228]

schematically depicted in Figure 18 and involves five stages. Initially, gas molecules R and O diffuse from the outer gas phase and reach the proximity of the catalyst surface. Next, gas molecules are chemisorbed to form R_{ad} and O_{ad} on the catalyst surface with a part of the adsorbate desorbed to the gas phase. Furthermore, chemisorbed R_{ad} and O_{ad} react to produce chemisorbed RO_{ad} on the surface. Next, the reaction product RO is desorbed from the surface. Finally, RO diffuses off to the gas phase. Upon exposure to different organic vapors, the CTL emission effect has been observed on a variety of nanosized materials with different particle sizes such as MgO (~28 nm), TiO_2 (~20 nm), Al_2O_3 (~18 nm), Y_2O_3 (~90 nm), $LaCoO_3$:Sr^{2+} (~50 nm), and $SrCO_3$ (~25 nm).[245] ZnO nanoparticles were shown to have the CTL upon exposure to ethanol.[246]

The rate of CTL emission strongly depends on temperature through the rate of formation of chemisorption surface state

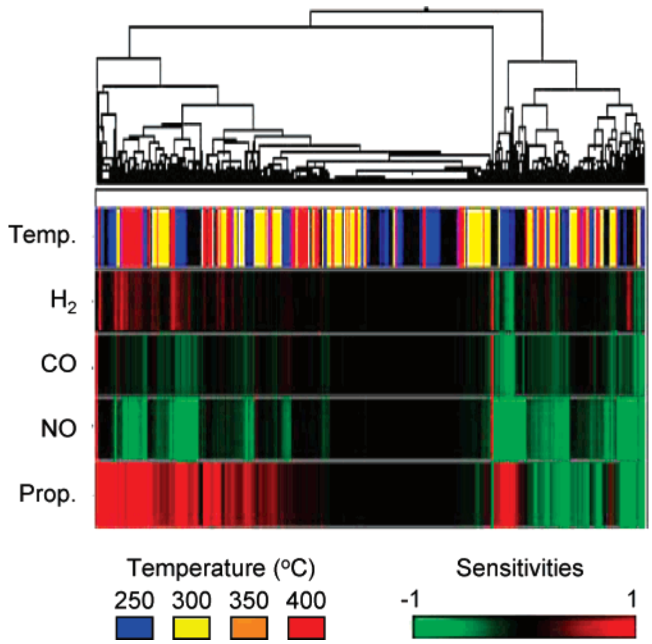

Figure 17. Hierarchical clustering map of 2112 responses of diverse sensing materials to H_2, CO, NO, and propene (Prop.) at four temperatures established from the high-throughput constant current measurements and processed with Spotfire data-mining software (clustering algorithm was "complete linkage" of the Euclidean distances). Reprinted with permission from ref 232. Copyright 2006 Molecular Diversity Preservation International.

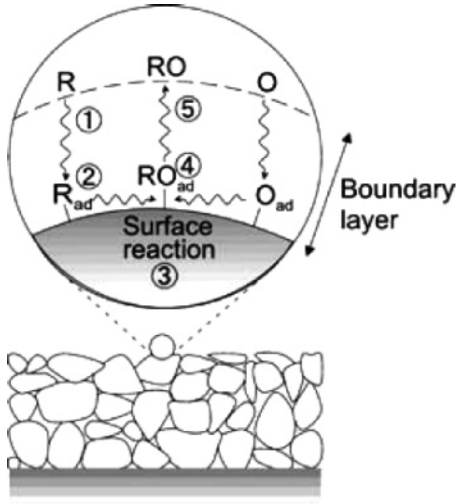

Figure 18. Five stages of the heterogeneous catalytic reaction process that produce cataluminescence emission through the recombinant radiation and radiation from excited species. See text for details. Reprinted with permission from ref 244. Copyright 2005 Springer.

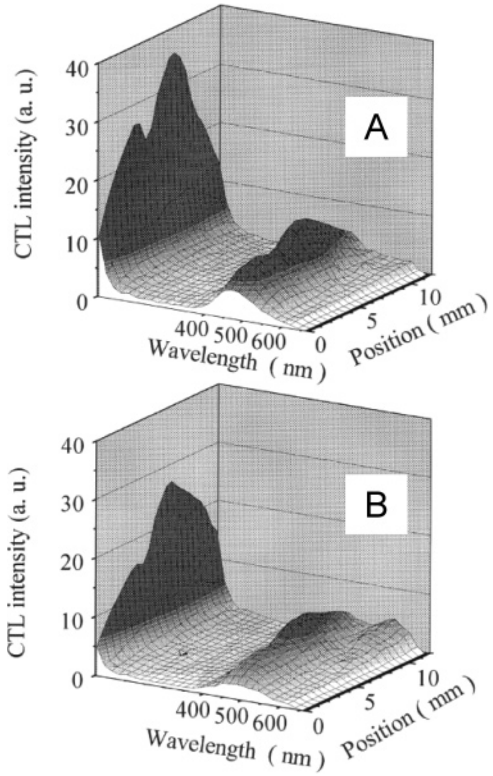

Figure 19. Spectroscopic images on the cataluminescence emission-based sensor under the gradient temperature distribution from 440 to 530 °C over the 12 mm of heater length: (A) response to 800 ppm of ethanol in air; (B) response to 250 ppm of acetone in air. Reprinted with permission from ref 247. Copyright 1998 Elsevier.

or production of excited species. Nakagawa and co-workers[247] developed a temperature gradient technique coupled with spectroscopic imaging to evaluate the sensing capabilities of different candidate materials during catalytic oxidation of organic vapors as a function of temperature and wavelength. A 12 mm long gradient heater was operated to produce a 90 °C temperature gradient from 440 to 530 °C. Figure 19 illustrates typical results obtained from the temperature gradient experiments.

Several degrees of freedom were suggested for the discrimination of different vapors. These included the vapor-dependent ratio of CTL emission peaks, the activation energy of the CTL, and the temperature at the turning point of the CTL intensity peak in temperature dependence. In addition, it was possible to construct a sensor array that contained nanosized $SrCO_3$, γ-Al_2O_3, and $BaCO_3$ for quantitative analysis of explosive gases such as propane, *n*-butane, and isobutane in tertiary mixtures with detection limits in the 5−80 ppm range.[248]

Future possible improvements for the CTL sensor materials could be in the areas of discovery of catalysts with better selectivity, more active catalysts for lower temperature of operation, activators of the catalysts that emit at shorter wavelengths to avoid incandescent radiation, and higher efficiency emission catalysts.[244]

3.3. Plasmonic Nanomaterials

3.3.1. Nanoscale Materials for Surface-Enhanced Raman

In a recent article,[249] Van Duyne provided a brief historical perspective on difficulties to accept unpredicted concepts in science. After numerous rejections, the eventual publication of the discovery of the surface enhancement Raman scattering (SERS) cross section[250] is a classical example of slow acceptance by fellow scientists of new phenomena that are difficult or impossible to predict using rational approaches. At present, two commonly considered mechanisms for SERS include an electromagnetic enhancement and a chemical enhancement.[251] For plasmonic structures and appropriate excitation conditions, the electromagnetic enhancement mechanism dominates. In this mechanism, the SERS enhancement factor EF at each molecule is a result of enhancing the incident excitation electromagnetic field $E_{\mathrm{out}}(\omega)$ and the resulting Stokes-shifted Raman electromagnetic field $E_{\mathrm{out}}(\omega - \omega_\nu)$. The SERS electromagnetic enhancement factor is given by[252]

$$\mathrm{EF}_{\mathrm{SERS}}(\omega_\nu) = \frac{|E_{\mathrm{out}}(\omega)^2|\,|E_{\mathrm{out}}(\omega - \omega_\nu)^2|}{E_0^{\,4}} \qquad (4)$$

where E_0 is the magnitude of the applied field. On the basis of experimental measurements, the enhancement factor can be calculated from the SERS-enhanced Raman intensity $I_{\mathrm{SERS}}(\omega_\nu)$ normalized by the number of molecules bound to the enhancing metallic substrate N_{surf} by dividing the normal Raman intensity $I_{\mathrm{NRS}}(\omega_\nu)$ normalized by the number of molecules in the excitation volume N_{vol} given by[252]

$$\mathrm{EF}_{\mathrm{SERS}}(\omega_\nu) = \frac{\{I_{\mathrm{SERS}}(\omega_\nu)/N_{\mathrm{surf}}\}}{\{I_{\mathrm{NRS}}(\omega_\nu)/N_{\mathrm{vol}}\}} \qquad (5)$$

Reports on the enormously large SERS enhancement factors of $10^{14}-10^{15}$ have facilitated the single-molecule detection[253,254] and have inspired the development of new sensing materials. The SERS enhancements of $10^{8}-10^{10}$ are required to detect a single molecule.[255] The maximum electromagnetic enhancement factor at the single-particle level was calculated[256] to be $\sim 10^{11}$ and can be obtained at interstitial sites between particles and at locations outside sharp surface protrusions. It was suggested that the rest of the enhancement has to be contributed from the chemical enhancement. There are three types of the charge-transfer process that contribute to the chemical enhancement:[257] (1) the change of molecular polarizability when the molecule interacts with the surface or other surface species; (2) the change of molecular polarizability when the molecule forms a surface complex with a metal ion or electrolyte ion; and (3) the photon-driven charge-transfer process that occurs when the incident laser energy matches the energy difference between the surface molecules' HOMO or LUMO and Fermi level or surface state of the metal substrate. A chemical enhancement of 10^7 from Au bow-tie nanoantennas has been reported,[258] which is much larger than previously believed ($10-10^4$). Detection of SERS has been accomplished on chemical systems with small or no plasmon resonance contributions, including small Ag clusters such as Ag_8 and Ag_{20} (10^5 enhancement)[259,260] and semiconductor nanocrystals (10^4 enhancement).[261,262]

Combinatorial approaches have been applied to optimize metallic SERS substrates. These approaches include 2-D variation of nanoparticle density to discover the existence of an optimal surface coverage for the most effective SERS enhancement[132] and combinatorial exploration of the roughness effects of metallic substrates.[263] Natan and co-workers[132] proposed that the SERS enhancement of optimized periodic

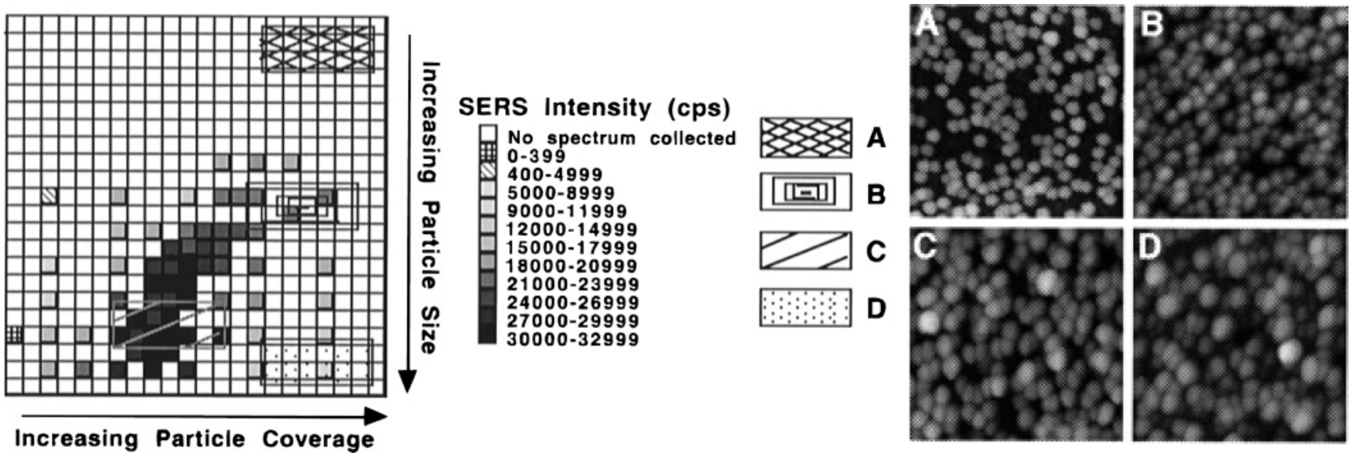

Figure 20. Combinatorial discovery of the most active SERS region from a 2-D gradient of variable surface coverage of 12 nm diameter Au nanoparticles and the variable thickness of Ag shell: (left) background-subtracted SERS intensity map for the 1168 cm^{-1} phenylnitroso stretch of *p*-nitrosodimethylaniline (each shaded box represents one SERS spectrum collected in a 1 × 1 mm^2 area); (right) AFM images of nanoparticles (500 × 500 nm^2) from regions A−D. Reprinted with permission from ref 132. Copyright 1996 American Chemical Society.

structures can be much larger than that of simple island films. They demonstrated the power of solution-based combinatorial approaches for synthesis of surfaces exhibiting nanometer-scale variation in mixed-metal composition and architecture. The SERS response with a variable surface coverage of colloidal Au and the amount of Ag coating on Au nanoparticles (Ag staining) was studied in detail. A gradient in particle coverage was produced along the direction of immersion of a glass slide by a fixed rate immersion of the (3-mercaptopropyl)trimethoxysilane-coated glass slide into an aqueous solution of 12 nm diameter colloidal Au particles. The slide was further rotated by 90°, and fixed-rate immersion was performed into an Ag-ion-containing solution for Ag staining of Au. This second immersion step produced a gradient in particle size over the new immersion direction. The resulting surface exhibited a continuous variation in nanometer-scale morphology as was defined by particle coverage and particle sizes. The SERS signal for adsorbed *p*-nitrosodimethylaniline was measured over a 2 × 2 cm sample exhibiting continuous gradients in Au coverage, and Ag cladding thickness showed a spatial map of the background-corrected SERS intensity for the phenylnitroso stretch at 1168 cm^{-1}. A detailed interrogation revealed a region that was $>10^3$-fold more SERS-enhancing than the least active sites (see Figure 20). The nanometer-scale morphology at positions of interest was determined by atomic force microscopy. These results showed the significant changes in SERS enhancement factor over only small alterations in surface morphology.

Reproducible surface enhancement and surface treatment conditions that extend the shelf life of SERS surfaces have been recently reported (for several examples, see refs 264 and 265). The combinatorial computational approaches will play an increasingly important role for the identification of the best morphologies for “hot spots” and their gaps,[266] for the best surface treatment conditions to extend the shelf life of SERS surfaces, and for deeper understanding of the effect of chemical enhancement.[267,268]

3.3.2. Nanoscale Materials for Plasmon Resonance

First explanations of colored effects from colloidal Au were reported by Faraday in his Bakerian lecture.[269,270] At present, for sensing applications, plasmon resonance on metal nanoparticles and surface plasmon resonance on thin metallic films are widely used for chemical and biological sensing as summarized in recent reviews and books.[252,271−275] In SPR with a uniform film, the sensor response *R* can be defined either as the shift in the wavelength $\Delta\lambda$ or angle $\Delta\theta$ of the SPR minimum in reflected light intensity associated with analyte adsorption. The SPR sensor response *R* is related to the change in the refractive index Δn due to the presence of adsorbed species as[276]

$$R = m\Delta n \{1 - \exp(-2d/L_\mathrm{d})\} \qquad (6)$$

where *m* is the refractive index sensitivity, *d* is the effective thickness of a layer that experiences the change in the refractive index, and L_d is the characteristic electromagnetic field decay length. The localized surface plasmon resonance (LSPR) response is measured as the change in the extinction (or scattering) wavelength maximum, which is related to Δn also through eq 6 but with a shorter L_d.[252] The nanoparticle LSPR approach was established for biosensing with the pioneering work of Mirkin and co-workers, who demonstrated the selective colorimetric detection of polynucleotides with the use of the distance-dependent optical properties of Au nanoparticles.[22] The approach that utilizes the aggregation-induced, red-to-blue color change associated with Au nanoparticles is attractive for myriad applications ranging from screening of combinatorial libraries of DNA-binding molecules with DNA-functionalized Au nanoparticles[277] to chemical sensing.[278−281] Analysis of hybridization events in combinatorial DNA arrays using oligonucleotide-modified and Ag-stained Au nanoparticle probes on a conventional flatbed scanner had a detection sensitivity exceeding that of the analogous fluorophore system by 2 orders of magnitude.[282]

Although plasmonic nanoparticles potentially offer properties that are unavailable in molecular or mesoscopic systems, in order to benefit from these properties in new functional components such as sensors, it is critical to develop methods for placing particles into chemically and structurally well-defined environments.[283] To generate 2-D and 3-D assemblies of plasmonic nanoparticles, Genzer and co-workers developed an approach to use polymer brushes that offer environments for controlled organization of nanoparticles within polymer matrices.[283−286] This desired arrangement of nanoparticles in polymers requires control of several parameters

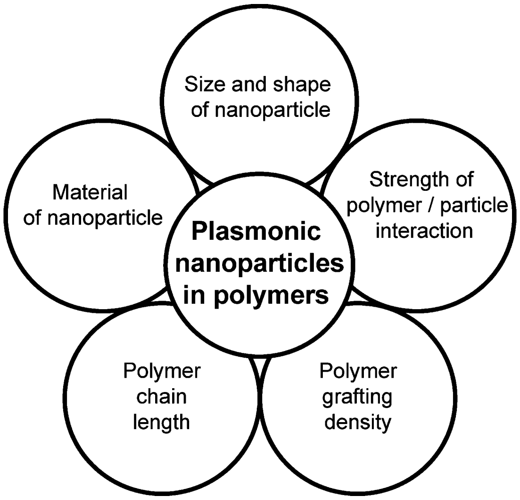

Figure 21. Diversity of optimization parameters during the preparation of polymeric sensing materials with plasmonic nanoparticles.

shown in Figure 21. The large number of parameters made probing the behavior of brush/nanoparticle hybrids very difficult without a combinatorial approach.[285,287] Systematic studies of the effects of the loading of nanoparticles and polymer structure were performed by fabricating orthogonal polymer gradient substrates, in which the polymer molecular weight (MW) and grafting density σ were changed independently in two orthogonal directions (see Figure 22). The citrate-covered Au nanoparticles were attached to a poly(dimethylaminoethyl methacrylate) (PDMAEMA) polymer brush grafted on a silica substrate as shown in Figure 22A. The electrostatic interaction between the positively charged DMAEMA groups and citrate ions attached to the surface of Au nanoparticles at pH 6.5 was responsible for binding the nanoparticles to the underlying brush. Thus, the extinction wavelength maximum of plasmonic nanoparticles caused the color of the slide in Figure 22B to change from light red (region of low MW and low σ) to dark violet blue (region of high MW and high σ), indicating interparticle plasmon coupling associated with an increase in uptake of particles in the brush upon an increase of MW and σ. The increase in intensity of the plasmon absorbance peak in the direction of increasing MW or σ (see Figure 22C) was due to the increasing number of particles attached to the polymer chains. The concomitant red shift of the plasmon peak position suggested intensified interparticle plasmon coupling accompanying the nanoparticle crowding on the substrate. Upon variation of σ, the color variation was more pronounced for low MW (shorter) chains relative to longer chains, suggesting that the number of particles bound to the brush was dependent on the number of favorable sites that particles have access to.[284]

Initially employed Au nanoparticles were relatively large (16 nm) to penetrate the brush; however, the use of smaller ones (3.5 nm) made it possible to load the nanoparticles inside the polymer.[285] In subsequent studies, Bhat and Genzer also developed an approach to control the number density of citrate-stabilized Au nanoparticles on flat substrates by varying the concentration of the grafted amino groups on the surfaces and their degree of ionization. The concentration of grafted amino groups was controlled by decorating silica-based substrates with a molecular gradient of (3-aminopropyl)triethoxysilane (APTES). The degree of ionization of the $-NH_2$ groups in APTES was controlled by varying the pH of the Au colloid.[286]

To visualize and quantify the gradient distribution of plasmonic nanoparticles in sensing films, Dovidenko, Potyrailo, and co-workers developed an approach based on focused ion beam (FIB) cross-sectioning of a sensing film followed by the 3-D reconstruction of the spatial distribution of nanoparticles (see Figure 23).[280] These new methods for controlled organization of nanoparticles within polymer matrices[283−286] coupled with the visualization and quantitation of nanoparticles in the polymer[280] are important for the development of chemical and biological sensors with the tailored dynamic range of sensor response.

Plasmonic nanoparticles are also attractive for deposition onto solid sensor substrates in desired discrete arrangements. Numerous lithographic and other nanofabrication techniques are readily applicable for the formation of nanoparticle arrays.[288−293] Among the lithographic techniques, dip-pen nanolithography[294−296] is one of the most versatile for the fabrication of combinatorial materials libraries for their screening of ligand-binding events. Dip-pen nanolithography, when operated in nanoplotter mode, is a powerful tool for combinatorial nanotechnology[297] because it can be programmed to generate a series of patterns that vary with respect to composition, feature size, and feature spacing and can be deposited onto different substrates. These patterns subsequently can be used to study chemical and biochemical recognition in the combinatorial fashion as was recently demonstrated for several combinatorial applications.[298−300] The use of dip-pen nanolithography with conventional cantilevers offers a 5 nm spatial resolution,[301] making it a straightforward tool to arrange plasmonic nanoparticles in a nanoarray format.[302]

The addressable combinatorial arrays were successfully used for light-directed, spatially addressable parallel chemical synthesis,[178] combinatorial synthesis of materials arrays,[89] light-directed assembly of metallic nanoparticles,[303] and combinatorial patterning of nanocrystals[304] and were proposed for catalytic metal film sensors.[131] Koenderink and co-workers[305] have theoretically demonstrated an approach for addressable combinatorial arrays using the principles of surface plasmon resonant nanolithography.[289,290] The distinct emission patterns of hot spots from 1-D or 2-D arrays of plasmonic subwavelength nanoparticles were created even though all particles in the array were irradiated.[305] Illumination with unfocused light of all particles in the array allowed optical addressing of particles by varying the wavelength, incidence angle, and polarization of the incident wave. The coherent coupling of all fields in closely spaced particles in an array was tuned through the relative phases with which particles were excited to controllably create hot/cold spots of constructive/destructive interference on a single or several dipoles depending on array geometry and illumination conditions.[306] Figure 24 illustrates all five symmetry-distinct patterns that were created by illuminating a 2 × 2 square array of Ag particles (radius = 25 nm, spacing = 75 nm) with linearly polarized light under various angles. When symmetry was taken into account, combinatorial 2^4 binary combinations of four particles that can be exposed or unexposed was reduced to five unique patterns with at least one particle exposed.

Such on-demand combinatorial excitation of particles in the array upon an illumination of the whole array with an unfocused light brings a host of opportunities for sensing,

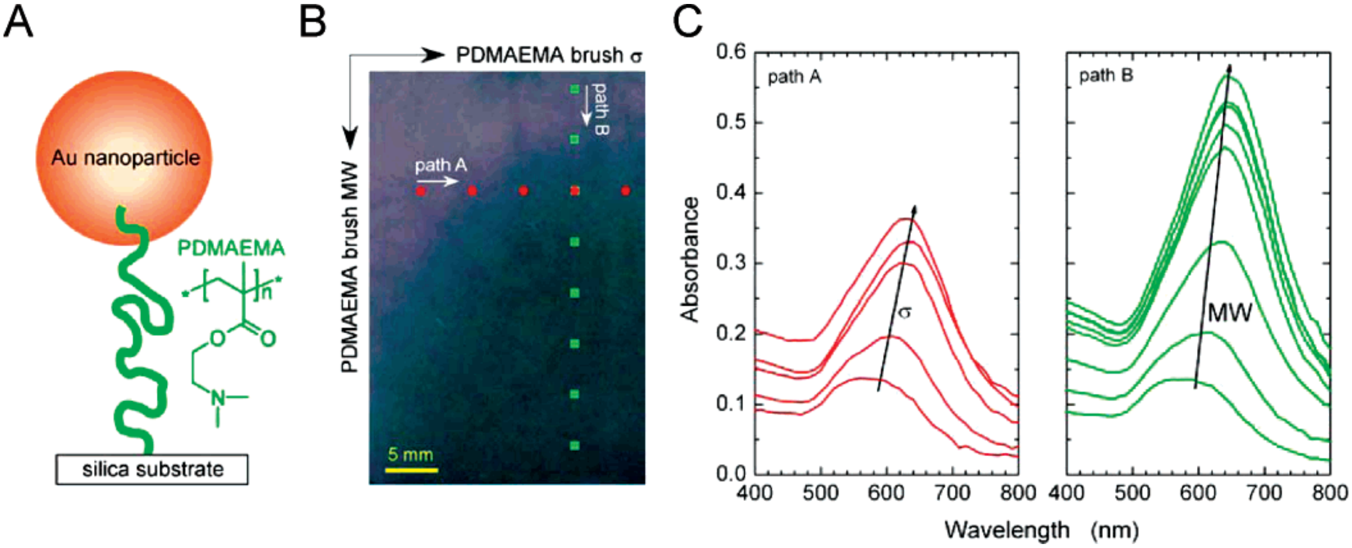

Figure 22. Combinatorial approach for systematic studies of the simultaneous effects of the loading of Au nanoparticles and polymer structure: (A) schematic of the attachment of citrate-covered gold nanoparticles to a PDMAEMA polymer brush grafted on a silica substrate; (B) photograph of a glass slide showing a reflected light color originated from 16 nm diameter Au nanoparticles bound to an orthogonal σ-MW gradient of surface-grafted PDMAEMA; (C) visible light absorbance spectra taken along red circles (path A, constant MW, σ gradient) and green squares (constant σ, gradient MW) shown in (B). Reprinted with permission from ref 284. Copyright 2004 Wiley-VCH Publishers.

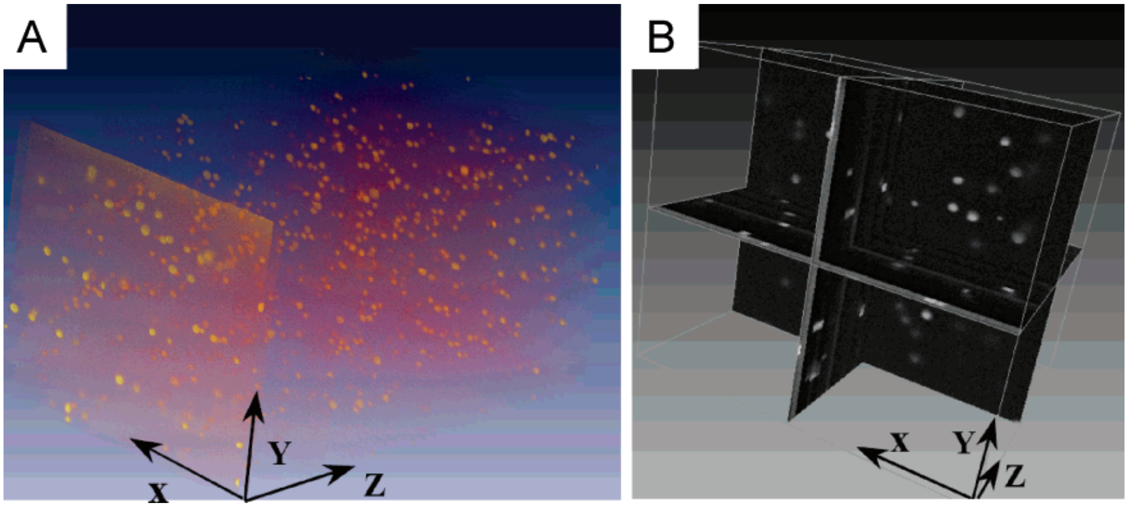

Figure 23. Visualization and quantitation of the gradient distribution of plasmonic nanoparticles in sensing films utilizing FIB cross-sectioning followed by the 3-D reconstruction: (A) 3-D representation of the set; (B) demonstration of ability to visualize data along *X*, *Y*, and *Z* axes by moving one slice at a time along *Z* and continuously in *X* and *Y* directions. Data sets of ~25 nm thick FIB serial slices are sectioned normal to *Z* direction in the picture (lateral dimensions, $X = Y = 3.4$ μm). Reprinted with permission from ref 280. Copyright 2006 Materials Research Society.

ranging from sequential excitation of differently functionalized particles in the array that have the same optical response to sequential metal-enhanced fluorescence readout to avoid photobleaching of the whole array at once.

Further implementation of local plasmonic effects in sensors requires the development and optimization of highly reproducible yet cost-effective surfaces containing plasmonic nanostructures.[251,307] High-thoughput materials development techniques for optimization of these structures as well as computational and combinatorial development of plasmonic negative refractive index metamaterials[308,309] for sensors[310,311] will be critical for the timely introduction of these new physical phenomena in practical bioanalytical applications.

3.4. Semiconductor Nanocrystals

Semiconducting nanocrystals were independently introduced by Alivisatos and co-workers[312] and Nie and Chan[313] as labels for biodiagnostic applications and biotechnology. Although at present organic fluorophores dominate sensing applications because of the diversity of their functionality and well-understood methods of their synthesis, new semiconducting nanocrystal labels have several advantages (photostability, relatively narrow emission spectra, and broad excitation spectra[30,314]) over organic fluorophores. Thus, finding a solution to complement the existing organic fluorescent reagents with more photostable, yet chemically or biologically responsive, nanocrystals is very attractive. It is known that a variety of photoluminescent materials are sensitive to the local environment.[315] In particular, polished or etched bulk CdSe semiconductor crystals[316,317] and nanocrystals[318,319] were shown to be sensitive to environmental changes. To better understand the environmental sensitivity of semiconductor nanocrystals upon their incorporation into polymer films, Potyrailo and Leach incorporated mixtures

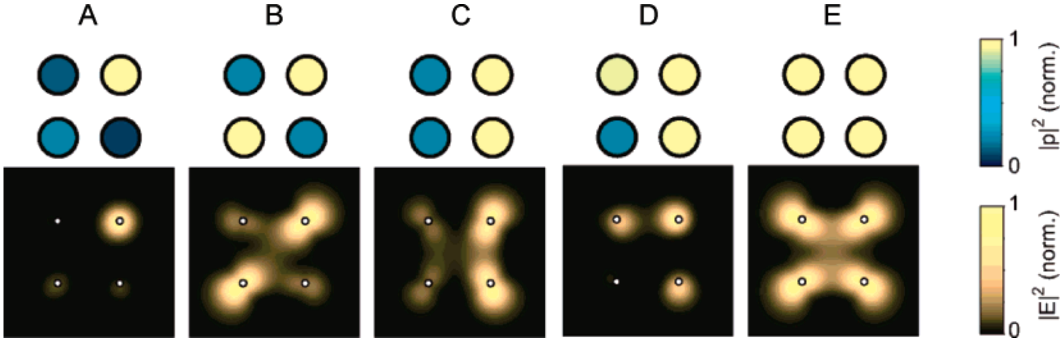

Figure 24. Individual addressing of all combinations of Ag nanoparticles in a 2 × 2 array. The filled-in dots show the relative amount of excitation on each sphere; the contour plots show the resulting electric field intensity in a plane just 5 nm above the array; the location of the spheres is indicated by open circles. Reprinted with permission from ref 305. Copyright 2007 American Chemical Society.

Table 3. Polymer Matrices for Incorporation of Different Sizes of CdSe Nanocrystals[322]

polymer	polymer type	rationale for selection as sensor matrix
1	poly(trimethylsilyl)propyne	polymer with largest known solubility of oxygen, candidate for efficient oxidation of CdSe nanocrystals
2	poly(methyl methacrylate)	polymer for solvatochromic dyes
3	silicone block polyimide	polymer with very high partition coefficient for sorbing organic vapors
4	polycaprolactone	polymer for solvatochromic dyes
5	polycarbonate	polymer with high T_g for sorbing of organic vapors
6	polyisobutylene	polymer with low T_g for sorbing of organic vapors
7	poly(dimethylaminoethyl) methacrylate	polymer for surface passivation of semiconductor nanocrystals
8	polyvinylpyrrolidone	polymer for sorption of polar vapors
9	styrene−butadiene ABA block copolymer	polymer for sorption of nonpolar vapors

of multisize CdSe nanocrystals into numerous rationally selected polymeric matrices (see Table 3) and screened these films for their photoluminescence (PL) response to vapors of different polarities upon excitation with a 407 nm laser.[320−322]

It was discovered that CdSe nanocrystals of different sizes (2.8 and 5.6 nm diameter) and passivated with tri-*n*-octylphosphine oxide using known methods[323,324] had dramatically different PL response patterns upon exposure to methanol and toluene after incorporation into polymeric matrices (see Figure 25A). As an example, Figure 25B shows response patterns of gas-dependent PL of the two sizes of CdSe nanocrystals in poly(methyl methacrylate) (PMMA) sensor film. The difference in the response patterns of the nanocrystals was attributed to the combined effects of the dielectric medium surrounding the nanocrystals, their size, and surface oxidation state. The sensing films were tested for 16 h under a continuous laser excitation and exhibited a high stability of PL intensity.[325] Results of cluster analysis of PL response patterns upon exposure to methanol and toluene after incorporation into polymeric matrices are demonstrated in the dendrogram in Figure 25C. The dendrogram was constructed by performing principal component analysis (PCA) on the data from Figure 25A and further using Mahalanobis distance on three principal components (PCs). From this dendrogram, it is clear that polymers 6 and 7 were the most similar in their vapor response with studied CdSe nanocrystals as demonstrated by a very small distance to K-nearest neighbor between them. Polymer 4 was the most different from the rest of polymers as indicated by the largest diversity distance to K-nearest neighbor. Such data mining tools provide a means to quantitatively evaluate polymer matrices. When coupled with quantitative structure−property relationship simulation tools that will incorporate molecular descriptors, new knowledge generated from high-throughput experiments may provide additional insights for the rational

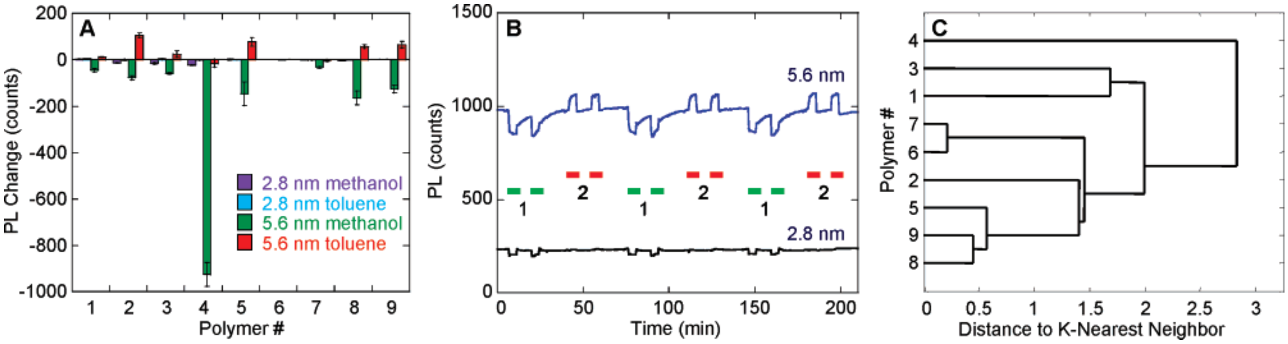

Figure 25. Diversity of steady-state PL response of two-size (2.8 and 5.6 nm) mixtures of CdSe nanocrystals to polar (methanol) and nonpolar (toluene) vapors: (A) magnitude of PL change in nine polymer matrices listed in Table 3 (reprinted with permission from ref 322; copyright 2006 Materials Research Society); (B) gas-dependent PL of the two-size CdSe nanocrystals sensor film (polymer 2) with emission of 2.8 nm nanocrystals at 511 nm and emission of 5.6 nm nanocrystals at 617 nm (reprinted with permission from ref 321; Copyright 2006 American Institute of Physics); (C) results of cluster analysis of PL response patterns upon exposure to methanol and toluene after incorporation into nine polymer matrices. Numbers 1 and 2 in (B) are replicate exposures of sensor film to methanol (6% vol) and toluene (1.5% vol), respectively.

design of gas sensors based on incorporated semiconductor nanocrystals. In the future, such work in vapor sensors promises to complement existing solvatochromic organic dye sensors with more photostable and reliable sensor materials.[319] In sensors for ionic species,[326] ligand screening will be also attractive to perform using combinatorial techniques.

4. Organic Sensing Materials

4.1. Indicator Dyes

Although photoluminescent nanocrystals are becoming attractive for sensing applications as discussed in section 3.4, development of new colorimetric and fluorescence dyes as analyte-responsive reagents remains important in the design of new sensors with improved selectivity and sensitivity. Using existing knowledge, it is possible to computationally predict general spectral features of dyes.[327,328] However, *quantitative* computations of the selectivity of analyte recognition, extinction coefficient, and quantum yield of emission for new reagents are very challenging. Additional practical challenges may occur from difficulties in the synthesis of those best reagent structures predicted from computations. Thus, combinatorial synthetic approaches have been applied for the development of new fluorescent[329−335] and colorimetric[336−339] reagents. Recent reviews are available on the fluorescent labels and probes.[340,341] Recent developments resulted in the discovery of a wide variety of new useful reagents for the detection of metal ions,[329,330,333,336] ATP,[334] GTP,[335] dipeptides,[338] tripeptides,[339] and reagents that selectively bind to amyloid[332] and different cell components.[342,343]

To navigate in the vast amount of data, Rosania, Chang, and co-workers[342,343] demonstrated a cheminformatic strategy for a multiparameter analysis of combinatorial libraries of dyes to predict not only their spectral properties but also their analyte-binding abilities. This approach has been demonstrated with a library of styryl dyes that were fluorescent lipophilic cations and that were selectively accumulated in mitochondria and other regions in living cells. Furthermore, it was suggested that in addition to organelle-specific binding, some dyes may possess DNA, RNA, or protein-specific binding features.[342] Dye synthesis (see Figure 26A) was done by the condensation of 41 aldehydes (building block **A**) that were of various sizes, conjugation lengths, and electron-donating or -withdrawing capabilities and 14 pyridinium salts (building block **B**) that were 2- or 4-methylpyridine derivatives condensed with each other with a secondary amine catalyst. Due to the structural diversity, the emission colors of the library of compounds covered a broad range from 470 to 730 nm. The binding ability of the dyes library in the cells was assessed by the incubation of dyes with live human melanoma cells. From the detailed analysis of 119 of 276 fluorescent compounds that localized to specific subcellular compartments (i.e., mitochondria, endoplasmic reticulum, vesicles, nucleoli, chromatin, cytoplasm, or granules), the structure-binding relationships have been developed as presented in Figure 26B. A model was developed that related the spectral and subcellular localization characteristics of styryl compounds to the two chemical building blocks **A** and **B** that were used to synthesize the molecules. The model predicted the subcellular localization and spectral properties of the styryl compounds from numerical scores that were independently associated with the individual building blocks of the molecule. It was found that more complex, nonadditive interactions between the two building blocks also played a role in determining the molecule's optical and biological properties.

Dynamic combinatorial libraries were utilized by Buryak and Severin as highly selective colorimetric sensors for dipeptides[338] and tripeptides.[339] An analyte-induced adaptation of a DCL was used to identify the respective analyte when the library was composed of compounds of different colors. The compounds in the libraries were chelating dye−metal salt complexes that were able to undergo ligand-exchange reactions. For such a sensor, the information about the sample was distributed over the entire UV−vis spectrum, which was a "fingerprint" for the analyte. In conventional sensor arrays, each sensor is independent, and the sample is identified by analysis of several nonspecific sensors with a construction of a characteristic fingerprint.[24] In contrast, a DCL sensor consisted of compounds that were connected by exchange reactions.[338] The addition of a target molecule that selectively interacted with some members of the library caused a re-equilibration of the whole library, and this adaptation was used to identify library members with a high affinity for the respective target molecule.

Crego-Calama and co-workers explored the surface-confinement effects in sensing self-assembled monolayers (SAMs) that were developed for determinations of cations and anions.[344−348] The key advantages of SAMs for surface-confined sensing are in the possibility of the introduction of additional chelating effects from the preorganization of the surface-immobilized reagent. The binding groups and fluorophore molecules in the SAM are in close enough proximity, thus the binding group−analyte interaction is communicated to the fluorophore, resulting in a modulation of the fluorescence intensity (see Figure 27A). Sensing SAMs were made on glass tailored with two building blocks. One block included small molecules that supplied different functionalities acting as binding groups (e.g., ureas, amides, thioureas, sulfonamides). Another block included fluorescent dye molecules for reporting the recognition event. The properties of the layer were a result of the combination of the nature of the different binding groups, the fluorescent dye molecule, and surface functionalization. To make combinatorial libraries of sensing SAMs, glass slides were functionalized with a SAM of *N*-[3-(trimethoxysilyl)propyl]ethylenediamine, followed by the sequential covalent attachment of fluorophore molecules and small binding groups. These libraries were produced by two methods that were (1) a solution-based procedure with a sequential dipping and (2) a microcontact printing. For determination of anions, fluorophores in one of these combinatorial libraries[344] were lissamine rhodamine B sulfonyl chloride and tetramethylrhodamine-5-(and 6)-isothiocyanate, whereas the anion binding functional groups were amino, amide, sulfonamide, urea, and thiourea (see Figure 27B). From the fluorescence response of this combinatorial library to 10^{-4} M acetonitrile solutions of tetrabutylammonium salts of HSO_4^-, NO_3^-, $H_2PO_4^-$, and AcO^- anions (see Figure 27C), a general trend in the response magnitude between the library elements based on different fluorophores was discovered. This trend was attributed to the differences in the attachment point functionality of two fluorophores. From these experiments, the variables of fluorophores, binding groups, and their substituents that affected the sensitivity and selectivity of the sensing SAM were applied to develop more understanding

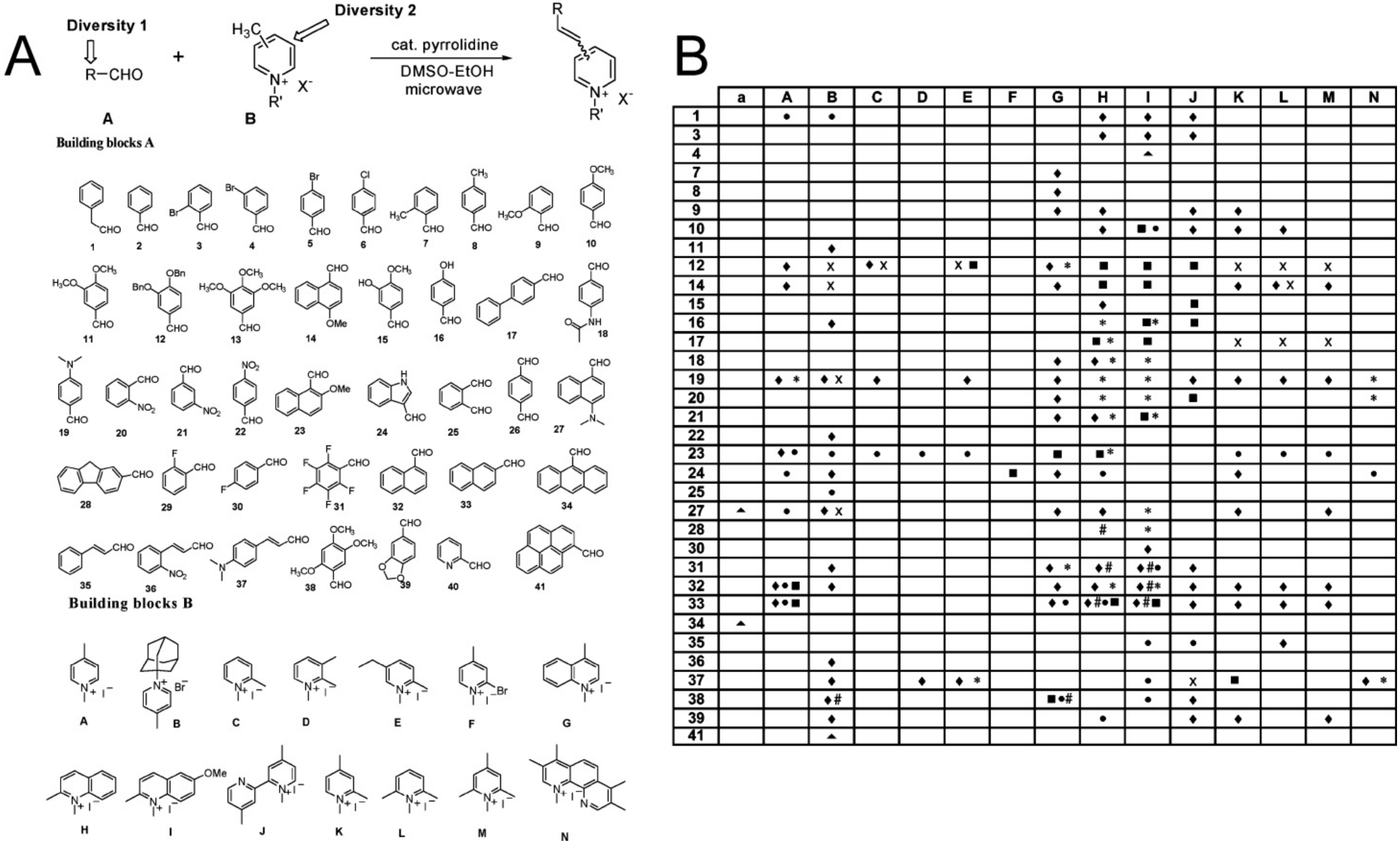

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Figure 26. Chemoinformatic strategy for a multiparameter analysis of combinatorial libraries of styryl dyes to predict their spectral properties and analyte-binding ability: (A) schematic of dye synthesis by the condensation of 41 aldehydes (building block **A**) and 14 pyridinium salts (building block **B**); (B) localization distribution of the organelle specific styryl dyes [(#) nuclear, (∗) nucleolar, (◆) mitochondria, (●) cytosolic, (×) endoplasmic reticular, (■) vesicular, and (▲) granular]. Reprinted with permission from ref 342. Copyright 2003 American Chemical Society.

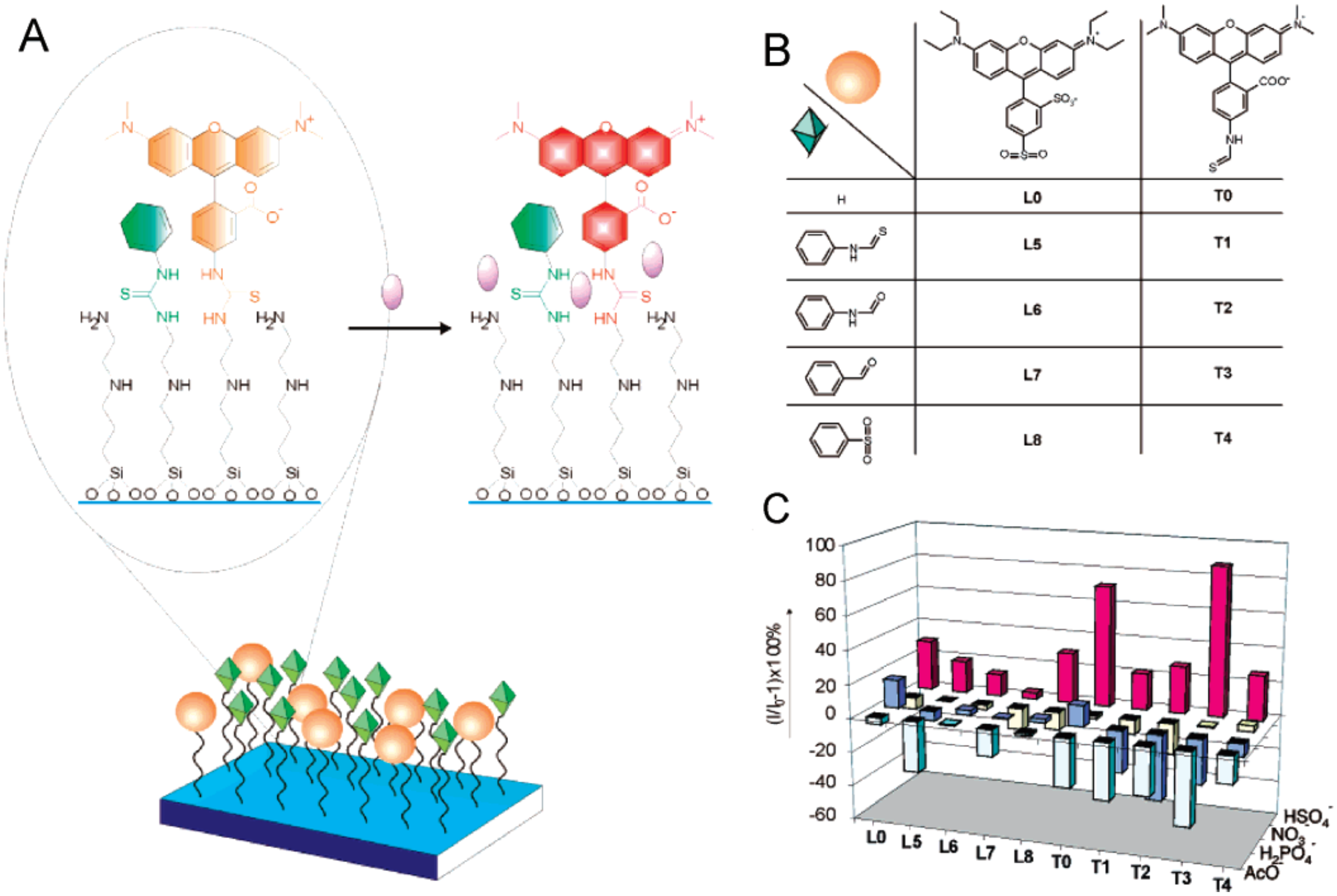


Figure 27. Combinatorial approach for sensing SAMs: (A) schematic representation of an analyte (purple ovals, top schematic) interaction with the SAM due to its coordinating properties followed by reporting of the interaction by the fluorophore [binding groups are depicted by octahedrons, and fluorescent groups are depicted by orange spheres (bottom schematic)]; (B) combinatorial SAM compositions of the anion-sensing library; (C) normalized fluorescence intensity of sensing SAMs in the presence of 10^{-4} M solutions of HSO_4^-, NO_3^-, $H_2PO_4^-$, and AcO^- as tetrabutylammonium salts in acetonitrile. Reprinted with permission from ref 344. Copyright 2004 American Chemical Society.

on the origin of selectivity and response magnitude for ion sensing.[344]

In the future, combinatorial techniques promise to provide experimental data to generate descriptors for further computational design of diverse indicator molecules to predict not only their optical properties but also their analyte-binding selectivity in the presence of interferences.

4.2. Polymeric Compositions

Applications of formulated compositions of analyte responsive reagents immobilized onto a solid support go back to ancient times when the Romans used papyrus impregnated with an extract of acorns for selective colorimetric determinations of iron sulfate and copper sulfate.[349] In those and many other more recent applications (for example, in the detection of acids and alkalis with a litmus paper by Lewis in 1767) only qualitative determinations were performed, yet they provided critical analytical information about the presence or absence of analytes of interest in a sample.

Modern sensing based on immobilized reagents is the most widely used sensing approach because of the diversity of analytes that can be detected and the diversity of transduction principles involved in detection that include radiant, electrical, mechanical, and thermal energies. The diversity of requirements for such sensors can be quite broad and can range from the need for the long-term autonomous monitoring in remote locations[350] without sensor film degradation to extra-stable and accurate performance of sensors in bioprocess control[351,352] over only several weeks of operation, to nonleaching of reagents from an immobilization matrix in the in vivo sensors for analysis of blood parameters,[353] to selective determination of a wide variety of ionic species in environmental and industrial water,[354−356] to extremely sensitive sensing of contaminants in drinking water.[357] For these and many other applications, the generally accepted strategy is to employ formulated sensing compositions.

The key components of formulated sensing films include analyte-responsive reagents, polymer matrices, functional additives, and common solvents. An extensive optimization is required to identify sensor formulations with best sensor performance (e.g., largest sensor sensitivity, smallest response to interferences, shortest response time, enhanced stability). There can be easily five or six functional additives in formulated sensing films for optical[358,359] and potentiometric[360] sensors, not taking into an account a solvent, which in turn can be binary or even ternary to ensure the solubility of all components. Figure 28 depicts needed types of formulation components to tailor dynamic range, selectivity, accuracy, sensitivity, long-term stability, spectral response, and response time of formulated materials. Often, optimization of formulated sensor materials requires evaluation of numerous polymeric matrices or multiple additives at their multiple concentrations and ratios. Of course, general knowledge exists for the design of formulated sensing films.

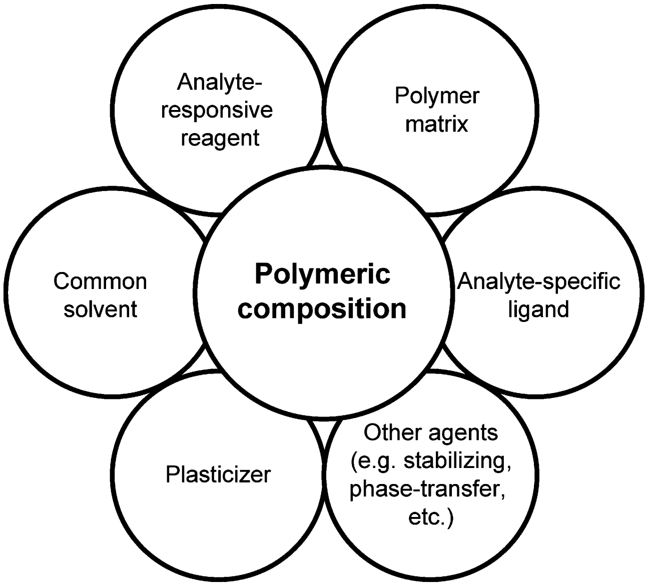


Figure 28. Diversity of optimization parameters during the preparation of formulated polymeric sensing materials.

However, rational design of formulated sensing materials is often limited by poor solubility and compatibility of formulation components, photobleaching, and other practical issues.[45,361−363] These significant knowledge gaps prevent a more efficient application of rational approaches of development of formulated sensor materials.

Walt and co-workers[44] pioneered in situ polymerization of combinations of starting monomers and an analyte-responsive indicator and employed this approach to fabricate discrete and gradient arrays of sensing films with responses that were not simply related to the proportion of the starting materials. Bright and co-workers[364,365] developed an approach to use a high-speed printer to rapidly produce and screen biodegradable polymer and xerogel-based formulations for biosensors. Robotic-based approaches for fabrication and testing of libraries of solvent-cast formulated sensing film compositions for gas and water analysis have been developed by Wolfbeis and co-workers[45,46] and Potyrailo and co-workers.[48,143,148,366]

Optimization of concentrations of formulation components can require significant effort because of the nonlinear relationship between additive concentration and sensor response.[44,367−373] For detailed optimization of formulated sensor materials, Potyrailo and co-workers[374] used concentration- and thickness-gradient sensor material libraries. The one-, two-, and three-component composition gradients were made by flow-coating individual liquid formulations onto a flat substrate and allowing them to merge under diffusion control when still containing solvents.[375] These gradient films were applied for optimization of sensor material formulations for the analysis of ionic and gaseous species.[143,375] A very low reagent concentration in the film is expected to produce only a small signal change. The small signal change is also expected when the reagent concentration is too high. Thus, the optimal reagent concentration will depend on the analyte concentration and activity of the immobilized reagent. Because the activity of reagents upon immobilization is too difficult to quantitatively predict, an optimization of reagent concentration is typically performed.

To illustrate this approach, concentration optimization of a colorimetric reagent was performed in a polymer film for the detection of trace concentrations of chlorine in water. A concentration gradient of a near-infrared cyanine dye was formed in a poly(2-hydroxyethyl methacrylate) hydrogel sensing film. The optical absorption profile $A_0(x)$ was obtained before analyte exposure to map the reagent concentration gradient in the film. A subsequent scanning across the gradient after the analyte exposure (1 ppm of chlorine) resulted in the determination of the optical response profile $A_E(x)$. The difference in responses, $\Delta A(x) = A_0(x) - A_E(x)$, revealed the spatial location of the optimal concentration of the reagent that produced the largest signal change (see Figure 29A). Unlike traditional concentration optimization approaches,[372,373] the new method provided opportunities for time-affordable optimization of the concentration of multiple formulation components using concentration gradients. Sensing films with the optimized concentration of the cyanine dye for chlorine determinations in industrial water were further screen-printed as a part of sensing arrays[355] onto conventional optical disks as shown in Figure 29B. The quantitative readout of changes in film absorbance was performed in a conventional optical disk drive in a recently developed laboratory-on-a-disk system.[354−356] With this system, it was possible to quantify signal changes from sensing films with dimensions down to several tens of micrometers, limited only by the size of the laser beam on the disk surface.[354,356]

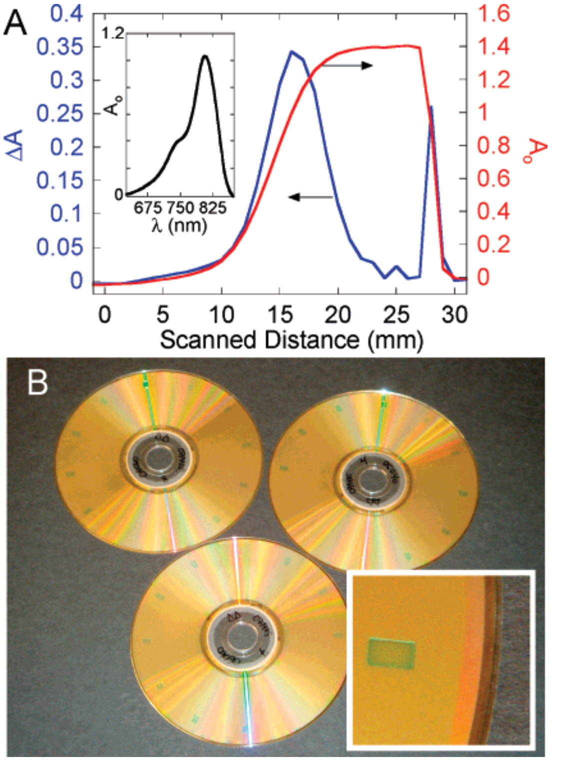


Figure 29. Colorimetric formulated poly(2-hydroxyethyl methacrylate) hydrogel sensing films for detection of ions in water: (A) concentration optimization of a colorimetric chlorine-responsive reagent in a formulated polymeric gradient sensing film [exposure, 1 ppm of chlorine; (inset) spectrum of the optimal dye concentration in the film]; (B) conventional optical disks with printed sensing regions with optimized concentration of the reagent immobilized into sensing films for detection of chlorine in water [(inset) close-up of the screen-printed sensing film].

The effect of the thickness of sensor films on the stability of the response in water to ionic species has been also evaluated using gradient-thickness-sensing films.[143] Sensor reagent stability in a polymer matrix upon water exposure is one of the key requirements. In the gradient sensor arrays,

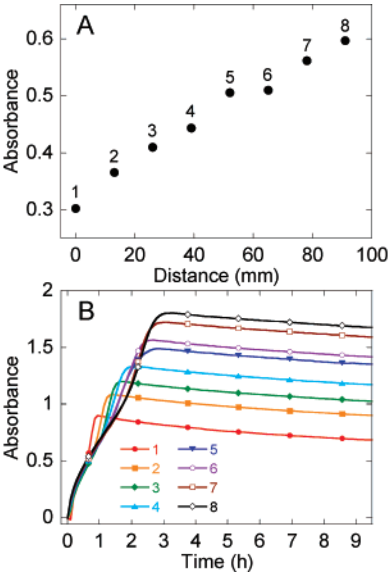


Figure 30. Application of gradient-thickness sensor film arrays for evaluation of reagent leaching kinetics: (A) variable film thickness; (B) reagent-leaching kinetics at pH 10. Reprinted with permission from ref 143. Copyright 2005 American Institute of Physics.

the thickness of sensor films was determined from the absorbance of the film-incorporated bromothymol blue reagent (Figure 30A). When these arrays were further exposed to a pH 10 buffer (Figure 30B), an “activation” period was observed before leaching of the reagent from the polymer matrix became detected as the absorbance decrease. This apparent activation period was roughly proportional to the film thickness. However, the leaching rate was independent of the film thickness as indicated by the same slopes of the response curves at 3−9.5 h exposure time periods.

In sensing materials based on solid polymer electrolytes [e.g., polyethylene oxide,[376] poly(dimethyldiallylammonium chloride),[377] Nafion,[378] etc.], the conductivity depends on ionic mobility rather than electron mobility. Modifications of selectivity patterns of this type of sensing materials in response to different analytes have been achieved by formulating them with different functional additives. For example, Nafion films have been formulated with hydrogels,[379] ionic liquids,[380] salts,[381] surfactants,[382] and many other additives. Potyrailo and Morris[378,383] recently demonstrated an approach for multianalyte sensing using a single conventional radio frequency identification (RFID) tag that has been adapted for chemical sensing. Unlike other approaches of using RFID sensors, where a special tag is designed at a much higher cost, conventional RFID tags (<\$1) were utilized and simply coated with chemically sensitive films (see Figure 31A). In such RFID chemical sensors, both the digital tag ID (see Figure 31B) and the complex impedance of the resonant circuit of the RFID antenna were measured.[378,384] The measured digital ID provided information about the sensor and the object onto which the sensor was attached. By measuring simultaneously several parameters of the complex impedance from a Nafion-coated resonant *LC* circuit of the RFID sensor and applying multivariate statistical analysis methods, the identification and quantitation of several vapors of interest with a single RFID sensor were demonstrated with parts per billion vapor detection limits.[378]

To induce an additional selectivity in vapor response and to study long-term stability, Potyrailo and co-workers[385] employed several different phthalic acid derivatives as additives in Nafion. Phthalate plasticizers in different polymeric films were used previously to induce the diversity in vapor response.[386−389] Potyrailo and co-workers formulated five different phthalate plasticizers in Nafion at 10% vol, and the films were deposited onto RFID sensors. An array of 48 RFID sensors was formed[390] as shown in Figure 31C and further arranged on a gradient temperature heater to generate a linear temperature gradient from 40 to 140 °C. The interrogation of RFID sensors in the array was done with a single transmitter (pick-up antenna) coil positioned on an X−Y translation stage and connected to a network analyzer. After temperature annealing in air, the differential impedance response after and before the annealing from each sensor was calculated (see Figure 31D). The smallest response was associated with the most stable film composition after annealing. This demonstrated approach provided the capability of using conventional passive RFID tags as high-performance transducers for rapid aging studies of sensing materials. As pointed out earlier by Potyrailo and co-workers,[140] in general, the increase of the level of environmental stress may be problematic if the correlation with traditional test methods is lost. To avoid this situation, it will be critical to plan the detailed accelerated-aging high-throughput experiments with positive and negative controls.

4.3. Homo- and Copolymers

At Pittcon of 1963, King reported a new gas-sensing technique with thickness shear mode (TSM) resonators (aka quartz crystal microbalances, QCMs) coated with a variety of sorbing materials including several types of hydrophilic polymers.[391] This study has inspired many generations of scientists to explore the use of different films on acoustic-wave resonant and cantilever devices to develop sensors for practical gas- and liquid-phase analysis. Numerous reviews and books provide a comprehensive coverage of the current state of the art in such transducers, (see, for example, refs 392 and 393).

In gas sensing with polymeric materials, polymer−analyte interaction mechanisms include dispersion, dipole induction, dipole orientation, and hydrogen bonding.[394,395] The response of polymeric matrices was shown to be stable over several years.[56,396,397] Although there have been several models developed to calculate polymer responses,[398−402] the most widely employed model is based on the linear solvation energy relationships (LSER).[398,399] The LSER method systematically explores the role of vapor-solubility properties and fundamental interactions in selectivity and diversity of sensing polymers. The LSER modeling was initially performed using ∼2000 compounds with the goal of understanding the development principles of more effective stationary phases for gas chromatography.[399,403] The results were further expanded into sensor applications.[398,399] The LSER method calculates polymer/gas partition coefficients as a linear combination of terms that represent several molecular types of interactions,[398,399]

$$\log K = c + rR_2 + s\pi_2^{\mathrm{H}} + a\Sigma\alpha_2^{\mathrm{H}} + b\Sigma\beta_2^{\mathrm{H}} + l\log L^{16} \tag{7}$$

where R_2, π_2^{H}, α_2^{H}, β_2^{H}, and $\log L^{16}$ are parameters that characterize the solubility properties of the vapor in a sorbent polymer, coefficients *r*, *s*, *a*, *b*, and *l* are the corresponding sorbent polymer parameters, and *c* is the regression constant.

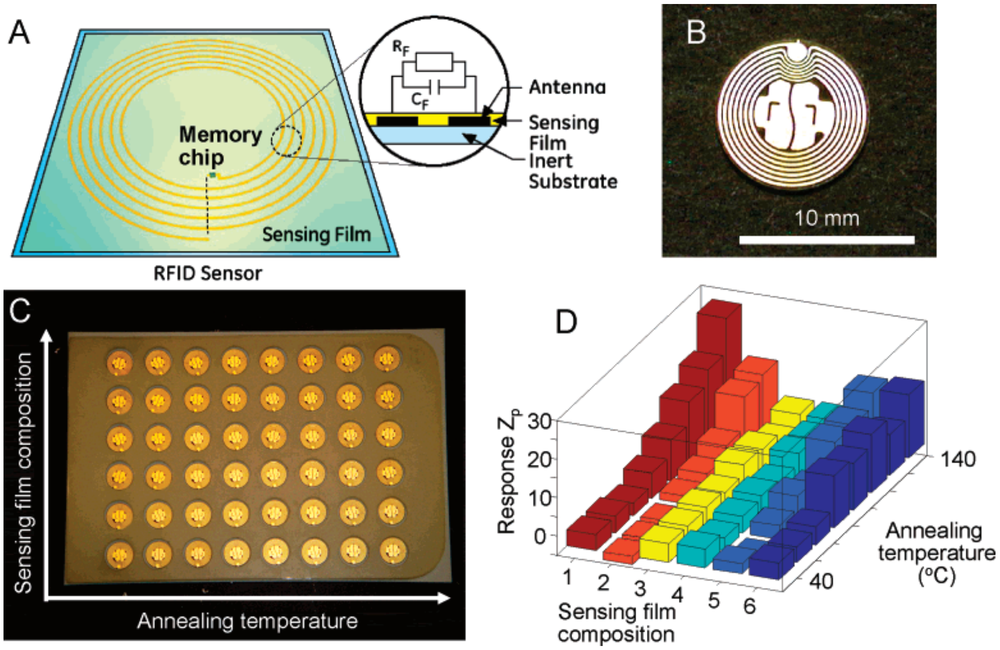


Figure 31. Combinatorial screening of stability of sensing film compositions using passive RFID sensors: (A) strategy for adaptation of conventional passive RFID tags for chemical sensing by deposition of a sensing film onto the resonant circuit of the RFID antenna [(inset) analyte-induced changes in the film material affect film resistance (R_F) and capacitance (C_F) between the antenna turns]; (B) photo of a typical employed RFID sensor (memory chip type = I*CODE1, memory chip ID = 0900 000 457D 5E12); (C) photo of an array of 48 RFID sensors prepared for temperature-gradient evaluations of response of Nafion/phthalates compositions; (D) results of temperature annealing of 48-film library in air plotted as the differential impedance response Z_p after and before the annealing from each sensor as a function of annealing temperature and material composition. Nafion sensing film compositions: 1, control without plasticizer; 2, dimethyl phthalate; 3, butyl benzyl phthalate; 4, di-(2-ethylhexyl) phthalate; 5, dicapryl phthalate; 6, ditridecyl phthalate.

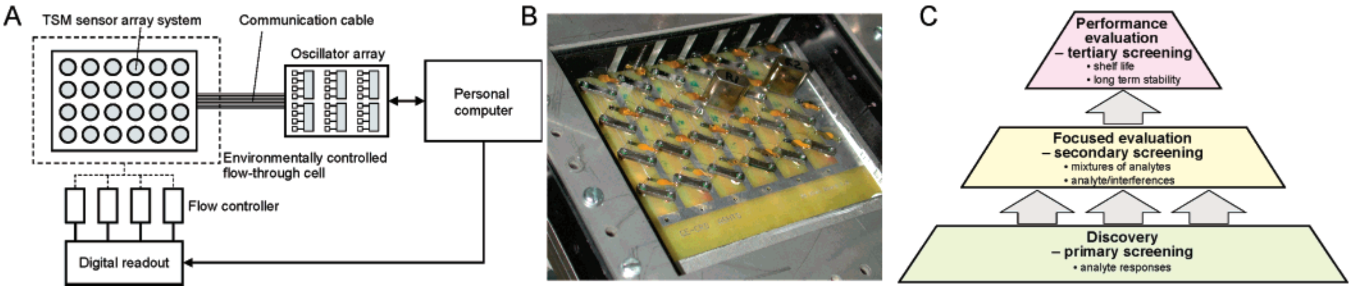


Figure 32. Approach for high-throughput evaluation of sensing materials for field applications: (A) setup schematic of a 24-channel TSM sensor array for gas-sorption evaluation of sorbing polymeric films (reprinted with permission from ref 412; copyright 2004 American Institute of Physics); (B) photo of 24 sensor crystals (including 2 reference sealed crystals) in a gas flow cell; (C) multilevel high-throughput materials screening strategy of sensing materials.

Experimentally, the polymer/gas partition coefficients are measured as the ratio of the analyte concentration in the polymer sensor film to the analyte concentration outside the film.[404,405] The LSER method has proven to be very effective at correlating the polymer-vapor sorption properties with $R > 0.95$ correlation between the predicted and experimentally obtained partition coefficients for single vapors.[406,407]

Potyrailo and co-workers applied the LSER method as a guide to select a combination of available polymers to construct a TSM sensor array for the determination of organic solvent vapors in the headspace above groundwater.[408] Field testing of the sensor system[409] demonstrated that its detection limit with available polymers was too high (several parts per million) to meet the requirements for the detection of groundwater contaminants. Potyrailo and Sivavec have found a new polymer for sensing (silicone block polyimide) that had the partition coefficient >200,000 to parts per billion concentrations of trichloroethylene (TCE) and provided at least a 100 times more sensitive response for the detection of chlorinated organic solvent vapors than other known polymers.[56,410] To provide discrimination between analytes and interfering species, polymer modifications have been introduced to the base silicone block polyimide polymer. For screening of sensing materials candidates, a 24-channel TSM sensor system was built that matched a 6 × 4 microtiter wellplate format (Figure 32A,B). A comprehensive materials screening was performed with three levels[411,412] as shown in Figure 32C. In the primary (discovery) screen, materials were exposed to a single analyte concentration. In the secondary (focused) screen, the best materials subset was exposed to analytes and interferences. Finally, in the tertiary screen, remaining materials were tested under conditions mimicking the long-term application. Although all of the screens were valuable, the tertiary screen provided the most intriguing data because aging of base polymers and copolymers is difficult or impossible to model.[41] From the tertiary screening, the decrease in materials response to the nonpolar analyte vapors

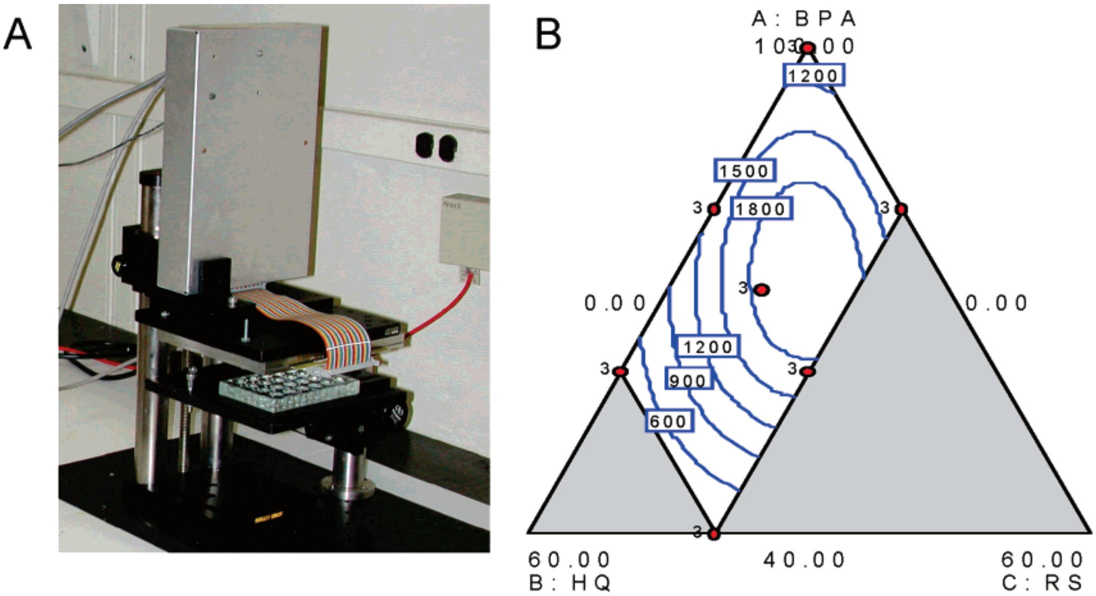


Figure 33. Application of the 24-channel TSM sensor array system for mapping of solvent resistance of polycarbonate copolymers: (A) general view of the screening system with a 6 × 4 microtiter wellplate positioned below the sensor array (reprinted with permission from ref 150; copyright 2004 American Chemical Society); (B) example of property/composition mapping of solvent resistance of polycarbonate copolymers in tetrahydrofuran (reprinted with permission from ref 414; copyright 2006 American Chemical Society). Numbers in the contour lines are normalized sensor frequency shift values (hertz per milligram of polymer in a well of the microtiter wellplate).

and the increase in response to a polar interference vapor were quantified.

This 24-channel TSM sensor array system was further applied for the high-throughput screening of solvent resistance of a family of polycarbonate copolymers prepared from the reaction of bisphenol A (BPA), hydroquinone (HQ), and resorcinol (RS) with the goal to use these copolymers as solvent-resistant supports for deposition of solvent-containing sensing formulations.[413] During the periodic exposure of the TSM crystals to polymer/solvent combinations (Figure 33A[150]), the mass increase of the crystal was determined, which was proportional to the amount of polymer dissolved and deposited onto the sensor from a polymer solution. The high mass sensitivity of the resonant TSM sensors (10 ng), use of only a minute volume of a solvent (2 mL), and parallel operation (matching a layout of the available 24 microtiter wellplates) made this system a good fit with available polymer combinatorial synthesis equipment. These parallel determinations of polymer−solvent interactions also eliminated errors associated with serial determinations. The data were further mined to construct detailed solvent-resistance maps of polycarbonate copolymers and to determine quantitative structure−property relationships (see Figure 33B[414]). The application of this sensor-based polymer-screening system provided a lot of stimulating data that were difficult to obtain using conventional one-sample-at-a-time approaches.

To eliminate the direct wiring of individual TSM sensors and to permit materials evaluation in environments where wiring is not desirable or adds a prohibitively complex design, Potyrailo and Morris[415] developed a wireless TSM sensor array system in which each sensor resonator was coupled to a receiver antenna coil and an array of these coils was scanned with a transmitter coil (Figure 34A). Using this sensor wireless system, sensing materials can be screened for their gas sorption properties, analyte binding in liquids, and changes in chemical and physical properties upon weathering and aging tests. The applicability of the wireless sensor materials screening approach has been demonstrated for the rapid evaluation of the effects of conditioning of polymeric sensing films at different temperatures on the vapor-response patterns. In one set of high-throughput screening experiments, Nafion film-aging effects on the selectivity pattern were studied. Evaluation of this and many other polymeric sensing materials lacks the detailed studies on the change of the chemical selectivity patterns as a function of temperature conditioning and aging. Conditioning of Nafion-coated resonators was performed at 22, 90, and 125 °C for 12 h. Temperature-conditioned sensing films were exposed to water (H_2O), ethanol (EtOH), and acetonitrile (ACN) vapors, all at concentrations (partial pressures) ranging from 0 to 0.1 of the saturated vapor pressure P_0, and their responses were measured using a network analyzer. The collected data were processed using PCA as shown in Figure 34B−D. It was found that conditioning of sensing films at 125 °C compared to room temperature conditioning provided (1) an improvement in the linearity in response to EtOH and ACN vapors, (2) an increase in relative response to ACN, and (3) a 10-fold increase of the contribution to principal component 2. The latter point signifies an improvement in the discrimination ability between different vapors upon conditioning of the sensing material at 125 °C. This new knowledge will be critical in designing sensors for practical applications when a need exists to preserve sensor response selectivity over long exploitation times or when there is a temperature cycling for an accelerated sensor-film recovery after vapor exposure.

In the area of homo- and copolymers, combinatorial technologies have been also employed for the development of sensing materials for chemical analysis in liquids. Using biocatalytic polymer synthesis, Dordick and co-workers[416,417] created a 15-member library of polyphenol polymers. Although the general knowledge exists on complexation of polyphenol polymers with metal ions,[416] the origin of the selective response to different metal ions is less known, and when a more selective polymer response is desired, it is more difficult to predict such responses quantitatively. Thus, this only general knowledge inspired a detailed exploration of combinations of a variety of starting monomers with an

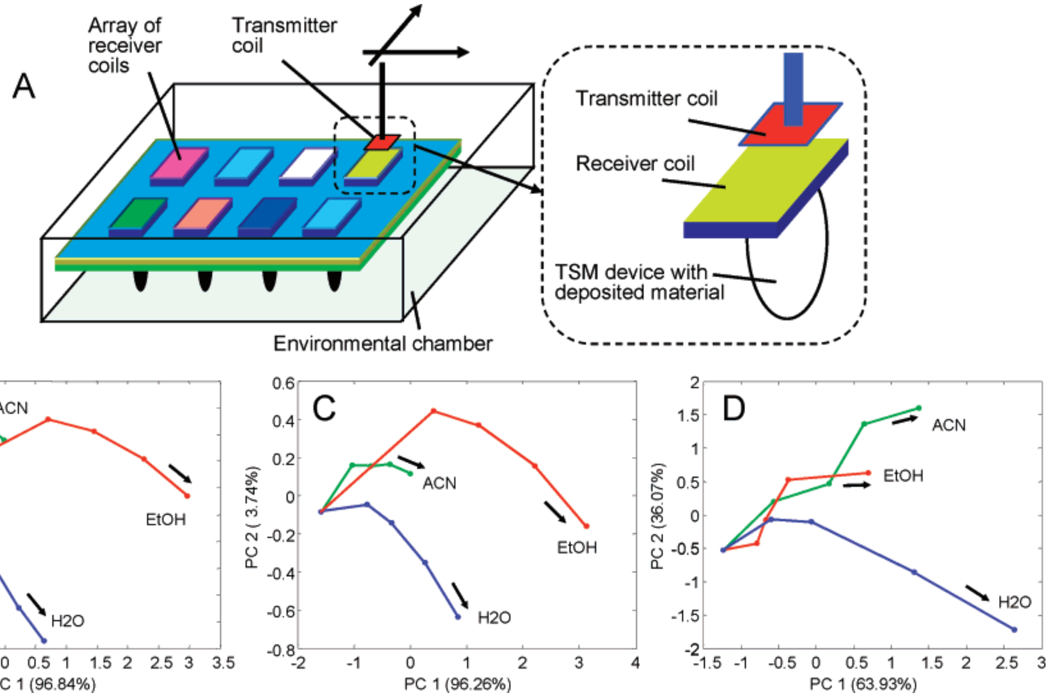


Figure 34. Concept for wireless high-throughput screening of materials properties using thickness shear mode resonators: (A) configuration of a wireless proximity resonant sensor array system for high-throughput screening of sensing materials with a single transmitter coil that scans across an array of receiver coils attached to resonant sensors; (B−D) evaluation of selectivity of Nafion sensing films to several vapors after conditioning at different temperatures [(B) 22, (C) 90, and (D) 125 °C]. Vapors: H_2O (water), EtOH (ethanol), and ACN (acetonitrile). Concentrations of vapors are 0, 0.02, 0.04, 0.07, and 0.10 P/P_0. Arrows indicate the increase of concentrations of each vapor. Reprinted with permission from ref 415. Copyright 2007 American Institute of Physics.

expectation to find polymeric materials for high-selectivity determination of metal ions of environmental importance. An array of 15 phenolic homopolymers and copolymers was combinatorially generated from 5 phenolic monomers by peroxidase-catalyzed oxidative polymerization. These polymers were screened for their intrinsic UV fluorescence (322 nm excitation) response to Fe^{3+}, Cu^{2+}, Co^{2+}, and Ni^{2+} ions at 0.2−1 mM concentrations.[416,417] As shown in Figure 35, the combinatorial approach generated a diverse metal ion response of new polymers from a limited number of phenolic monomers. New polymers demonstrated preferential selectivity to certain metal ions yet with some cross-sensitivity.

4.4. Conjugated Polymers

Conjugated polymers are organic polymers with conjugated bonds between single monomers that have electrical, electronic, magnetic, and optical properties similar to the properties of metals and semiconductors while preserving the processability and other properties of conventional polymers.[418] Examples of conjugated polymers include polyparaphenylene, polyphenylenevinylene, polypyrrole, polyacetylene, polythiophene, polyfuran, polyheteroaromatic vinylenes, polyaniline, and numerous derivatives of these compounds. Conjugated polymers have found their wide applicability as unique sensing materials[28,419−423] because recognition and transduction can be performed within the same chemical moiety. This feature is complementary to immobilization of individual recognition and transducing additives into sensing films based on nonconjugated polymeric compositions.

Current efforts in the development of conjugated polymers as sensing materials include introduction of diverse receptors into polymers, copolymerization with monomers that have desired receptor groups, incorporation of biological receptors, and molecularly imprinted polymerization. Several roles of conjugated polymers in sensing films include catalytic layers, redox mediators, molecular recognition receptors, analyte preconcentrators, and electrical and optical transducers.[424−429]

Properties of conjugated polymers for sensing applications depend on many factors summarized in Figure 36. Synthesis of conjugated polymers is typically realized either by the addition of oxidizing agents or by electrochemical oxidation.[430,431] The type and physical conditions of polymerization, choice of solvent, counterions, and the presence and type of additional dopants affect final properties.[432] Upon careful selection of the factors shown in Figure 36, these polymers can recognize, transduce, and, sometimes, amplify chemical or biological information into an optical or electrical signal.[433,434] Specifics of immobilization of receptor biomolecules include adsorption onto electropolymerized films, entrapment during the electropolymerization process, covalent binding on electrogenerated polymers, and anchoring by affinity interactions between biomolecules and conjugated polymers.[435]

To effectively evaluate the complexity of the composition and process parameters space, combinatorial approaches have been applied for screening of conjugated polymers for numerous applications.[436−438] Manipulation of reaction components during combinatorial synthesis of conjugated polymers include microfluidic and liquid-dispensing approaches. Microfluidic and microflow systems are well established in combinatorial chemistry[439−442] because of several important features they provide that include high efficiency, short time scales, safe conditions, and low amounts of waste. Microfluidic systems for combinatorial materials science have been

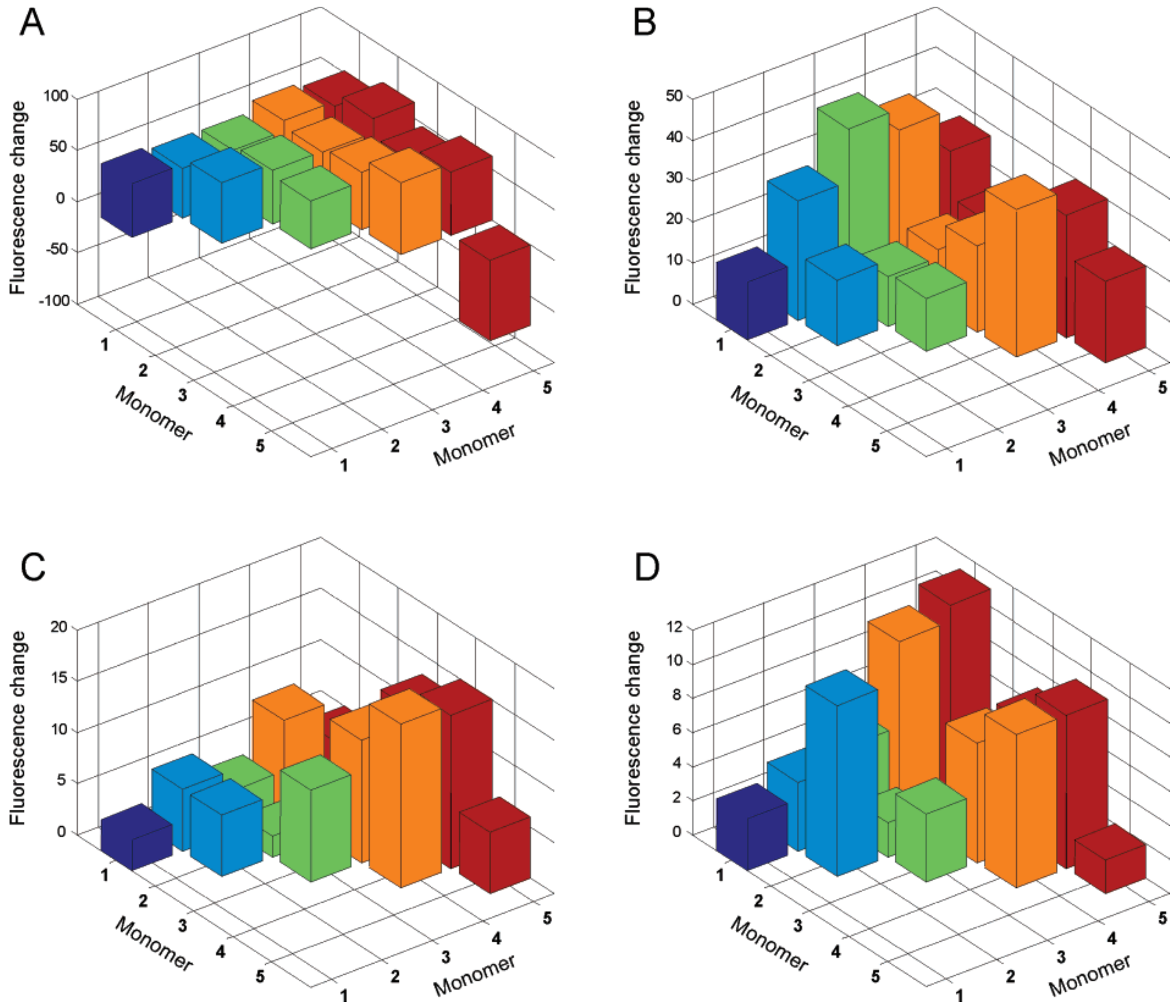


Figure 35. Results of combinatorial synthesis of a 15-member array of metal-ion sensitive homo- and copolymers from five phenolic monomers **1**−**5**; fluorescence responses of 15 materials to 4 metal ions: (A) 0.2 mM Fe^{3+}; (B) 1.0 mM Cu^{2+}; (C) 1.0 mM Co^{2+}; (D) 1.0 mM Ni^{2+}. Phenolic monomers: **1**, *p*-cresol; **2**, *p*-phenylphenol; **3**, *p*-methoxyphenol; **4**, *p*-hydroxyphenylacetic acid; **5**, *p*-hydroxybenzoic acid. Results were calculated from data reported by Dordick and co-workers.[417]

previously applied for organic phase synthetic reactions, formation of surface composition gradients, and many other applications.[366,443−445]

Combinatorial synthesis of polypyrrole-based polymers reported by Xiang and LaVan[446] involved a microfluidic system for gradient mixing of reagents and subsequent parallel electropolymerization in multichannels (see Figure 37). The microfluidic electrochemical polymer reactor generated stable concentration gradients of solutions of pyrrole and the sodium salt of polystyrenesulfonate (PSS) acid and other additives that resulted in controlled deposition of polypyrrole films with different thicknesses (see Figure 38). Doping of conjugated polymers [e.g., polypyrrole, polyaniline, poly(3,4-ethylenedioxythiophene)] with PSS is known to provide an improvement in chemical sensing ability via self-doping.[447−449] Multiple polypyrrole compositions were synthesized in 11 parallel fluidic channels over 4 electrodes per channel. However, with the gradient mixer it was possible to generate multiple but *fixed* compositions, and such a device did not allow any arbitrary ratio of reactants when multiple constituents were used. By using immiscible liquid plugs that form a droplet-based microfluidic system,[445] Xiang and LaVan demonstrated that it was possible to produce arbitrary compositions from more than two starting constitu-

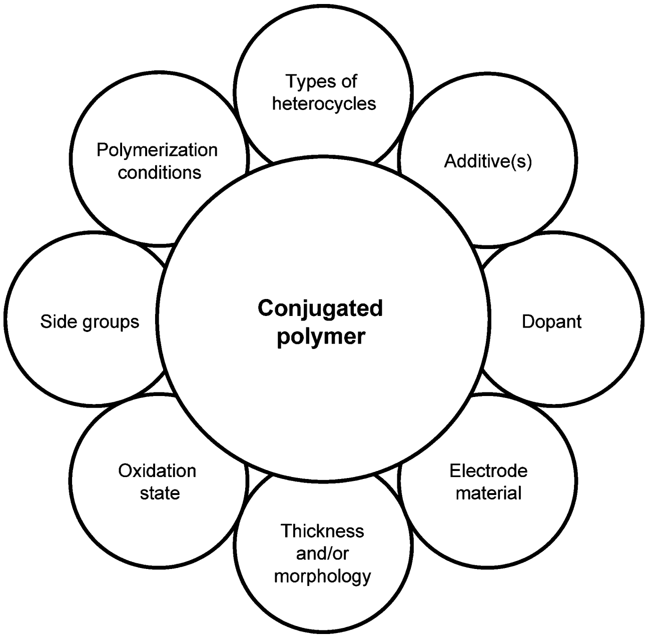


Figure 36. Diversity of optimization parameters during the preparation of conjugated polymer sensing materials.

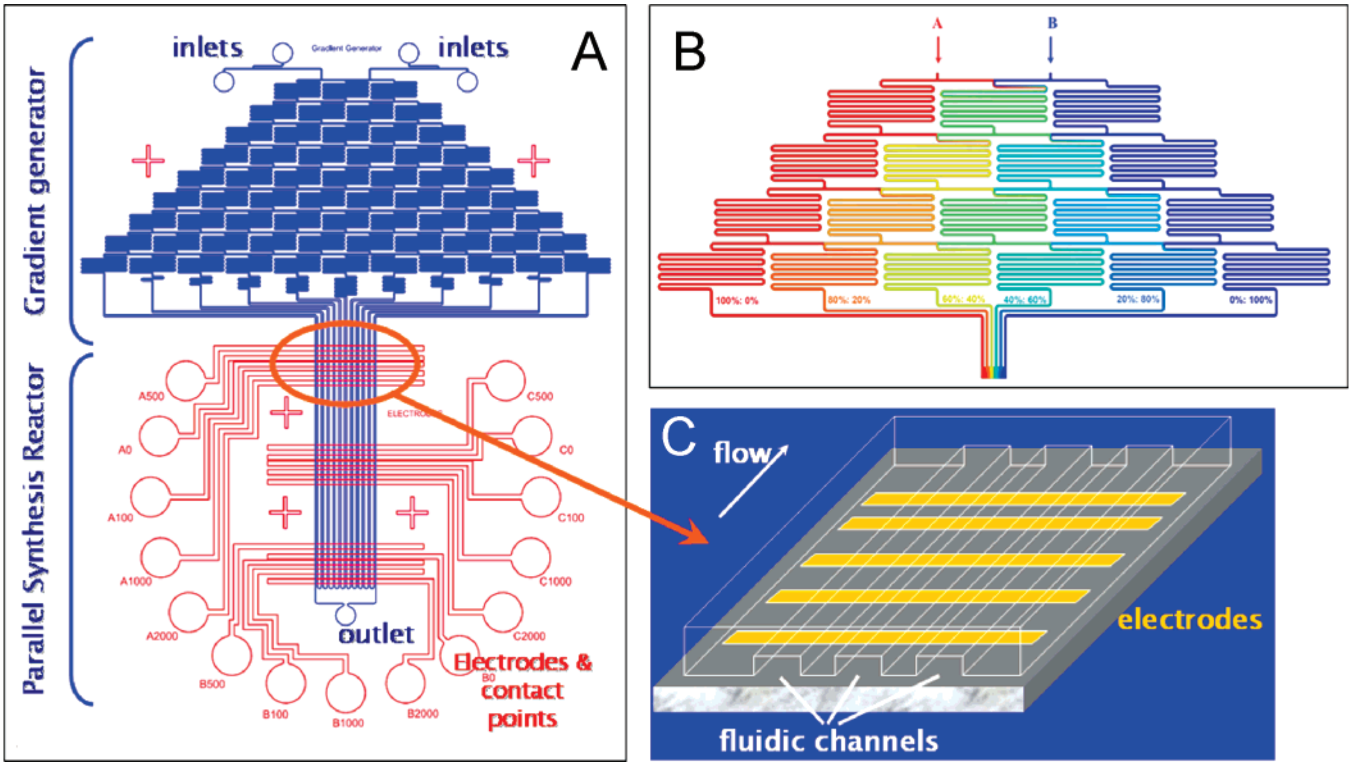


Figure 37. Design of a microfluidic system for combinatorial electrochemical synthesis of conjugated polymers: (A) general schematic of the system (the microfluidic channels are shown in blue and electrodes in red); (B) gradient generator [two different species **A** (red) and **B** (blue) were injected into the gradient generator from the top]; (C) parallel electrochemical synthesis reactor. Reprinted with permission from ref 446. Copyright 2006 The Institute of Electrical and Electronics Engineers, Inc.

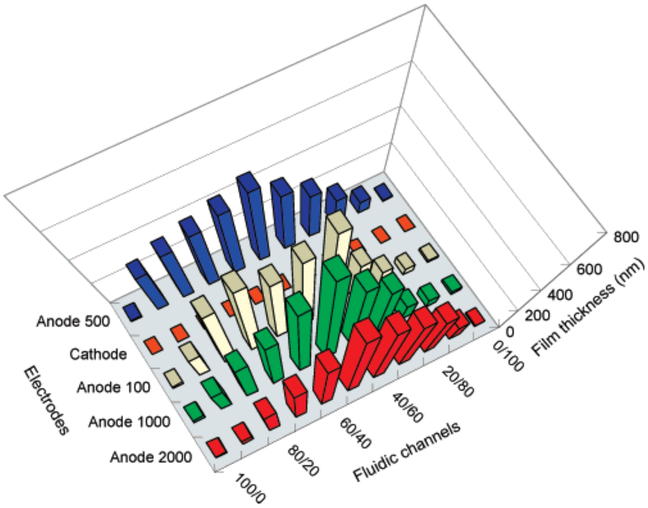


Figure 38. Combinatorial polymer deposition from the mixture of pyrrole and polystyrene sulfonic acid on platinum anodes placed at distances of 500, 100, 1000, and 2000 μm from the platinum cathode. Reprinted with permission from ref 446. Copyright 2006 The Institute of Electrical and Electronics Engineers, Inc.

ents.[446] Immiscible liquid plugs can provide rapid mixing of components, control of the timing of reactions, control of interfacial properties, and the ability to synthesize and transport solid reagents and products.[445] A developed prototype was composed of a plug microgenerator and a multiwell polymer microreactor. A microarray of as many as 100 plugs was generated, and redox reactions of monomers and dopants were conducted by properly activating microelectrodes installed in each microwell. By varying the ratio of input constituents, such a device was able to form droplets with any arbitrary composition and to deliver them within the immiscible carrier fluid to the prescribed locations.

Mirsky and co-workers developed an approach based on electrically addressed polymerization that did not require a controlled liquid flow or delivery to each individual polymerization region.[151,152,450,451] Instead, the addressable electrochemical polymer synthesis on the defined electrodes was performed by controlling the electrical potential of the given electrode group of the electrode array while all other electrode groups were kept below the required polymerization potential. To deposit different materials onto sensing regions in the electrode array, polymerization solutions in the electropolymerization microcell were simply changed between the polymerizations. For combinatorial electrochemical polymerizations, Mirsky and co-workers developed a screening system that utilized a chip with 96 groups of electrodes. Each electrode group had a size of 400 × 400 μm^2 and consisted of four electrodes designed for two- and four-point measurements. The 96-element chip operated in an electropolymerization microcell through an electronic multiplexer. The delivery of polymerization solutions and rinsing between individual polymerizations was performed with an automated dosing station.

To provide an automated high-throughput screening capability of chemosensitive properties of synthesized materials, the system was integrated into the combinatorial information workflow with the automated data analysis of analyte exposures of sensing films (see Figure 39). The key aspects of the workflow are summarized in Figure 39A.[452] The developed automated procedure to test polymerized conjugated sensing films included two analyte-pulsed exposures at one concentration and a sequence of analyte-pulsed exposures at increasing concentrations. An automated data analysis of materials responses included calculated absolute and relative analytical sensitivity, response and recovery rate, recovery efficiency, reversibility, reproduc-

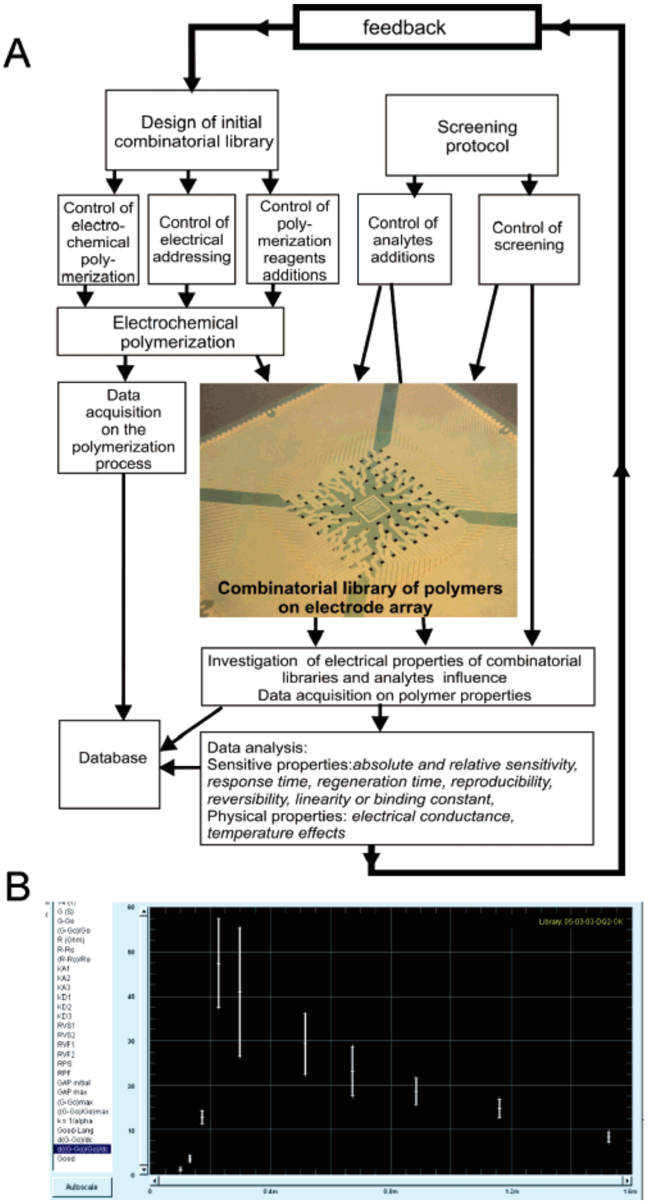


Figure 39. Combinatorial electrochemical polymerizations of conjugated sensing polymers: (A) combinatorial information workflow with the automated data analysis of analyte exposures of the sensing films (in the photo of 96-element combinatorial library of sensing films, dark regions in the center of the combinatorial library are formed by synthesized polymers) (reprinted with permission from ref 452; copyright 2005 American Chemical Society); (B) example of user interface demonstrating automatically computed relative sensitivity of response of combinatorial library of sensing films to 3.5 ppm of HCl gas as a function of polymerization charge. The leftmost region of the interface panel is the menu for selection of analyzed parameters for display. See text for details.

ibility, binding constant (for sensor materials that obey Langmuir's adsorption isotherm), and response linearity (for sensor materials that obey Henry's adsorption isotherm).[152]

This system was employed for screening a wide variety of sensing materials. In screening of chemosensitive properties of polyanilines, copolymers of anilines, and aniline derivatives, combinatorial libraries were tested for their response to HCl gas.[151,450] The measured electrical resistance was detected simultaneously by two- and four-point techniques.[451,453] Figure 39B illustrates an example of data analysis interface with a user-selected display of calculated parameters. As seen in Figure 39B, the relative sensitivity of response (normalized to initial conductance) of polymerized sensing materials had its optimal (maximum) value at the polymerization charge of ∼0.5 mC, further employed for more detailed studies.

A summary of exemplary screening results for different binary copolymers is presented in Figure 40. An introduction of nonconductive monomers into polymer decreased the polymer conductance and therefore decreased the difference between conductive and insulating polymer states. This caused a decrease of the absolute sensitivity (Figure 40A). Normalization to the polymer conductance without analyte exposure compensated this effect and demonstrated that the polymer synthesized from the mixture of anthranilic acid and aniline possessed the highest relative sensitivity (Figure 40B). This effect may be explained by the strong dependence of polymer conductance on the defect number in polymer chains. In comparison with pure polyaniline, this copolymer had better recovery efficiency but a slower response time (Figure 40C,D). The developed high-throughput screening system was capable of reliable ranking of sensing materials and required only ∼20 min of manual interactions with the system and ∼14 h of computer-controlled combinatorial screening compared to ∼2 weeks of laboratory work using traditional electrochemical polymer synthesis and materials evaluation.[151]

Mirsky and co-workers used the developed system also for optimization of enzymatic biosensors for glucose with electrocatalytic transduction.[151] Developed sensing films for glucose were multilayer systems that contained an electrocatalyst, an enzyme, and a conjugated polymer. To form glucose-sensitive films, a layer of variable thickness of Prussian Blue (an electrocatalyst for decomposition of hydrogen peroxide) was electrochemically synthesized on the electrode groups in the array. Then the films were exposed to hydrogen peroxide, and their electrochemical response was compared to optimize the thickness of the catalyst layer. Next, a solution of pyrrole-containing glucose oxidase was electropolymerized with variable thickness on the electrode groups in the array, and the electrocatalytic currents observed upon glucose additions were analyzed to determine the best sensing film candidates. This convenient layout of combinatorial libraries in the form of small amounts of polymers of a few micrograms on the surface of the electrode array allowed not only characterization but also further storage and organization of banks of sensing materials for further investigations.

Schuhmann and co-workers developed a general purpose setup for combinatorial electrochemistry by combining a liquid-dispensing mechanical robot and electrochemical system.[454] The setup operated with one electrode set (consisting of classical three-electrode configuration), moving it between different cells or with an eight-electrode set providing simultaneous eight-channel measurements compatible with a microtiter wellplate layout. Such a system was applied successfully for high-throughput investigation of porphyrins[455] and would be certainly very helpful for screening of other types of combinatorial libraries, for example, of metallic nanoparticles.[456,457] This system was used by Bäuerle and co-workers[458] for high-throughput electrochemical characterization of combinatorial libraries of π-conjugated oligothiophenes. Such materials are widely used for optical and electrical detection of gases and metal ions.[459−462] A regioregular head-to-tail coupled quater(3-arylthiophene) was

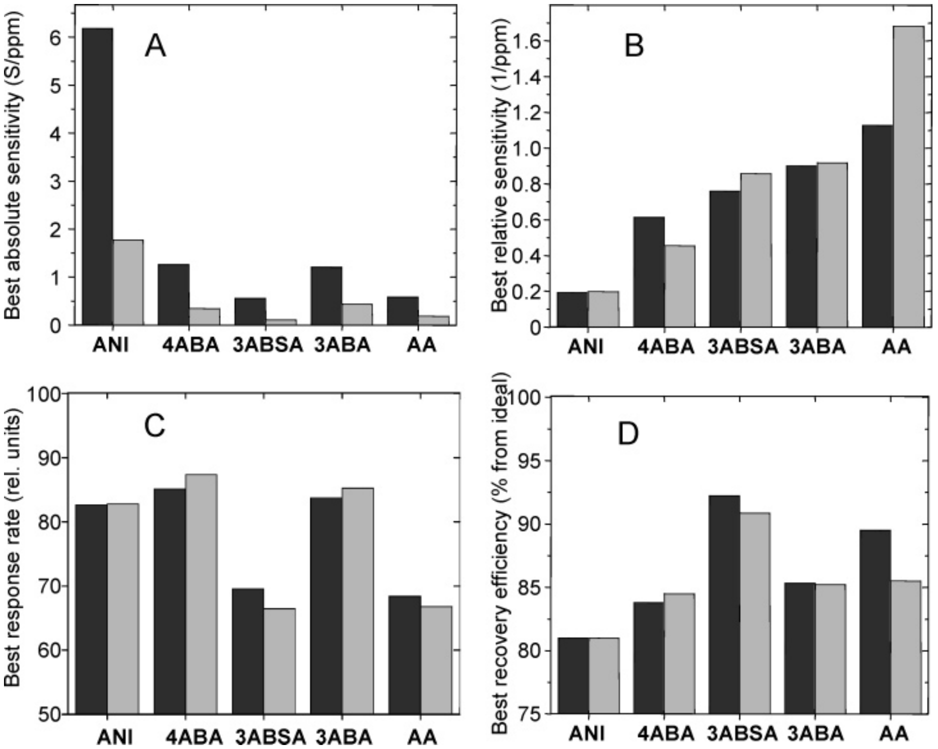


Figure 40. Selected results of screening of sensing materials for their response to HCl gas: (A) best absolute sensitivity; (B) best relative sensitivity; (C) best response rate; (D) best recovery efficiency, performed by heating. Sensor materials: ANI indicates polyaniline; 4ABA, 3ABSA, 3ABA, and AA indicate polymers synthesized from aniline and 4-aminobenzoic acid, 3-aminobenzenesulfonic acid, 3-aminobenzoic acid, and anthranilic acid, respectively. Gray and black bars are the results obtained by two- and four-point techniques, respectively.

selected as the lead structure (Figure 41A) for combinatorial synthesis to systematically investigate the substitutent influence on the energy levels of the molecular orbitals and to develop structure−property relationships. This oligothiophene was substituted at the 3-position of each thiophene subunit with phenyl groups and at the para positions with one of four groups (CF_3, H, CH_3, OCH_3). These four groups have different electronic nature expected to affect the electronic structure of the quaterthiophenes without greatly changing the overall geometry of the molecule. The synthesized 256-oligomer library included all possible permutations of the four diversity elements. The electronic consequences of the oligomer substitution on the relative energy levels of the frontier orbitals were further investigated by automated cyclic voltammetry to obtain the data on the substituent effects on redox potentials. A systematic shift to the higher first oxidation potentials E_1^0 occurred when the substituents had a more pronounced acceptor character as shown in Figure 41B. A similar trend was also found for the second oxidation potentials E_2^0 of the quaterthiophenes. The correlation of the collected redox potentials was further established with the substituent descriptor $\Sigma\sigma_p^+$. This descriptor was defined as the sum of the Hammett constants σ_p^+ of the individual substituents and numerically reflected the overall contributions of the individual substituents. The relationship between the first E_1^0 and second E_2^0 oxidation potentials and substituent descriptor $\Sigma\sigma_p^+$ is illustrated in Figure 41C. Thus, combinatorial methodologies allowed the synthesis and evaluation of carefully planned libraries of conjugated polymers to deduce structure−property relationships.

In the future, combinatorial screening of electrical properties of conjugated polymers can be combined with automated analysis of optical properties to gain more insight into the function of differently doped conjugated polymers. Electropolymerization can be combined with electrochemical deposition of metals or other types of conductive or nonconductive layers with different functions. Postsynthetic chemical modifications or grafting photopolymerization can be also additional ways for formation of more advanced structures.

4.5. Molecularly Imprinted Polymers

The key feature of molecularly imprinted materials is their engineered selectivity of binding to an analyte of interest. These synthetic materials mimic the hypothesis of generation of antibodies by the immune system and trace their origin to the works of Mudd[463] and Pauling.[464] The early work in molecular imprinting involved silica gels and was done in the 1930 and 1940s by Polyakov in the Soviet Union[465] and by Dickey in the United States.[466] Wulff and Sarhan were the first to synthesize and characterize molecularly imprinted organic polymers.[467] At present, the area of research on molecularly imprinted materials is not only tremendously active but also one of the most advanced in the combinatorial and rational aspects of materials design. A comprehensive database of literature on molecularly imprinted materials is accessible at the homepage of the Society for Molecular Imprinting (www.molecular-imprinting.org). Recent reviews are available in refs 468−477.

Synthesis of molecularly imprinted polymers (MIPs) includes several essential steps (Figure 42) such as (1) preparation of a non-covalent complex or covalent conjugate between polymerizable functional monomers and analyte or its analogue, (2) polymerization of these functional monomers, and (3) removal of the analyte or its analogue from the polymer. Thus, MIPs are synthesized using several functional monomers and an analyte molecule (known as a

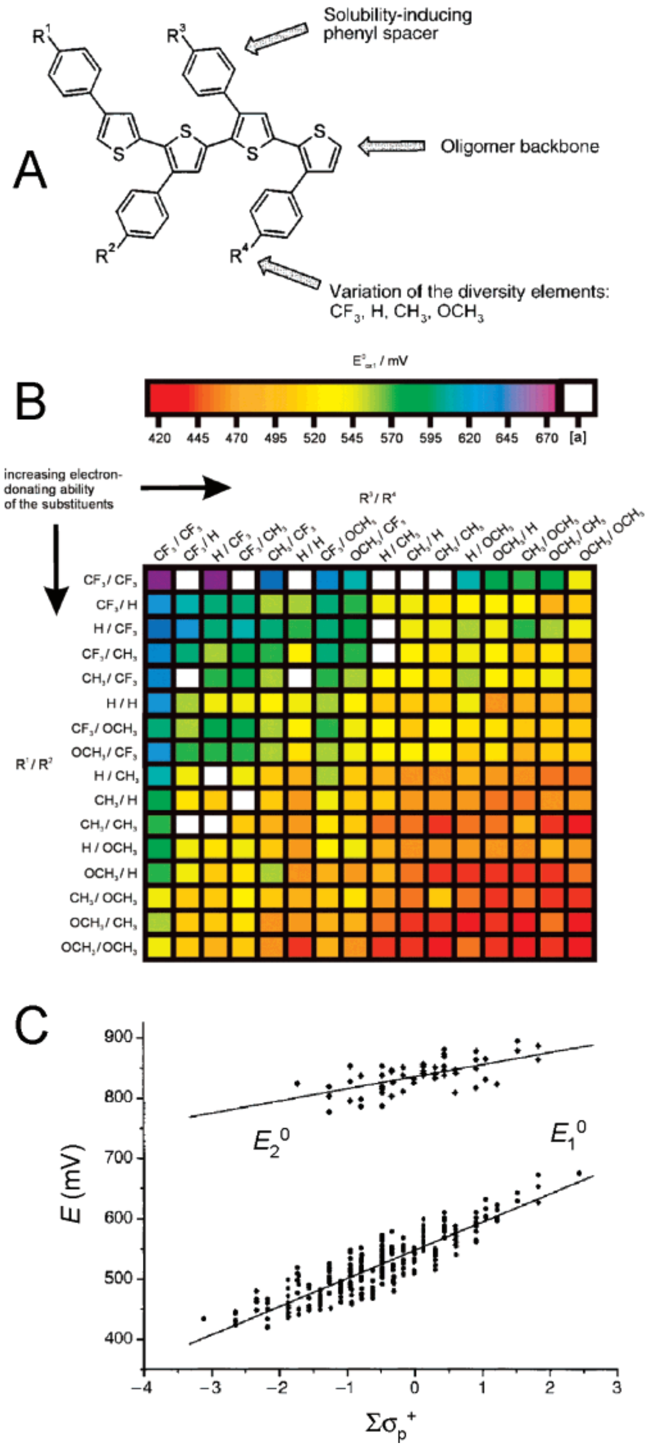


Figure 41. Deduction of structure−property relationships using combinatorial synthesis and high-throughput evaluation of quater-(3-arylthiophene)s library: (A) structure of quater(3-arylthiophene)s; (B) results from automated cyclic voltammetry determinations of the first oxidation potentials $E_1{}^0$ (in the color bar, [a] is not determined because of sample impurity); (C) relationship between the substituent descriptor $\Sigma\sigma_p{}^+$ and the first $E_1{}^0$ and second $E_2{}^0$ oxidation potential of the combinatorial library of quaterthiophenes. Reprinted with permission from ref 458. Copyright 2001 Wiley-VCH Publishers.

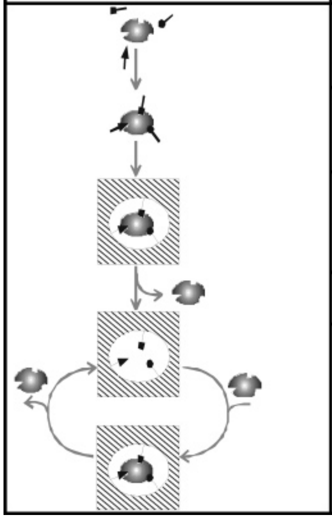
illustration	process	high-throughput techniques
	mixing of template, functional monomers, crosslinker and porogen	liquid handling robots, microtiter plates
	self-assembly of complex between functional monomers and template	complex optimization by: • screening in-silico • microcalorimetry • NMR
	polymerization of functional monomers and cross-linker	parallel polymerization
	template removing	comparison of template desorption by HPLC or other techniques
	analytical cycle	high-throughput functional tests by HPLC or by response analysis of sensor arrays (SPR-imaging, arrays for fluorescent, capacitive, electrochemical or other detection techniques)

Figure 42. Application of molecularly imprinted polymerization for development of chemical and biological sensing materials.

“template”). During the MIP synthesis, monomers self-assemble and cross-link around the template. The presence of template during the polymerization process of the MIP facilitates the formation of a cavity that closely matches the template. Once the template is removed from the fabricated MIP, the material can be used as a polymeric receptor for sensing applications with different types of transducers. In a liquid-phase detection, replacement of water by analyte molecules leads to changes of electrical (e.g., capacitance) and/or optical (e.g., refractive index) properties of the polymer layer, which may occur due to analyte binding or as a result of a subsequent osmotic swelling. These changes can be detected by impedance[478−481] or surface plasmon resonance[279,482,483] measurements. A “gate effect”[484,485] accompanying analyte binding to a MIP film can be detected by conductivity measurements. Mechanical changes of the polymer layer (including its mass and acoustic thickness) lead to broad applications of TSM transducers[486−488] for sensing with MIP films. Fluorescent sensing can be used for detection of fluorescent analytes in competitive assays[489,490] or in fluorescent MIPs.[491,492] Electrochemical techniques can be applied for direct detection of electrochemically active analytes or for replacement of electrochemically active markers in competitive assays.[493−495] Other detection approaches include colorimetric,[496,497] calorimetric,[498] and ISFET.[499,500] In addition to the use of various sensing platforms, detailed investigations of affinity of MIPs are performed by HPLC.

There are two specific aspects for MIP-based receptors for application in chemical sensors. The first aspect is related to the polymer morphology and thickness and is driven by the relatively slow analyte diffusion in MIPs. In conventional 3-D imprinting, the thickness of the employed polymer layers is from several nanometers to about a micrometer. A deposition of thin polymer layers can be performed by spin-coating, electropolymerization, and grafting photopolymerization.[478−480,501] In many detection techniques the sensor signal can be increased by increasing the sensor surface; this is a motivation for development of MIPs based on immobilized dendrimers or nanoparticles.[279,502] The second aspect of MIPs is related to the heterogeneity of their binding sites with only scarce reports on quasi-homogeneous binding sites. This heterogeneity causes broad distribution of the binding constants of different binding sites of the same polymer. This leads to a broader range of measured analyte concentrations, but this advantage is compromised by a less predictable sensor behavior. After analyte removal, some of the analyte molecules remain in the stronger binding sites,

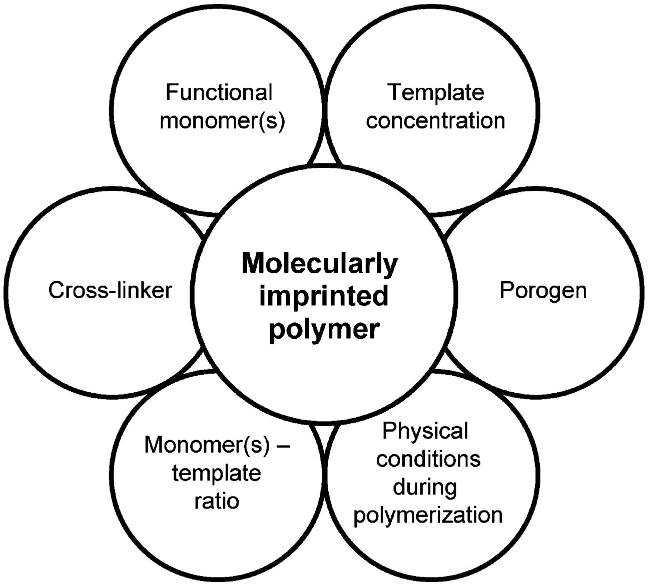


Figure 43. Diversity of optimization parameters during the preparation of molecularly imprinted polymers.

and only weak binding sites can be occupied during the next analyte exposure. Thus, the binding constant and binding kinetics of such a sensing material will be defined mainly by the weak binding sites. This results in the dependence of apparent sensor affinity on the desorption efficiency. Therefore, the critical requirement for analyte quantitation using MIP materials is the reproducible desorption of analyte.

The complex between analyte and polymerizable monomers can be stabilized by cleavable covalent bonds and/or by non-covalent interactions. Advantages and disadvantages of covalent and non-covalent types of complexes were summarized earlier.[470] Covalent imprinting was primarily developed by Wulff and co-workers.[467,503−505] An example of the functional monomer that is often used for covalent imprinting is phenylboronic acid as a receptor for *cis*-1,2- and *cis*-1,3 diols, including saccharides, nucleotides, AMP, and NAD(P).[506−508] A more sophisticated covalent imprinting typically requires a synthesis of cleavable polymerizable derivative of an analyte and results in the formation of more homogeneous binding sites.

Non-covalent imprinting, introduced by Mosbach and co-workers,[509] is more flexible but leads to higher heterogeneity of binding sites.[510] The non-covalent interactions are provided by hydrogen bonds, ionic bonds, van der Waals forces, and hydrophobic interactions. Higher flexibility and simplicity of the non-covalent approach are, of course, very attractive. However, at the same time this flexibility makes an optimization of sensing materials extremely resource- and time-consuming. Figure 43 illustrates the diversity of parameters involved in the fabrication of MIPs with desired selectivity and capacity. Molecular organization around the template is provided by the non-covalent interactions between the template and the functional and cross-linking monomers. The morphology and selectivity of the resulting MIP are affected by the stoichiometry and concentration of the template and monomers.[511] The timing of the phase separation during polymerization that influences the binding properties of the resulting MIP is determined by the polymerization porogen (solvent) and by the physical conditions (temperature, pressure) during polymerization.[511−514] A number of successful imprintings of different analytes by exactly the same mixtures of polymerization monomers were reported,[479−481] indicating the possibility of finding a mixture of monomers that can be used for more than one application for molecular imprinting.

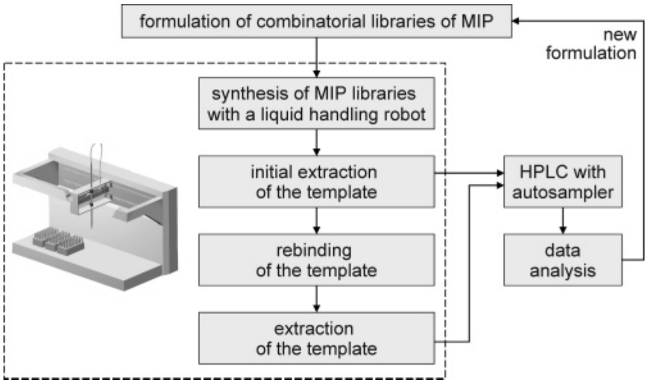


Figure 44. Workflow for automated analyte-binding evaluation of combinatorial libraries of MIPs.

In 1999, groups of Takeuchi[515] and Sellergren[516] independently introduced combinatorial technologies into molecularly imprinted polymerization. In these first combinatorial studies, both groups selected herbicides as model analyte substances and validated the high-throughput combinatorial molecularly imprinting technique as a working method for finding optimal conditions of MIP preparation. Following these pioneering studies, the combinatorial screening technology has been improved by decreasing the sample volumes in combinatorial libraries to ∼50 mg, increasing the size of combinatorial libraries up to 60 polymer samples, and application of additional initiation approaches such as thermoinitiation.[517] The MIP synthesis was further performed by liquid-handling robots in 96-well microtiter plates with the automated binding detection analyzed by analytical instrumentation designed for combinatorial screening[518−523] as shown in Figure 44.

Multiple parameters shown in Figure 43 that could be optimized to find an ideal MIP material may lead to a costly and complicated workflow even when high-throughput automated systems are employed. Thus, it may be attractive to optimize not the final MIP product but rather each step of the product preparation. A complex formation between functional monomers and template shown in Figure 42 is the crucial step in the synthesis of effective MIPs. Therefore, recent optimization efforts have been focused on the template−functional monomer complexes. The complex stoichiometry has been evaluated with microcalorimetry.[524] Also, ^{1}H NMR was used for the fast evaluation of functional groups of the template that can form bonds with functional monomers.[525,526] The Job's plot of chemical shifts measured for binary mixtures of the template−functional monomer complex demonstrated the 1:1 stoichiometry of the complex.[525,526] Both methods belong to simple prescreening techniques that can be used for further design of combinatorial libraries for functional screening.

Besides the growing range of combinatorially developed artificial receptors,[527] the data mining technologies also have been significantly improved. Simple comparisons of trends and maxima of the most important analytical characteristics such as binding and selectivity have been complemented with the multivariate statistical data analysis.[528−531] An application of this approach for development of MIP for sulfonamides is shown in Figure 45. The optimal molar ratio of template,

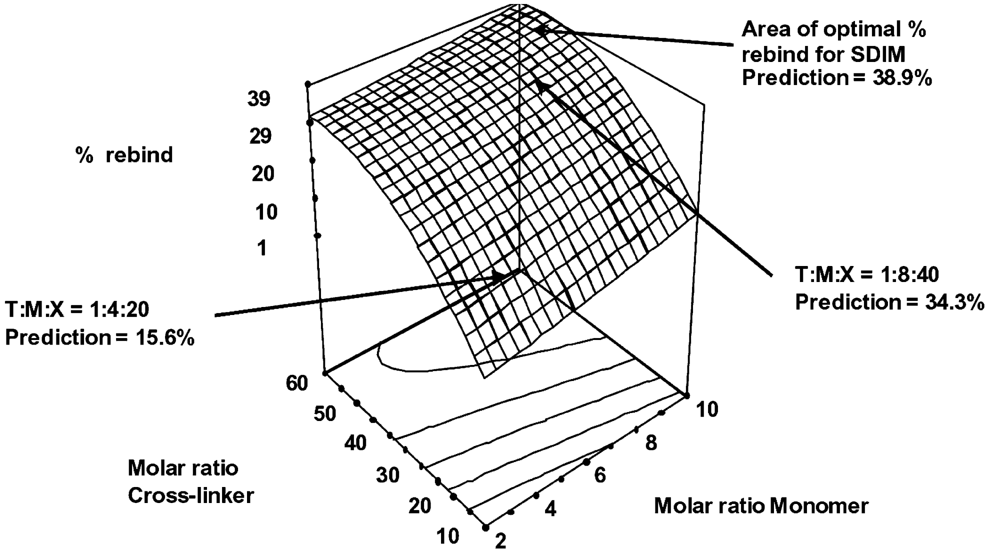


Figure 45. Optimization of the template/monomer/cross-linker (T:M:X) ratio of the MIP using a three-level full-factorial design. Reprinted with permission from ref 530. Copyright 2004 Elsevier.

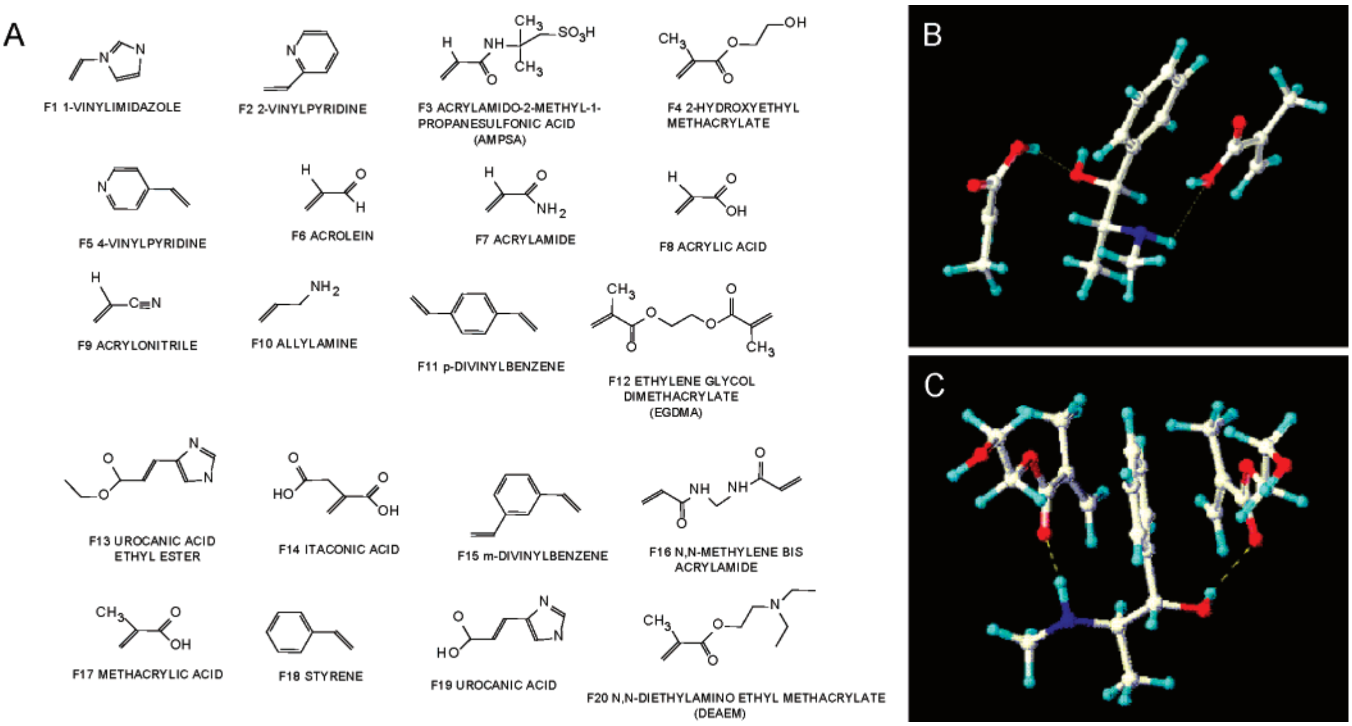


Figure 46. Rational design of MIPs: (A) virtual library of 20 monomers used for in silico optimization of the complex with ephedrine; computed structures of the ephedrine complex with (B) methacrylic acid and (C) hydroxyethyl methacrylate. Reprinted with permission from ref 534. Copyright 2001 The Royal Society of Chemistry.

monomer, and cross-linker (T:M:X) was predicted from statistical analysis and confirmed by a direct experiment.[530] Independent multivariate analysis was applied for optimization of MIP for bisphenol A. In addition to the T:M:X ratio, a concentration of initiator, a polymerization porogen (tetrahydrofuran, chloroform, toluene, or acetonitrile) and an initiation procedure (photochemical or thermal) were optimized.[529]

The goal to find approaches for rational design of MIPs was formulated in 1998.[532,533] However, the task was considered to be too complicated.[492] The first study to replace experimental screening of molecularly imprinted polymers by screening in silico was performed by Piletsky and co-workers.[534] To develop a MIP specific to ephedrine, a virtual library of 20 functional monomers was developed and computationally evaluated (see Figure 46). Molecular modeling was used to calculate binding energy between the monomers and the template. Although effects of cross-linker and porogen were not considered during the calculations, a good correlation between calculated results and a further HPLC study was obtained. Later, this approach was used by Piletsky and co-workers to design MIPs for creatinine,[535] microcystin,[536] biotin,[537] and carbaryl.[538] Table 4 demonstrates a comparison of properties of MIPs optimized by molecular modeling with properties of mono- and polyclonal antibodies.[536] Molecular modeling was also implemented by other scientific groups, and MIPs for other analytes were developed.[487,539−543]

Table 4. Comparison of MIPs Based on Methacrylic Acid, MIPs Optimized by Computational Design, and Polyclonal and Monoclonal Antibodies (Adapted from Reference 536)

properties of sensitive materials		MIP optimized by computational design	MIP based on methacrylic acid	monoclonal antibodies	polyclonal antibodies
binding properties	reciprocal binding constant, nM	0.3 ± 0.1	0.9 ± 0.1	0.030 ± 0.004	0.50 ± 0.07
sensitivity range, μg/L	0.1−100	0.8−100	0.025−5	0.05−10	
cross-reactivity, %	Microcystin-RR	21 ± 1	19 ± 1	106 ± 1	92 ± 2
Microcystin-YR	27 ± 2	30 ± 3	44 ± 2	142 ± 1	
Nodularin	22 ± 2	36 ± 1	18 ± 1	73 ± 1	
stability under harsh conditions	80 °C	89 ± 1	52 ± 2	17 ± 5	9.9 ± 0.2
(remaining affinity of receptors)	80% DMF	102 ± 2	97 ± 2	19 ± 4	18 ± 1
pH 2	100 ± 3	102 ± 2	16 ± 1	94 ± 2	
pH 11	102 ± 3	118 ± 5	18 ± 5	44 ± 7	
10 mM $CuSO_4$	98 ± 1	56 ± 2	24 ± 1	17 ± 1	

Artificial receptors synthesized by molecularly imprinted polymerization were also formed as 2-D structures on solid supports. The development of 2-D molecular imprinting was initially independent from 3-D imprinting. One of the first observations of this effect was reported by Sagiv,[544] who described a memory effect and molecular shape recognition for the monolayers of octadecyltrichlorosilane. This effect was further observed for non-cross-linked self-assembled monolayers of alkylthiols on gold.[545] Further attempts to stabilize the system resulted in the development of the spreader-bar approach, in which the template molecules were not removed.[545−547] The principle of the spreader-bar approach is illustrated in Figure 47A.[547] This approach was evaluated to prepare large amounts of different receptors that can distinguish not only molecules of different compounds[547] but also the molecules with different chiralities.[548] However, a number of factors complicate an affinity prediction of these spreader-bar structures. First, a design of preparation conditions of mixed monolayers in equilibrium conditions requires information on the affinity of corresponding compounds to the electrode surface,[549] which is currently available only for a few compounds. Additionally, mixed monolayers from compounds with strong intermolecular interaction leading to the formation of domains should be excluded. Detailed structural investigation of such systems is time-consuming.[293,550] Even for well-characterized mixed monolayers it

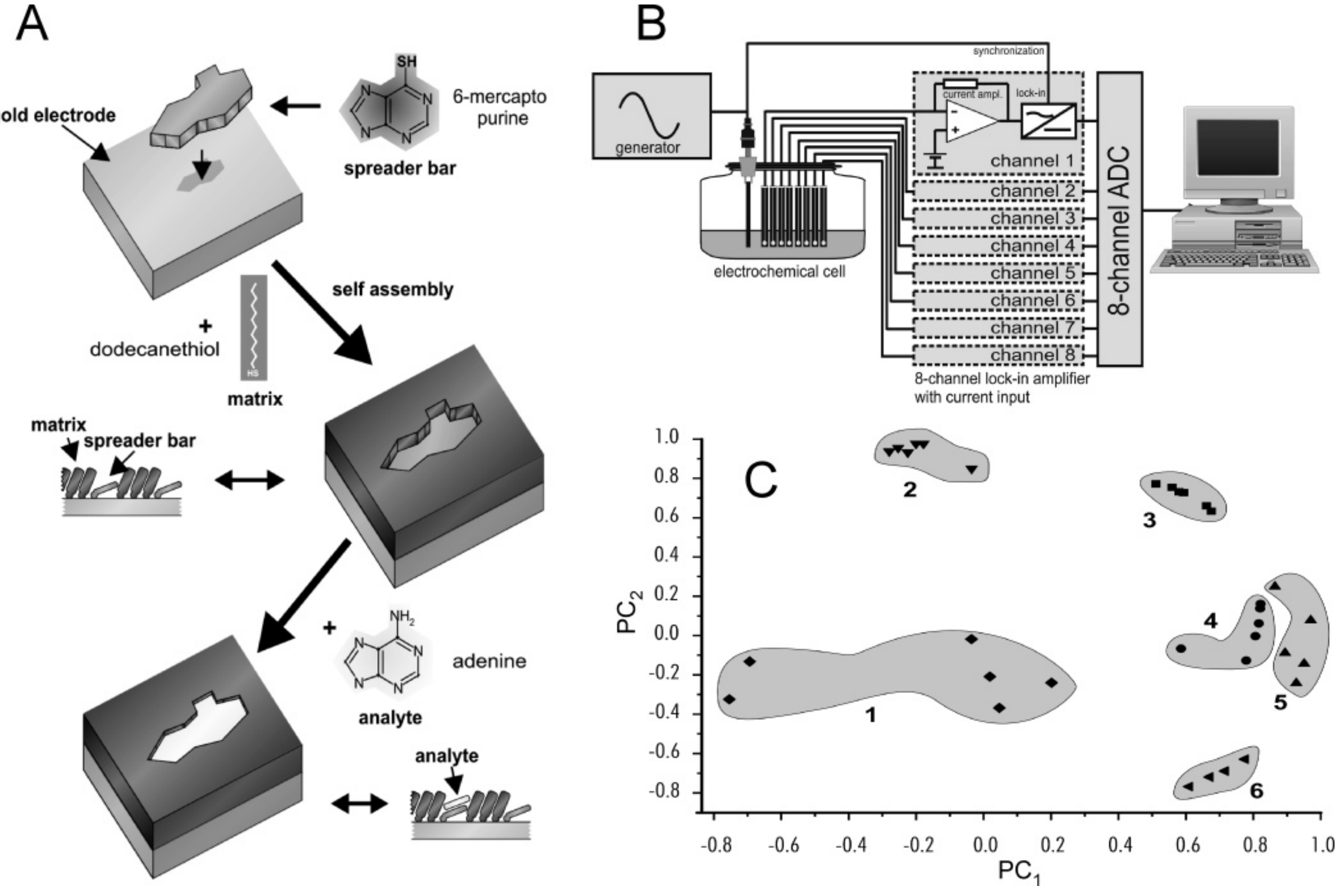


Figure 47. Approach for high-throughput development of 2-D imprinting with stabilization by the molecular spreader-bar technique: (A) principle of the spreader-bar technique (reprinted with permission from ref 547; copyright 2003 The Royal Society of Chemistry); (B) schematic of an electrochemical system for parallel investigation of biosensing materials formed by the spreader-bar technique; (C) responses of 2-D imprinted materials (as a scores plot of the first and second principal components) on additions of caffeine (1), uracil (2), adenine (3), cytosine (4), thymine (5), and uric acid (6) (reprinted with permission from ref 547; copyright 2003 The Royal Society of Chemistry).

is not easy to predict their affinity properties. This was the motivation for the development of a system for high-throughput impedance screening of affinity properties. The system for simultaneous capacitance measurements was based on eight lock-in amplifiers with current input as shown in Figure 47B. This approach was used for the development of a sensor array for the determination of purines and pyrimidines using PCA (Figure 47C).[547]

The true 2-D molecularly imprinted polymers, with polymerization and removal of the template, have been developed mainly for large analytes (e.g., proteins and bacteria) that are difficult to extract from the bulk polymer.[488,551−554] Typical technologies of their preparation are very similar to that for 3-D MIPs. For example, Tappura et al. reported 2-D imprinting of morphine[555] when the structure of binding sites was optimized by molecular dynamic simulation. Most of the approaches developed for high-throughput screening of 3-D polymers can be adapted for 2-D imprinted materials. In the future, promising approaches for the design of MIPs may be based on a two-step procedure including an initial optimization of the complex content and stoichiometry (by either experimental combinatorial screening of binding or/and theoretical modeling) and a final experimental functional optimization of the imprinted polymer.

5. Summary and Outlook

Combinatorial and high-throughput technologies in materials science have been successfully accepted by research groups in academia and governmental laboratories that have overcome the entry barrier of dealing with new emerging aspects in materials research such as automation and robotics, computer programming, informatics, and materials data mining. The main driving forces for combinatorial materials science in industry include broader and more detailed explored materials and process parameters space and faster time to market. Industrial research laboratories working on new catalysts and inorganic luminescent materials were among the first adopters of combinatorial methodologies in industry. The classical example of an effort by Mittasch, who has spent 10 years (over 1900−1909) to conduct 6500 screening experiments with 2500 catalyst candidates to find a catalyst for industrial ammonia synthesis,[556] will never happen again because of the availability and affordability of modern tools for high-throughput synthesis and characterization.

In the area of sensing materials, reported examples of significant screening efforts are less dramatic, yet also breathtaking. For example, a decade ago, Cammann, Shulga, and co-workers[386] reported an “extensive systematic study” of more that 500 compositions to optimize vapor-sensing polymeric materials. Walt and co-workers[57] reported screening of over 100 polymer candidates in a search for “their ability to serve as sensing matrices” for solvatochromic reagents. Seitz and co-workers[557] investigated the influence of multicomponent compositions on the properties of pH-swellable polymers by designing 3 × 3 × 3 × 2 factorial experiments. Clearly, combinatorial technologies have been introduced at the right time to make the search for new materials more *intellectually rewarding*. Naturally, numerous academic groups that were involved in the development of new sensing materials turned to combinatorial methodologies to speed knowledge discovery.[44,45,152,161,219,221,365]

From numerous results achieved using combinatorial and high-throughput methods, the most successful have been in the areas of molecular imprinting, polymeric compositions, catalytic metals for field-effect devices, and metal oxides for conductometric sensors. In those materials, the desired selectivity and sensitivity have been achieved by the exploration of multidimensional chemical composition and process parameters space at a previously unavailable level of detail at a fraction of the time required for conventional one-at-a-time experiments. These new tools provided the opportunity for the more challenging, yet more rewarding, explorations that previously were too time-consuming to pursue.

Future advances in combinatorial development of sensing materials will be related to several key remaining unmet needs that prevent researchers from having a complete combinatorial workflow and to “analyze in a day what is made in a day”.[122]

First, new fabrication methods of combinatorial libraries of sensing materials will be implemented ranging from those adapted from other materials synthesis and fabrication approaches[558,559] to those developed specifically for sensing applications.[356]

Second, although the evaluation of performance properties of sensing material has been automated and numerous sensing systems have been developed to collect reliable response data from sensing materials, the remaining need is to develop screening tools for high-throughput characterization of intrinsic materials properties to keep up with the rates of performance screening of sensing materials candidates. For example, in the area of conductometric metal oxide sensors, a variety of employed techniques (e.g., Hall, catalytic conversion, and work function measurements, DRIFT spectroscopy) are at different stages in their high-throughput screening capabilities.

Third, certain portions of the data management aspects of the combinatorial workflow are still under development as summarized in Table 2. However, over the past several years, there have been a growing number of reports on data mining in sensing materials.[232,414,528,531] “Searching for a needle in the haystack” was popular in the early days of combinatorial materials science.[59,560,561] At present, it has been realized that screening of the whole materials and process parameters space is still too costly and time prohibitive even with the availability of existing tools. Instead, designing the high-throughput experiments to discover relevant descriptors will become more attractive.[562]

Fourth, predictive models of behavior of sensing materials under realistic conditions over long periods of time are needed. These modeling efforts will require inputs not only from screening of the performance and intrinsic properties of sensing materials but also from screening of the effects of interfaces between sensing materials and transducers.

This review has attempted to critically analyze the benefits of combinatorial technologies from the standpoint of practitioners of these tools. Perhaps the best response to one’s possible skeptical arguments that “this is not intellectually satisfying”, “this is not science”, and “this is too Edisonian” is two observations. The first observation is a quote from a book chapter by Göpel and Reinhardt[563] published in 1996 before the broad acceptance of combinatorial technologies into materials science. Göpel and Reinhardt mentioned “...it is surprising that no sensor group has so far screened systematically the many well-established metal oxide based catalysts for their potential use as sensor materials. On the other hand, it is surprising that only a few catalysis groups make use of the possibility of characterizing their catalysts by complementary monitoring their sensor properties." The second observation is that 10 years later, the multidisciplinary essence of combinatorial technologies has brought together sensor and catalysis groups[221,230−232, 564] and many other diverse research groups and has affected researchers as well. At present, an effective combinatorial scientist acquires skills as diverse as experimental planning, automated synthesis, basics of high-throughput materials characterization, chemometrics, and data mining. These new skills can be now obtained through the growing network of practitioners and through the new generation of scientists educated across the world in combinatorial methodologies. Combinatorial and high-throughput experimentation was able to bring together several previously disjointed disciplines and to combine valuable complementary attributes from each of them into a new scientific approach.

6. Acknowledgments

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