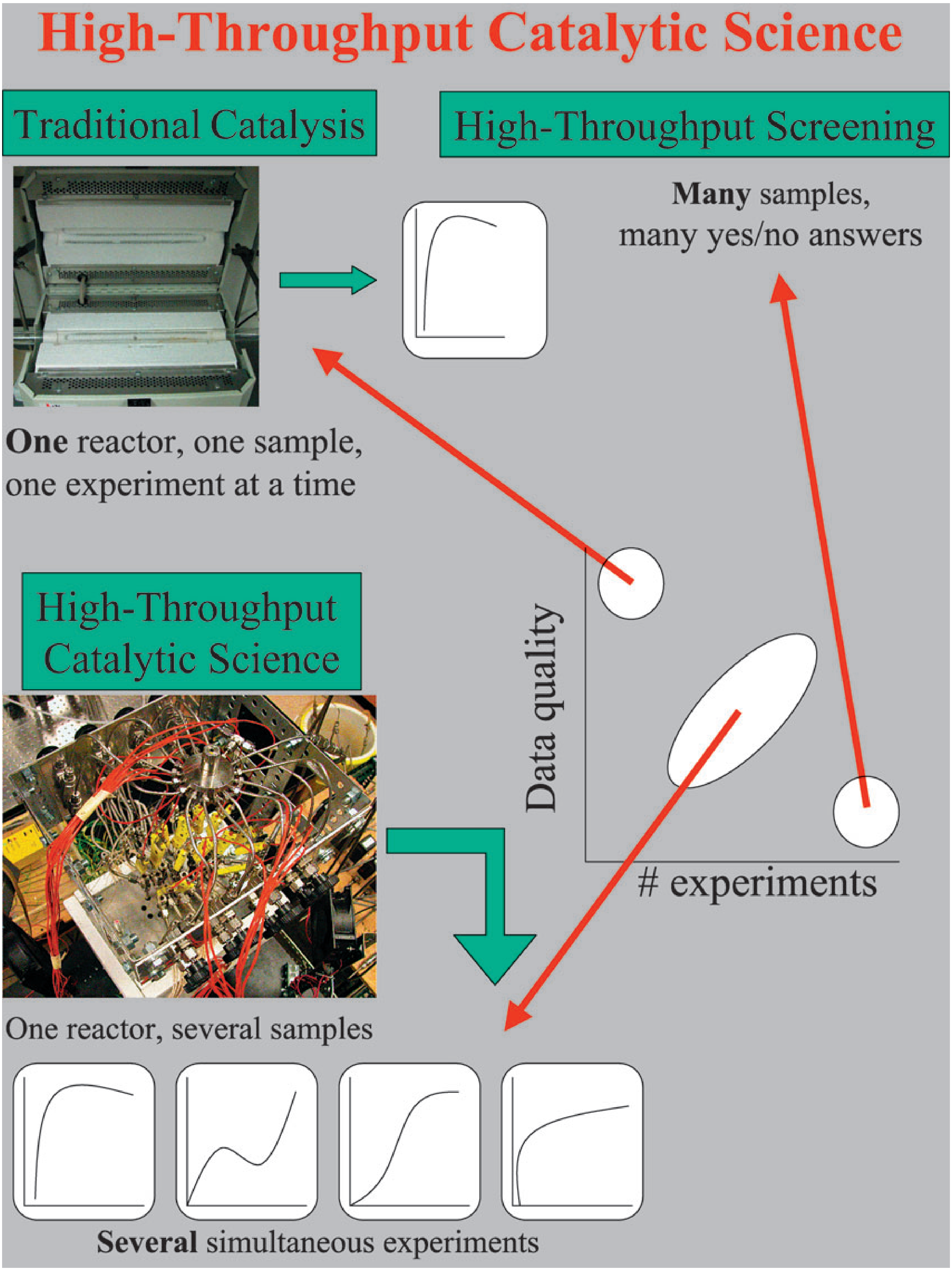

High-Throughput Catalytic Science

Traditional Catalysis

One reactor, one sample,
one experiment at a time

High-Throughput Screening

Many samples,
many yes/no answers

High-Throughput Catalytic Science

One reactor, several samples

Several simultaneous experiments

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High-Throughput Heterogeneous Catalytic Science

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Abstract: High-throughput experimentation in heterogeneous catalysis has recently experienced nearly exponential growth. Initial qualitative screening has evolved into quantitative high-throughput experimentation, characterization, and analysis. This allows high-throughput catalysis now to rise above simple screening to the level of fundamental understanding of reaction mechanisms, which will lead on a faster path to the Holy Grail of catalysis: rational catalyst design.

Keywords: combinatorial chemistry · heterogeneous catalysis · high-throughput screening

Introduction

The theoretical parameter space for possible active catalytic materials combinations is larger than 38 million combinations for 10 elements at 25 different concentration levels.[1] When one, in addition, considers the variety of preparation methods and reaction conditions that a given catalyst could be subjected to, the total number of possible experimental combinations grows even larger. It is therefore easy to understand the appeal of high-throughput experimentation (HTE) in catalysis. The application of HTE to the development and study of heterogeneous catalysts in particular has experienced significant growth recently. For instance, the number of scientific publications referring to HTE in heterogeneous catalysis has grown exponentially since 1991, as can be seen in Figure 1, which shows the results of a search performed using the phrase "high and throughput and catalyst*" on the ISI Web of Science database. Similarly, a large number of high-throughput patents and pending applications have been submitted by various companies and universities.[2]

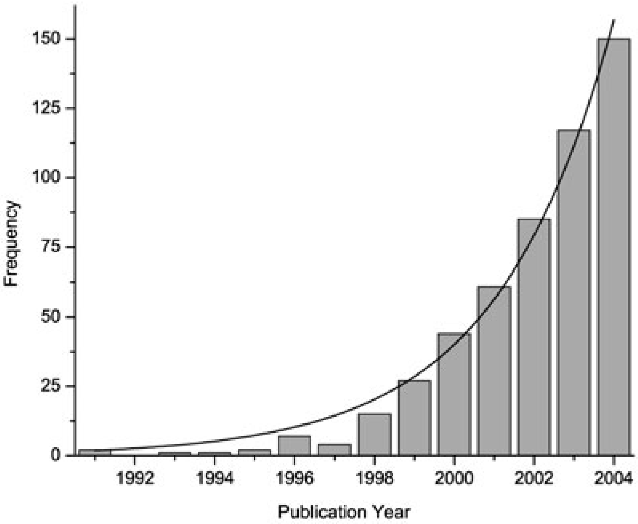

Figure 1. Numbers of papers published each year related to high-throughput catalysis. The line shows an exponential fit to the frequency of papers each year. Note: The data for 2004 are an extrapolation based on the number of papers in the ISI database on May 15, 2004.

The Early Beginnings

The genesis of combinatorial experimentation in materials science has been reviewed recently by Schubert et al.,[3] in which they discuss "combinatorial" experiments that have been performed as early as the late 1800s. In 1970, Hanak outlined the basic methodology still in use today in high-throughput experimentation, seen in Figure 2,[4] when he searched for new binary superconducting compositions. To our best knowledge, the first reference in the open scientific

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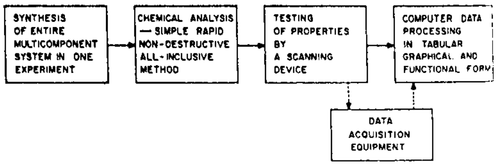

Figure 2. A representative flow chart of the high-throughput experimentation paradigm. This Figure was first published in 1970. Reproduced with permission from *J. Mat. Sci.* **1970**, *5*, 964–971. Copyright 1970 Chapman and Hall Ltd.

literature in heterogeneous catalysis that refers to the use of parallel reactors to study catalysts appeared as early as 1980.[5] The authors later reported that the idea of testing catalysts in parallel was not seen as very novel to catalysis researchers at that time, and therefore few detailed reports appeared about parallel reactors in the open literature.[6] In 1986, Creer et al. published a detailed report about the implementation and verification of six parallel reactors for testing heterogeneous catalysts.[7] Figure 3 is a reproduction of the schematic of their "automatic catalyst screening microreactor system." This publication clearly describes the multiple sample concept in heterogeneous catalysis. It has unfortunately not received much credit from the high-throughput community, as can be seen from the fact that it had only five citations as of May 2004. These initial studies, however, already demonstrated the allure of high-throughput experimentation to catalysis researchers.

An excellent review of the field of high-throughput heterogeneous catalysis was published by Senkan in 2001,[1] and the majority of the work cited there will not be repeated in this article. Likewise, the patent literature will not be reviewed since this was recently covered by Dar.[2] This article will mainly focus on recent advances in the field of high-throughput studies of heterogeneous catalysts, reported in the open scientific literature, demonstrating the evolution of the field from often qualitative studies to more quantitative experimental studies incorporating chemical and statistical models. This brings us closer to the development of new catalysts and, even more important, will aid us in acquiring new scientific understanding of heterogeneous catalysts using the high-throughput methodology.

The Maturation of High-Throughput Experimentation

The argument has often been presented that data collected through high-throughput experimentation has only modest scientific value, because the data were not collected in the traditional, one-at-a-time approach and therefore the quality must be reduced. Indeed, initial studies in high-throughput experimentation, as applied to heterogeneous catalysis, frequently focused on rapid and qualitative yes/no answers to catalytic activity questions. Researchers were chiefly concerned with the development of techniques to screen very large arrays of catalysts, a so-called primary screen. As the field progressed, an increasing number of studies displayed the development of experimental methodologies that were more quantitative and comparable to the traditional single reactor studies. In addition to quantitative catalytic testing tools, high-throughput characterization techniques have also been developed to aid in understanding catalytic behavior. The large quantities of data collected, and the large parameter space that can now systematically be investigated in high-throughput experimentation, also led to the need to implement experimental planning and data analysis tools to navigate the multidimensional experimental space. All of these recent developments demonstrate the evolution of high-throughput catalytic science from high-throughput screening.

Synthesis of Catalysts

Although the main focus of this article is the recent development of high-throughput screening methods, we will brief-

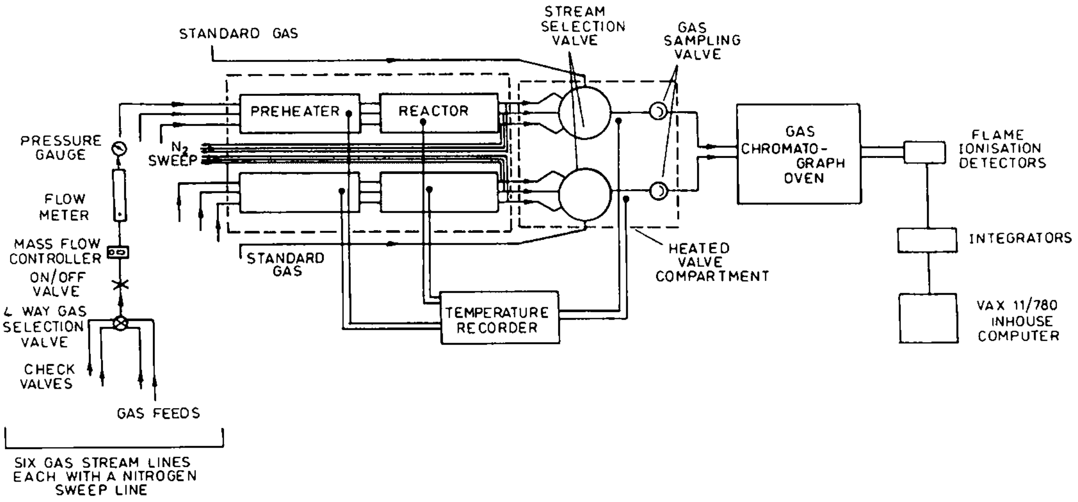

Figure 3. Six channel reactor for heterogeneous catalyst testing first published in 1986. Reproduced with permission from *Appl. Catal.* **1986**, *22*, 85–95. Copyright 1986 Elsevier Science Publishers B.V.

ly review synthetic methods for solid state material libraries. For primary screens, continuous compositional spreads or discrete compositions can be employed.[8] Such libraries are typically produced using techniques such as rf sputtering, pulsed laser deposition, molecular beam epitaxy, and chemical vapor deposition.[8,9]

Although useful for the primary screening of compositions, it can be difficult to extrapolate final catalyst properties from thin film libraries to supported catalyst materials. For supported heterogeneous catalysts, a typical synthesis requires the reaction of solution precursors with support materials. Liquid precursors can be used with automated dispensing robots to synthesize libraries of more realistic catalytic materials. Another approach was developed for parallel hydrothermal synthesis for zeolites.[10]

The design of libraries is another research area that connects directly with the various synthetic methods. The synthesis of supported catalysts has a multitude of variables, including precursor materials, support materials, mixing temperature, and calcinations parameters. Different approaches within the design of experiments (DOE, see below) methods, such as split/pool synthesis can be used to initially determine library composition and synthesis control variables.[8,9]

High-Throughput Screening

One of the first approaches reported in the mid-1990s in high-throughput heterogeneous catalysis consisted of a reactor capable of holding 16 catalyst pellets combined with an infrared camera for analyzing the temperature of the pellets under reaction conditions. The system was used to test the catalytic activity of 16 catalysts for the oxidation of H_2.[11] Temperature differences upon catalyst light-off were detected in parallel, as seen in Figure 4, indicating relative activity differences. Later, IR thermography was extended to less exothermic reactions[12] and even to endothermic reactions.[13]

Another pioneering approach applied resonance-enhanced multiphoton ionization (REMPI) to rank various catalysts for the conversion of cyclohexane to benzene.[14] Although it was stated that quantitative studies were possible, no attempts to correlate the signal intensity to the concentration were shown. This technique was well suited for the reaction studied, but has been found to be difficult to apply to a larger diversity of reactions. To the best of our knowledge, there have been no published reports detailing the use of REMPI to study catalysts since these early reports, possibly due to its difficulty in implementation.

These initial studies concentrated on the development of screening tools for catalytic activity through heats of reaction or the monitoring of a single reaction product. However, this is often insufficient for more detailed studies and consequently, more quantitative experimental methodologies that incorporated selectivity measurements were developed.

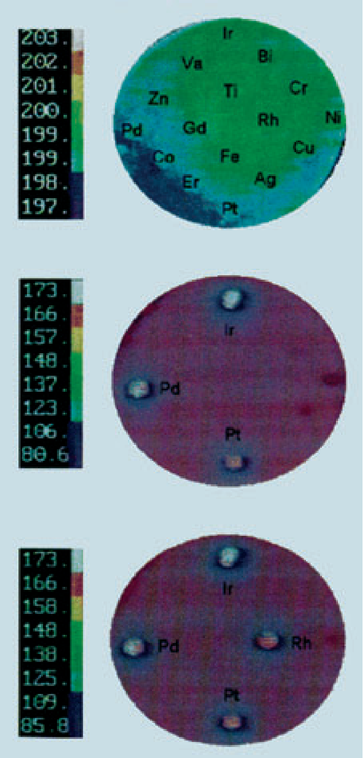

Figure 4. The first implementation of parallel catalyst activity screening employed IR thermography during H_2 oxidation. In this experiment, the Ir, Pd, Pt, and Rh catalysts are identified as the most active. Reproduced with permission from *Ind. Eng. Chem. Res.* **1996**, *35*, 4801–4803. Copyright 1996 American Chemical Society.

High-Throughput Experimentation under Realistic Conditions

For most applications, the selectivity of a catalyst is more important than its activity. To this end, the development of high-throughput tools to test the activity and selectivity of heterogeneous catalysts were developed. Research efforts were focused on three fronts: the development of reactors capable of testing multiple catalysts under realistic conditions, the development of analytical techniques to quantify the reaction products, and the development of analytical tools capable of high-throughput characterization.

Most of the initial work on the development of reactors for high-throughput testing of heterogeneous catalysts consisted of the development of reactor systems amenable to a specific analytical technique.[11,12,15,16] Many researchers began to recognize the value in developing high-throughput reactors that tested catalysts under nearly conventional conditions.[17] The results from these reactors could be validated using accepted techniques, and the confidence in the data quality thereby increased. One of the first academic groups to report on the development and testing of such a reactor was the research group of Schüth.[18] They developed a flow through reactor capable of testing 16 catalysts simultaneously under well controlled similar conditions, and compared results to conventional catalytic studies. They found that their high-throughput experimental setup gave results similar to single reactor studies. They further developed a parallel reactor that could be pressurized to 50 bar and test 25 catalysts in gas or liquid phase reactions.[19,20] Other research groups also developed reactors to test catalysts under realistic conditions.[21–23]

Our group developed a high-throughput reactor that thermally isolated each reactor channel and maintained plug flow conditions for all reactor channels.[24] For example, our reactor is capable of following oscillations in temperature and reaction products during reaction over supported transition metal catalysts during CO oxidation. Thus, it was demonstrated that it was possible to investigate not only steady state reactions, but also transient and non-linear phenomena in a high-throughput fashion.

To progress towards high-throughput catalytic science, chemically sensitive and quantitative high-throughput analytical tools must be developed to enable researchers to study and compare the selectivity as well as the activity of multiple catalysts. The majority of high-throughput analytical techniques consisted of the adaptation of traditional analytical tools to high-throughput experimentation. The mass spectrometer has proven to be one of the most popular analytical tools due to its analysis speed, established technology, and versatility. Various approaches have been developed to transport the reaction products corresponding to different catalysts to the mass spectrometer. These techniques ranged from the straightforward use of switching valves,[23,25,26] to the more complex use of *x*,*y*,*z* motion control devices.[15,27]

Other analytical tools followed similar methods of adaptation of existing technologies to the analysis of multiple catalysts. These techniques included the use of gas chromatography,[20,21,28,29] gas sensors,[30] and other analytical techniques.[16,26,31] One technique implemented the use of a focal plane array detector in place of the standard single element IR detector in traditional IR spectroscopy, allowing the collection of spatially resolved IR spectra.[32] This instrument was the first chemically sensitive, quantitative, and parallel analytical technique applied to high-throughput experimentation.[26,33,34] More, recently this analytical tool has been extended to the analysis of multiple transient reactions in parallel.[35] One of the important uses of this rapid chemically sensitive parallel technique is the ability to observe transient reaction products, as seen in Figure 5. Here the absorbance intensity of the antisymmetric stretching band of nitrous oxide (N_2O) at 2240 cm^{-1} is followed for 16 NO_x storage and reduction (NSR) catalysts[36] during a change in the reaction conditions from fuel rich to fuel lean. The reaction products were monitored using FTIR spectroscopic imaging of the products from 16 parallel reactors. In Figure 5a, the intensity of the N_2O band is minimal in the effluent from all 16 reactors. In Figure 5b–f, the intensity of the N_2O band increases for 7 of the reactors and then decays to a small steady state value. Without the temporal analysis, the identification of N_2O would not have been possible and a key reaction intermediate would have gone undetected. In a related transient study development, a temporal-analysis-of-product (TAP) reactor has been constructed that permitted the rapid sequential TAP testing of up to 12 catalysts.[37] These developments of analytical techniques that can perform transient studies in a high-throughput manner extended the usefulness of high-throughput experimentation further into the kinetic modeling community. Transient studies are beneficial for distinguishing between competing kinetic models and in extracting kinetic and thermodynamic constants.

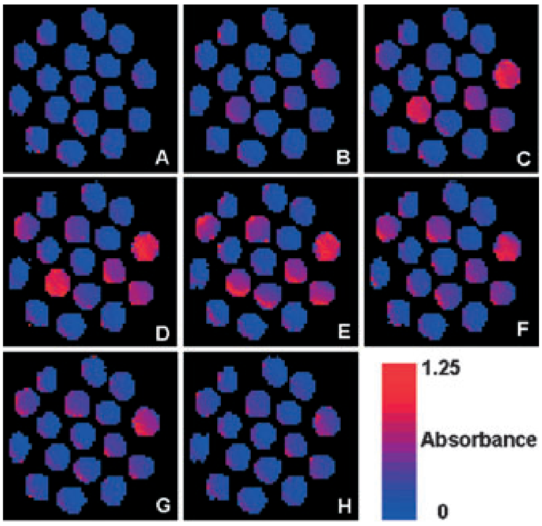

Figure 5. Spectral images of the anti-symmetric bending mode of nitrous oxide for the reaction products from 16 NSR catalysts during a reactant composition switch from fuel rich to fuel lean. The center circle is not connected to the effluent from a reactor. The images are each separated in time by 3 s.

High-Throughput Catalyst Characterization

To further advance the field of high-throughput experimentation from one of empirical models to truly high-throughput catalytic science, high-throughput characterization techniques are necessary to understand the catalytic chemistry. One of the first groups to report on the automated characterization of combinatorial materials was Maier and coworkers[38] using an X-ray diffractometer to characterize bulk material properties. Similarly, one of the first groups to develop a high-throughput surface characterization technique was our group. In 1999 and 2001,[33,39] reports were published detailing the construction and use of a system capable of analyzing adsorbates on 7 different supported catalysts using transmission IR imaging, as seen in Figure 6. This setup was used to observe how different IR absorption bands of adsorbed molecules changed with temperature[33] and dosing time.[39] Recently, details about a similar reactor system were published.[40] In this paper, a reactor capable of collecting transmission IR spectra of eight samples simultaneously was reported. As a validation study, they probed both physisorbed and chemisorbed pyridine on three different zeolites.

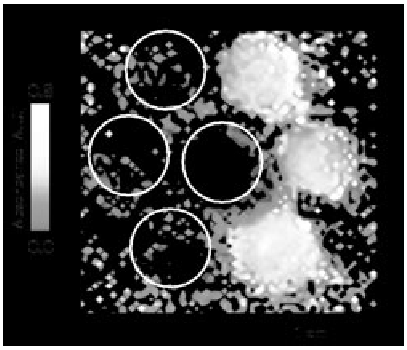

Figure 6. Parallel transmission FTIR imaging of adsorbates on pellets. Here the characteristic CO adsorbed on Cu-ZSM5 stretching frequency of 2157 cm^{-1} is shown. The three areas with high absorbance correspond to the location of the three zeolite pellets. The white circles show the remaining members of the catalyst library with no absorbance at this frequency. Reproduced with permission from *Opt. Lett.* **1999**, *24*, 1841–1843. Copyright 1999 Optical Society of America.

Recently, a different characterization technique was utilized to probe surface acidity of 10 zeolites.[41] Temperature programmed desorption (TPD) studies were carried out using a 10 well reactor attached to a multi-stream valve and a mass spectrometer. The results for an NH_3-TPD are seen in Figure 7. The authors claimed that almost all temperature programmed techniques could be similarly carried out using appropriately designed reactors. Other high-throughput serial characterization techniques have also been developed including XPS[42] and X-ray fluorescence.[43]

The development of parallel, chemically sensitive and quantitative analytical methods and parallel high-throughput characterization studies demonstrate the recent progress of the high-throughput experimentation field towards high-throughput catalytic science. High-throughput experimentation data can currently be collected in a fashion where the quality is similar to traditional studies, and characterization techniques are being developed to assist in understanding the chemistry of the systems studied.

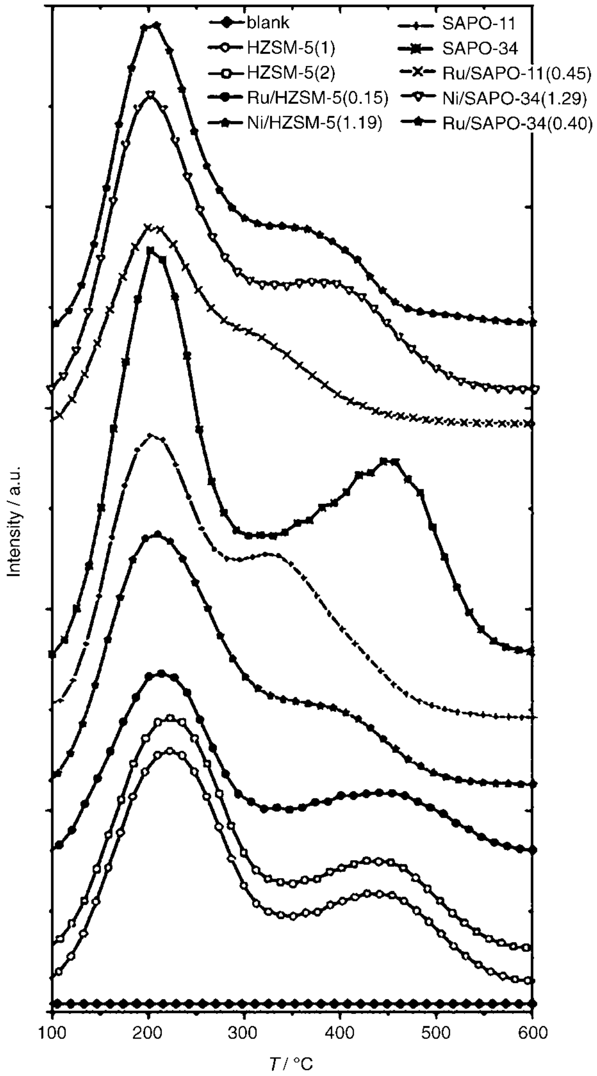

Figure 7. The application of NH_3 temperature programmed desorption for the high-throughput characterization of multiple catalysts. Reproduced with permission from *Catal. Commun.* **2004**, *5*, 55–58. Copyright 2003 Elsevier B.V.

Methodological Developments

With the development of parallel reactors and quantitative analytical tools for testing multiple catalysts under realistic conditions, new testing methodologies and modeling approaches are needed that can keep pace with the rate at which catalysts are tested. In the development of high-throughput experimentation, it was realized that it was not possible to collect data for all possible experimental combinations. Several research groups therefore started applying different experimental design strategies to reduce the number of experiments required to sample the parameter space.[8,44,45] Some have approached the experimental design using well established techniques, such as response surface methodology[29,46] and D-optimal designs.[47]

We recently displayed the use of statistical experimental design during all stages of the high-throughput experimentation process in optimizing NO_x storage and reduction catalysts.[36,46] In the screening design, the catalysts were synthesized following a full factorial design[48] of the three metals of interest, Pt, Ba, and Fe. In addition, the reaction conditions were also considered as a variable of interest in the initial screening design. A fractional factorial design was implemented in testing the catalysts for performance as a function of six different variables. Combining these two designs led to a nested experimental design, where all catalysts were tested at all reaction conditions. These screening experiments led to the conclusion that all six reaction conditions and metals were statistically significant in predicting the catalytic performance and led to a more comprehensive response surface study. The initial results from the response surface study indicated that this statistical methodology could be used to optimize the catalyst formulation.[46] The full response surface study for the reaction conditions and catalyst composition has recently been completed.[49] The results indicated that the influence of the reaction conditions on the catalytic performance could also be statistically modeled. An example of this for a 0.5 % *w*/*w*, 7.5 % *w*/*w* Ba, and 2.5 % *w*/*w* Fe on γ-Al_2O_3 catalyst is seen in Figure 8, where the saturation NO_x storage is modeled as a function of the reactor temperature and the composition of the reducing gas. The maximum in the saturation NO_x storage, which is known to be between 350–400 °C,[35,50] depended on the composition of the reducing gas. When the reducing gas was carbon monoxide the maximum in saturation NO_x storage was around 370 °C, while the maximum for ethylene as the reducing agent was around 400 °C and intermediate fractions of the two reducing agents fall between these two temperature maxima. This example demonstrated that experimental design techniques are beneficial for all stages of the high-throughput experimentation process to maximize the information obtained from the experiments performed.

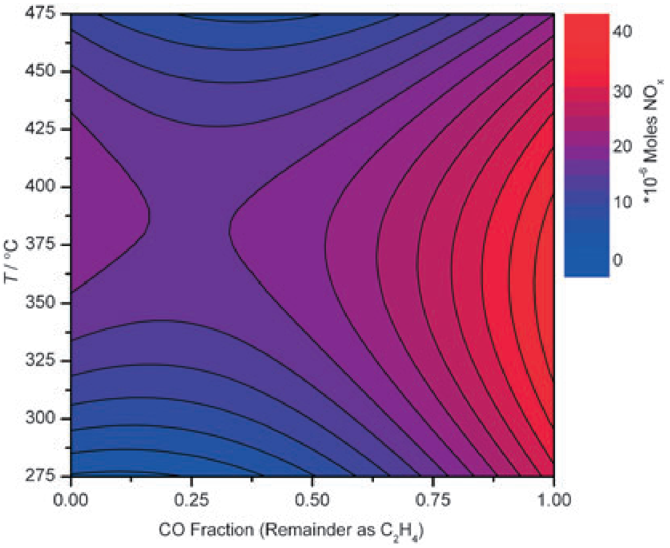

Figure 8. Saturation NO_x storage modeled for a NO_x storage and reduction catalysts as a function of reactor temperature and the fraction of the reducing that was carbon monoxide.

Other approaches in guiding high-throughput experimentation include the use of artificial neural networks[51] and the holographic research strategy.[52] A novel approach incorporating factor based methods from chemometrics,[53] that is, principle component analysis (PCA) was proposed to initially decrease the dimensionality of the experimental parameter space.[44,54] Once the parameter space has been reduced, D-optimal designs are performed to maximize the information content available in the experiments to be performed. After the D-optimal design has been completed, factor based methods such as principle component regression (PCR) or partial least squares (PLS) are then used to correlate the experimental parameters with the characteristics of interest. An adaptation of this methodology using chemometric techniques at all levels of the high-throughput experimentation strategy is presented in Figure 9. Another methodological development of particular interest has been the work presented by the group of Rothenberg,[55] which focuses on the problem of the time at which species concentration data should be collected if one is determining reaction rate constants for multiple catalysts in parallel using a serial analytical device. Additionally, Caruthers et al. has investigated the process of analyzing high-throughput data in order to extract chemical understanding using a process that was named “knowledge extraction.”[56]

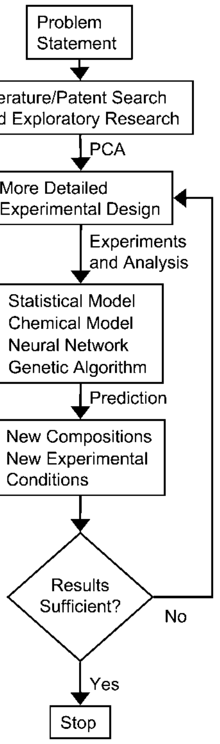

Figure 9. Workflow for high-throughput experimentation in catalysis, incorporating the use of principle component analysis, experimental design, and modeling techniques.

Conclusion

High-throughput catalytic science is the marriage of traditional catalytic research with the advances in high-throughput experimentation and modeling. The advent of high-throughput experimentation is not the demise of the thinking scientist, but it is another tool at the disposal of the researcher to augment current research capabilities. Thomas Edison was quoted as saying, “The only time I become discouraged is when I think of all the things I like to do and the little time I have in which to do them.” (as quoted in ref. [8]). As scientists, we normally have more ideas to test than time to test them. High-throughput experimentation does not supplant thinking; it actually requires more thinking because it allows researchers to explore more ideas.

In the field of catalysis, HTE has evolved from high-throughput screening to high-throughput catalytic science through the development of realistic parallel reactors, quantitative analytical tools, high-throughput characterization devices, and new methodologies to track the data and guide the discovery process. The use of HTE in the development and testing of heterogeneous catalysts and other fields will continue to grow as more research groups and companies recognize the value in high-throughput experimentation and implement HTE tools.

Acknowledgement

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