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Catalysis Today 107–108 (2005) 3–11
CATALYSIS TODAY
www.elsevier.com/locate/cattod

Heterogeneous combinatorial catalysis applied to oil refining, petrochemistry and fine chemistry

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Abstract

This work analyses the current situation regarding combinatorial and high-throughput techniques in the context of heterogeneous catalysis. The different experimental (hardware) and software techniques are critically revised, giving illustrative examples of their application in the development of new catalysts, for example, the application of a novel high-throughput characterization technique based on photoluminescence measurements and the application of *soft computing* algorithms for intelligent experimental design.

Keywords: Combinatorial catalysis; High-throughput screening; Data mining; Genetic algorithm; Neural networks; High-throughput characterization

1. Introduction

In the past, heterogeneous catalysts have been discovered and developed by following a time- and energy-consuming *trial and error* process, which involves separate synthesis, characterization and catalytic testing. In fact, the time required for the successful development of a new catalyst ranges from months to years. The chemical industry in developed countries requires improved research productivity for different reasons: (i) the growing pressures for investment return in a shorter term; (ii) an essential requirement for new eco-friendly production processes; (iii) the high competence of Third-World countries with low-cost manpower and less strict environmental legislation. As a result, chemical industries require the acceleration of the development and market launch of new catalysts and catalytic processes, particularly, at a time when R&D budgets are being drastically reduced. The pharmaceutical industry faced this paradigm more than a decade ago by initiating combinatorial techniques that involved the synthesis and assay of a large number of candidate molecules in a parallel and fast way (Fig. 1). This methodology involves high-throughput experimentation (HTE), as well as new techniques for the experimental design and experimental data analysis of very large libraries of molecules. This new methodology is now migrating to other fields (Fig. 2), such as materials science [1], catalysis, home-care product development, etc. New materials with improved chemical, optical and electric properties have been found using these accelerated experimentation techniques [2–6]. Despite the wide differences between the experimental techniques employed in the fields of drug discovery and heterogeneous catalysis, drastic changes in the conventional approach used in the latter involve parallel experimentation in miniature and the application of new software techniques for experimental design and data analysis. This is evidenced by the growing number of workshops and publications devoted to this field (Fig. 3), and the discovery of new, highly efficient materials using combinatorial techniques, such as the new amide–ether-based hafnium polyolefin catalyst [7].

Consequently, the application of new technologies, such as automation, micromechanics, robotics, computation and electronics to research in biochemistry, chemistry and materials science has led to progressive *industrialization* of discovery and development.

2. Combinatorial catalysis

Combinatorial catalysis is understood as a methodology by which a large number of solid materials are prepared and

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doi:10.1016/j.cattod.2005.07.117

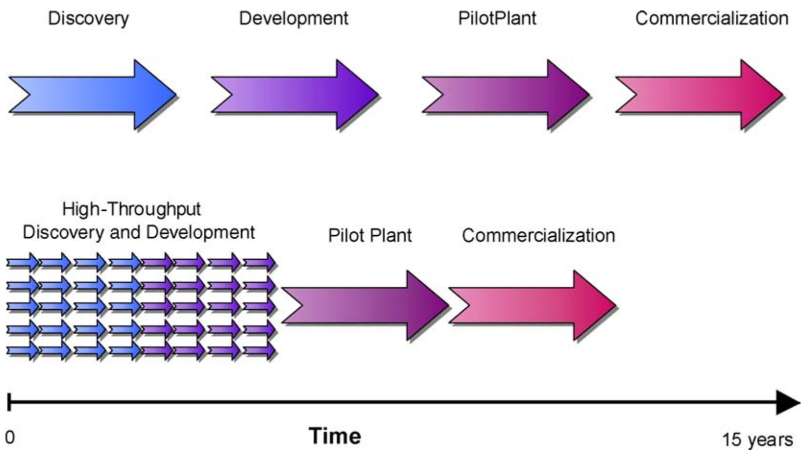

Fig. 1. Impact of high-throughput techniques in the development and launching of a new product.

tested in parallel using automated techniques. Due to the large amount of experimental data generated in this process, the development of powerful data management and mining techniques is also required for proper implementation of these combinatorial techniques. Consequently, the goal of combinatorial catalysis is the integration of the following elements: (a) fast synthesis of huge libraries of catalysts; (b) high-throughput catalyst testing and characterization; (c) data management and data mining; (d) powerful experimental design techniques for rapid optimization. The integration of the library synthesis and testing of catalysts with new software techniques is now a reality [8–11].

Two different approaches can mainly be distinguished in combinatorial catalysis [12–14], i.e., primary and secondary screening. They differ essentially in: (i) the number of samples that are processed simultaneously (library size); (ii) the amount of each material synthesized; (iii) the accuracy or reliability of the experimental results. In fact, the reliability of the screening decreases with increasing library size, since in this case, the experimental conditions for synthesis and catalytic testing are far from those applied at a larger scale. Thus, primary screening is better suited for preliminary exploration and detection of hits in a highly multi-dimensional space. Meanwhile, secondary screening deals with the optimization of more constrained spaces (detected hits) but still deals with multi-dimensional problems. Table 1 shows a summary of the main features of these two approaches.

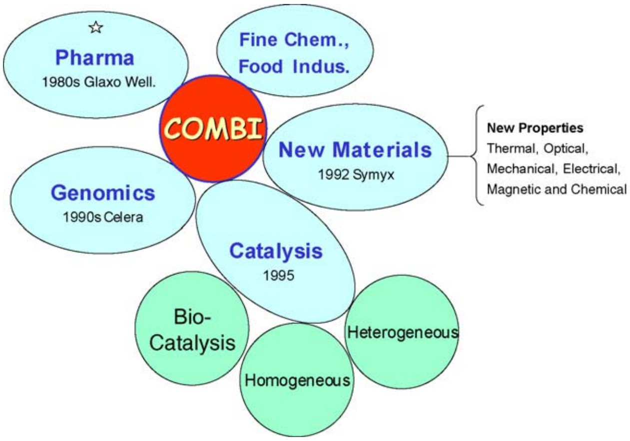

Fig. 2. Migration of combinatorial techniques to different fields.

2.1. Synthesis

The high-throughput synthesis techniques employed to date can be classified into: (a) solution-based synthesis, which involves the adaptation and automation of conventional catalyst synthesis procedures and (b) synthesis methods based on thin-film deposition techniques, including serigraphy, coating and surface treatment/modification techniques.

Solution-based preparations reproduce the conventional procedures used at the laboratory scale by means of automated robotic systems that deal with dosing of multiple liquids and solids, heating and stirring, libraries of liquid solutions and/or gels with a wide range of viscosities, filtration and washing of suspensions and resins, controlled solvent evaporation, etc. These automated systems can tackle a number of preparations in parallel, ranging from 15 to 96; usually, they handle standard microtiter plates of 24, 48 and 96 wells and the amount of solid catalyst ranges from 25 to 1000 mg. These systems allow preparative procedures, such as impregnation [15–18], multiple co-precipitation, ionic exchanges, sol–gel synthesis and hydrothermal synthesis [19–24]. However, further efforts are still required to increase the synthesis reproducibility and scalability when using fully automated systems, especially for hydrothermal synthesis procedures or when specific catalyst activation procedures are required.

Examples of the application of high-throughput tools to the hydrothermal synthesis of zeolite-based catalytic materials can be found in Refs. [21,24]. In the latter study, automated robotic systems were applied to intensively explore various synthesis variables (starting gel composition: water, pH, organics and sodium content), while the crystallization time and temperature were 48 h and 140 °C, respectively. This study accurately described a phase diagram

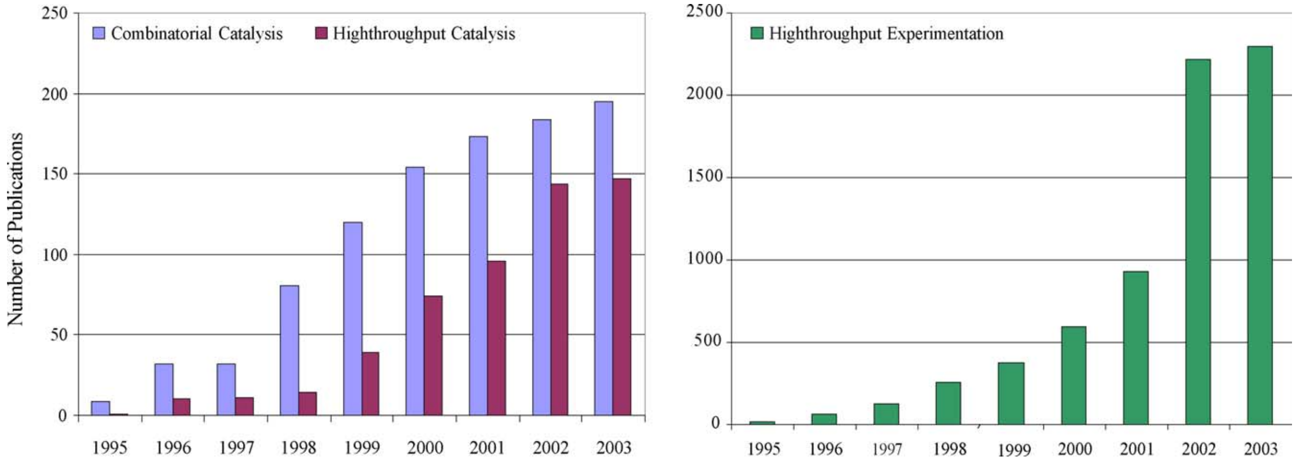

Fig. 3. Evolution of the number of publications dealing with the topics: combinatorial catalysis, high-throughput catalysis and high-throughput experimentation. (source SciFinder Scholar®).

for competing phases, making it possible to rationalize the influence of each synthesis variable on the occurrence and crystallinity of each phase, and to identify a non-linear model that describes the system. Thus, this methodology allows optimization of the properties of one specific material, e.g., crystallinity or acidity, as well as the discovery of new microporous structures.

The second type of preparation technique (primary) is based on the application of films by serigraphic methods. Furthermore, different techniques are employed to deposit arrays of different solid materials in the form of thin films to coat flat surfaces. These techniques are typically used to explore three- or four-component compositions (as well as the substrate nature) and usually the composition of deposited material depends linearly on its position in the array plate. Amongst other techniques, the fabrication of thin-film arrays can be carried out by RF spraying of solutions or powders using masking techniques [25–27] or micro-dosing of aliquots using *Ink-Jet* techniques, thermally driven techniques [28–30] or laser-driven techniques [31,32]. In this case, the amount of solid catalyst film is in the range from very few milligrams to 100 μg.

2.2. *Catalytic testing*

The reactors used for high-throughput catalytic testing can also be classified into two major groups: (a) primary systems allowing the screening of a very high number of catalysts in parallel and (b) secondary systems allowing the processing of a lower number of catalysts, but under realistic reaction conditions. The primary systems suffer from inaccuracy and low scalability due to factors, such as diffusion limitations, temperature gradients and low-precision analysis techniques, and therefore they can only be used for the detection of hits. The high-quality catalytic results obtained by secondary screening make studies of kinetics and scale-up possible.

Primary screening systems should process catalyst libraries deposited over flat plates or wafers as thin films. The catalytic assay typically involves putting all the catalysts under a common atmosphere and the most active materials are detected by optical imaging techniques [33]. IR thermography [34–36] has been widely applied to the fast detection of active catalysts for exothermic or endothermic reactions. However, the use of this technique is restricted to very specific reactions, since no information is gained about the reaction products (selectivity of the process). Another possibility [25] for the testing of thin-film libraries is sequential screening by using a bundle of tubes comprising the inlet and outlet gas and a capillary tube to detectors (MS). Analogously, the screening of hundreds of materials deposited into monolith channels [37–39] has been reported.

On the other hand, secondary high-throughput reactors are usually designed using parallel and miniature conventional catalytic reactors, such as fixed bed reactors [40–45] or continuous stirred tank reactors [46,47]. The following issues are very important to guarantee the correct reactor operation and reliability of the catalytic test results in such

Table 1
Comparison of state-of-art primary and secondary screening techniques

	Primary screening	Secondary screening
Library size	Very high (100–1000)	High (16–100)
Solid catalyst amount	Thin films (mg–100 μg)	Powders or pellets (1000–1 mg)
Synthesis and testing	Difficult quantification	Realistic conditions
Experimental design	Combinatorial	Knowledge-based design and/or guided by optimization strategies
Objective	Exploration: identification of hits	Exploitation: optimization and information for kinetic modeling and scale-up

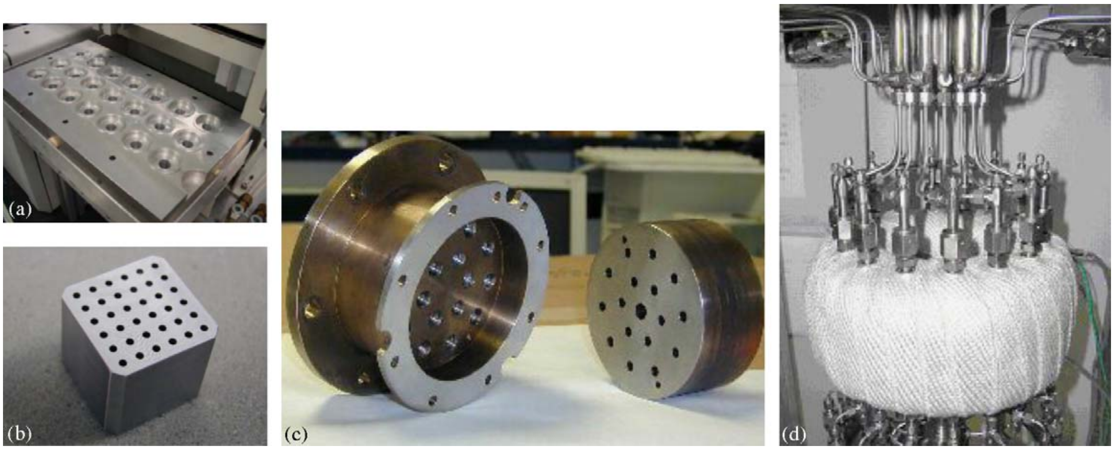

Fig. 4. High-throughput reactors developed at ITQ: (a) 21-batch (liquid/solid) reactor system endowed with a robotic arm for reactant feeding, sampling and injection in a GC; (b) 36-fixed bed reactor system (gas/solid) working at atmospheric pressure and catalyst amount ranging from 5 to 25 mg; (c) 16-fixed bed reactor system (gas/solid) working at atmospheric pressure and catalyst amount ranging from 100 to 1000 mg; (d) 16-fixed bed reactor system (gas/liquid/solid) working at high pressure up to 100 bar and catalyst amount ranging from 100 to 1000 mg.

reactor designs: (i) ultra-fast methods for the quantitative analysis of reaction products, such as the current techniques, μGC, ultrafiltration-GC and GC-MS, among others; (ii) controlled flow of gas and/or liquid reactants in each reactor channel for continuous operation reactors or controlled starting reactor composition for batch reactors; (iii) control of reaction temperature and pressure in each channel and capability of working under industrially realistic conditions [48,49]; (iv) representative sampling operation, minimizing the cross-talk between channels; (v) modular reactor design, allowing easy loading and unloading of catalysts (Fig. 4); (vi) possibility of carrying out in situ catalyst pre-treatment or activation. Fig. 4 shows different types of high-throughput reactors used for catalytic testing at our institute (ITQ).

Future design of high-throughput reactors in the field of heterogeneous catalysis [50–52] could involve arrays of nano-reactors integrating temperature and flow control elements for each channel, as well as arrays of detectors for chemical analysis of reaction products, allowing on-line monitoring of the catalytic performance of the complete array of materials. It is of paramount importance for these micro-integrated systems to be able to guarantee the scalability of the results and the modularity of the system, especially for materials loading, with in situ catalyst synthesis being preferred.

2.3. *Physico-chemical characterization*

The automation of characterization techniques would allow the determination of different physico-chemical properties of catalyst libraries in parallel, with the aim of further understanding the phenomena occurring during the catalytic reaction, and consequently, increasing the information available for subsequent material optimization. Few multi-sample characterization systems have been reported to date and only X-ray diffraction (XRD) high-throughput systems [53] are commercially available due to its development for drug discovery applications (isomorphism study). Recently, a system to determine the acidity of a library of solid catalysts by temperature-programmed desorption of ammonia (TPD-NH_3) was described [54]. Different characterization techniques are being developed, such as spectroscopic techniques [55–57], surface area determination and parallel TAP reactor studies [58], amongst others [59], which allow an in-depth understanding of the physico-chemical properties associated with the catalytic performance previously exhibited in testing. The eight-sample system reported by Schuth and co-workers [57] allows the accurate determination of Brönsted and Lewis acidity using pyridine as a probe molecule and a 2D-detector (focal-plane array, 64 pixels × 64 pixels), making it possible to carry out in situ adsorption/desorption of pyridine (high vacuum) and thermal treatments (up to 250 °C). The potential applications of this system include the determination of other solid surface properties and further parallelization; however, its main drawback is still the tedious and tricky sample preparation and the amount of sample required.

Recently, a novel characterization technique [60] was developed based on photoluminescence, which allows the analysis of 96-sample arrays (standard microtiter plate layout) in a few minutes and requiring low amounts of solids (10–20 mg). This system, shown in Fig. 5, allows different thermal treatments in situ under a controlled atmosphere, such as drying and adsorption/desorption of different probe molecules, as well as gas-phase catalytic reactions. The information obtained from the emission of each sample (fluorescence and/or phosphorescence) when excited by a Nd-YAG laser pulse allows quantification of the relative content of the different lumophoric species of the sample (which can be different transition-metal species, aromatic molecules, chalcogenides), as well as determination of the chemical environment of those species [61,62]. This system has been used [63] to optimize the synthesis of

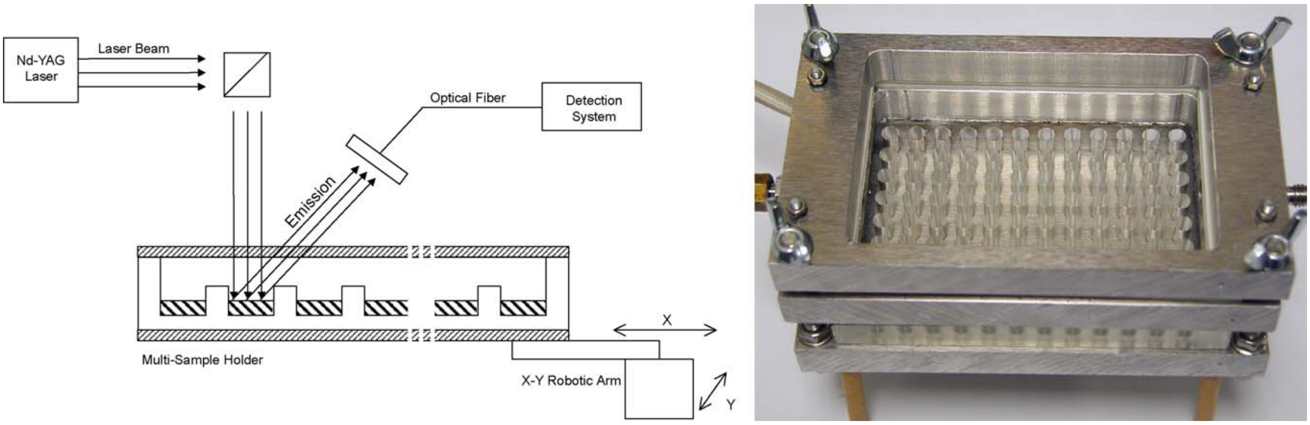

Fig. 5. High-throughput characterization system of solid materials based on photoluminescence.

electroluminescence polymers (PPV@zeolite, Fig. 6) and photocatalysts (TP@zeolite) for the abatement of organic pollutants from waste water.

2.4. Software

The rapid development of high-throughput experimental tools required the parallel development of software techniques for the management of the large amount of data generated by the synthesis, characterization and testing of catalyst libraries. Data management involves the software techniques applied for: (i) the efficient administration, visualization and scheduling of abundant experimental data [64] (databases); (ii) the comprehension and specific modeling of experimental data; (iii) the experimental design of subsequent catalyst libraries with the aim of optimizing specific catalytic performance.

2.4.1. Data mining

Traditionally, the processing and understanding of experimental results of characterization and catalytic testing were carried out by researchers, who applied previous experience, fundamental knowledge and intuition in order to: (i) design new catalyst libraries and (ii) analyze the data and establish relationships between the different experimental results. In the case of combinatorial catalysis, the large number of variables in play and the application of complex optimization algorithms for the experimental design make difficult the direct human interpretation of data derived from high-throughput experimentation. Data mining techniques allow thorough analysis of raw multi-dimensional data [65–69] in such a way that knowledge can be systematically extracted, establishing multifactor relationships and patterns amongst input variables (catalyst composition, preparation and reaction conditions), output

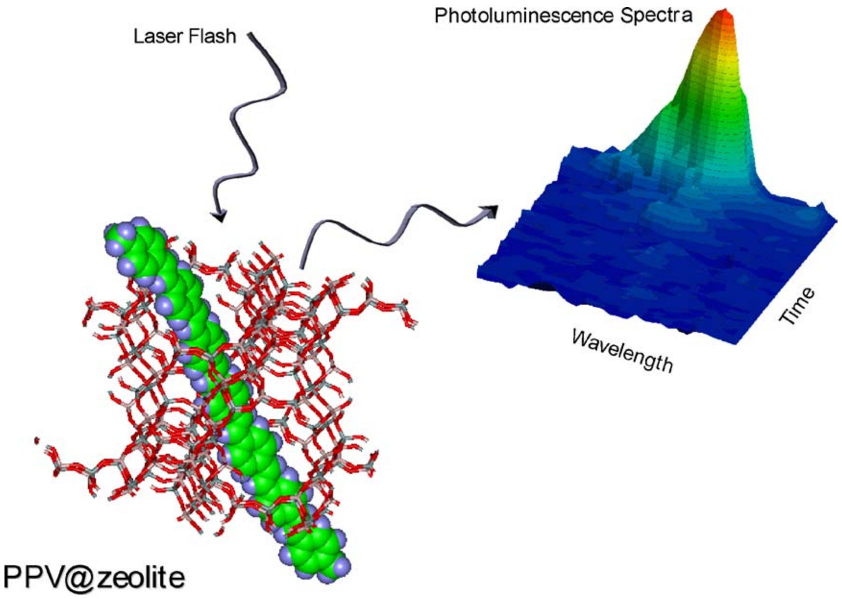

Fig. 6. Graphical representation of excitation and emission of PPV@zeolite system, showing the final photoluminescence spectrum (time scale: 0–1.2 μs, wavelength: 480–800 nm).

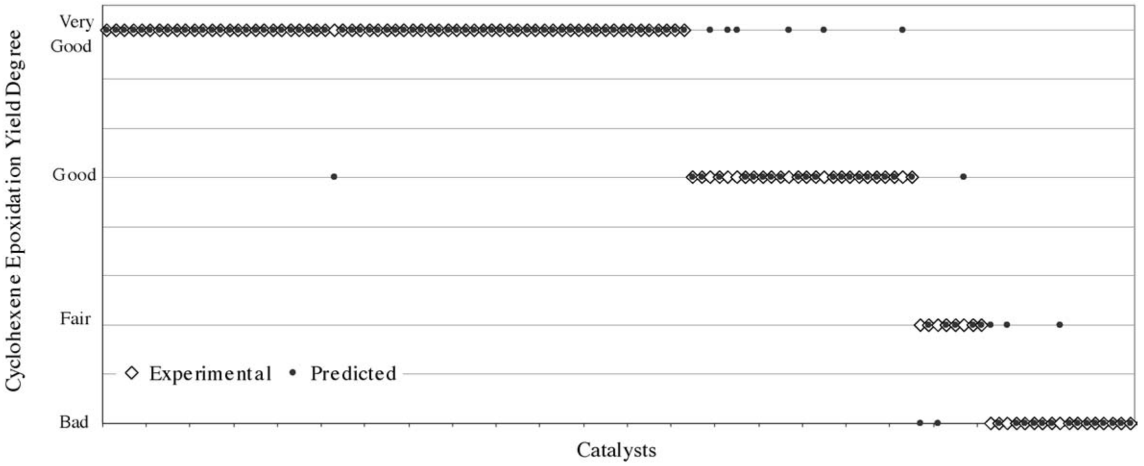

Fig. 7. Catalytic data modeling using artificial neural networks: predicted vs. experimental epoxidation yield degree, probe reaction was solvent-free epoxidation of cyclohexene with *tert*-butylhydroperoxide using Ti-silicate mesoporous catalysts. ANN model was a multi-layer perceptron with four input nodes, two nodes in first hidden layer, one node in second hidden layer and two output nodes, trained using Backpropagation algorithm with momentum (learning factor = 0.8 and momentum term = 0.5) with experimental data from three successive catalyst libraries.

variables (catalyst characterization and catalytic performance) and theoretical parameters of the catalyst components. Hereafter, this available *knowledge* could be applied to design a new subset of materials to be screened in a more intelligent and rational way [65,70]. Several data mining techniques have been applied in combinatorial chemistry, including clustering models and non-linear regression models, statistical models, association rules and decision trees, rule induction, and Kohonen and artificial neural networks.

Artificial neural networks (ANNs) [71,72] are complex mathematical systems (non-linear analytical tools) able to establish quantitative relationships between the input/output data without prior knowledge of the correlation between the variables involved in the system. ANNs have been successfully applied to model catalytic data [73–75], but their application in modeling complex multi-dimensional data derived from high-throughput experimentation is especially interesting. Therefore, in the context of combinatorial catalysis, it is possible to build ANN-based models

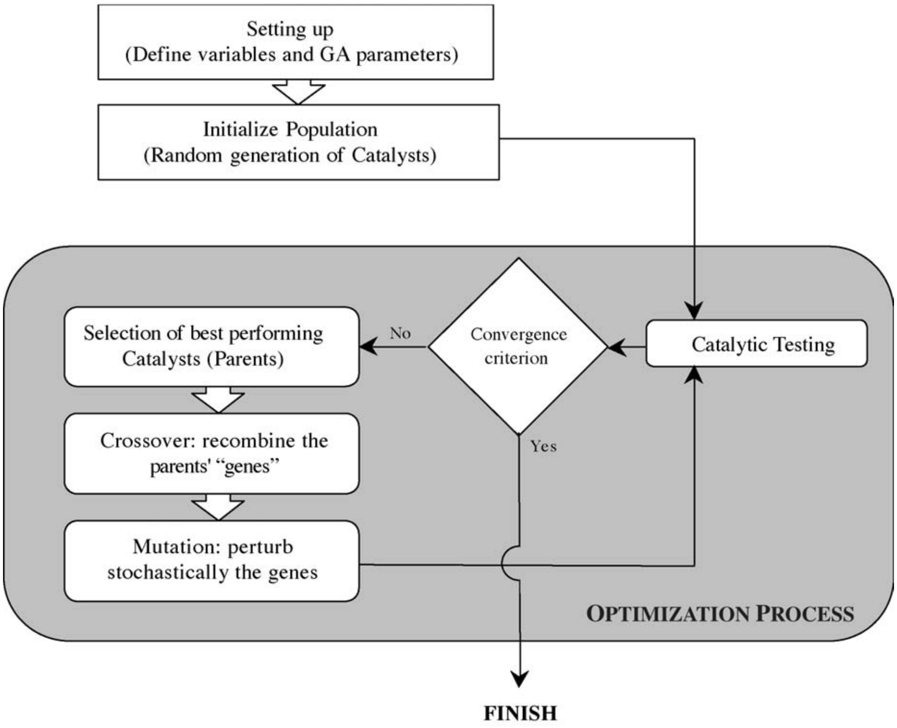

Fig. 8. Architecture of a conventional genetic algorithm.

for the prediction of: (i) catalytic performance of libraries of materials taking into account the input data of the library (material composition, synthesis conditions, etc.) and (ii) catalytic performance of a series of materials considering the reaction conditions [76,77] (*kinetic* ANN models). An example of the application of ANN to the prediction of catalytic performance taking into account synthesis variables is reported in Ref. [47] (Fig. 7). In this study, the epoxidation yield of mesoporous Ti-silicate catalysts was predicted considering the starting molar composition of the synthesis gel, i.e., [H_2O], [OH^-], [CTMA] and [TMA], as input variables. The prediction results allowed classification of the materials with respect to the catalytic performance, and this ANN model was subsequently used to assist experimental design of the next catalyst library.

2.4.2. Search strategies for experimental design

Another crucial issue in combinatorial catalysis is how to design experiments in order to explore and optimize a high-dimensional solution space at minimum cost (number of trials). Amongst the techniques used for experimental design, the following can be distinguished: (i) statistical procedures, such as factorial designs [78]; (ii) deterministic optimization procedures, such as simplex, holographic searches [79] or split-and-pool [80,81]; (iii) stochastic procedures such as simulated annealing or genetic algorithms (GA). Stochastic procedures are well suited for the optimization of multi-dimensional problems, for example, the fruitful application of genetic algorithms in the discovery of new heterogeneous catalysts [82–84]. This is especially due to the fact that: (i) GAs use a diverse population of points to conduct the search, preventing convergence towards a unique local maximum; (ii) GAs tolerate noisy experimental data; (iii) GAs can work properly with high-throughput experimentation tools.

Fig. 8 shows a diagram of the working principle of a conventional GA. GAs follow the Darwinian concepts of natural selection and evolution [85], whereby stronger individuals are the likely winners in a competing environment. Therefore, a GA designs subsequent catalyst generation by considering the catalytic performance (*fitness*) exhibited by the previous generation, following selection routines and crossover and mutation operators. The crossover operator is associated with the interpolation

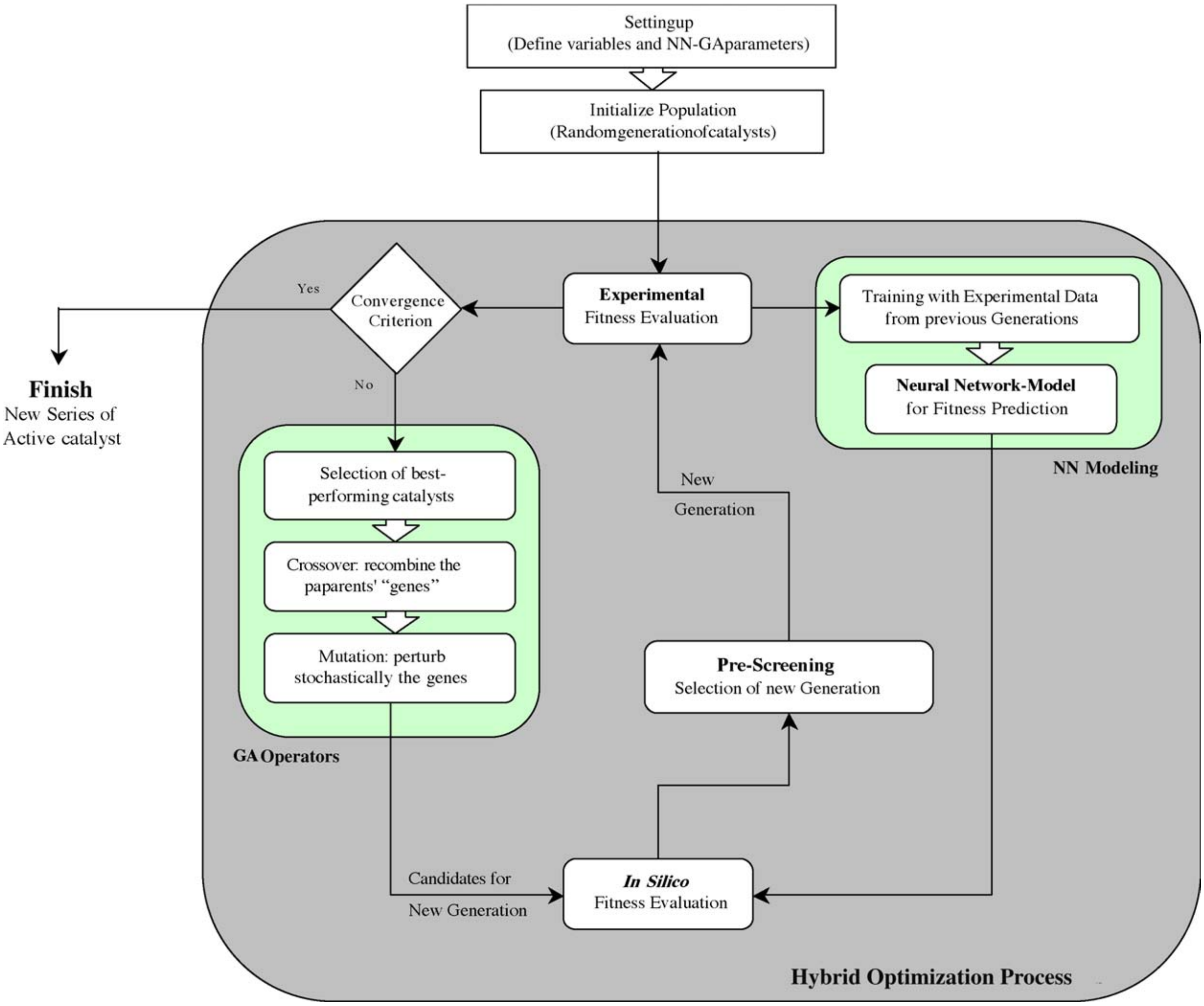

Fig. 9. Architecture of a soft computing algorithm comprising a genetic algorithm assisted by an artificial neural network.

capacity and convergence towards high-quality areas (*exploitation*), whereas the mutation operator is associated with the *exploration* capacity, allowing exploration of unknown areas of the multivariable space.

A further-step optimization approach [86–88] is the combined use of high multi-dimensional optimization algorithms with prediction models obtained by data mining, using an approach such that the knowledge extracted from all previous experimentation can be applied in the design of a new subset of catalysts to be screened in the next optimization cycle. One example of this approach is the integration of an ANN prediction model with a GA (so-called soft computing technique) in the optimization of epoxidation catalysts [47]. Fig. 9 shows the algorithm architecture employed in this work, in which a series of candidates for the new generation (*virtual* generation) was designed by GA operators and stochastic *pre-screening* was then carried to design the new generation (*real* generation) to be experimentally tested. The pre-screening process is carried out in two steps; first, the performance of the candidates is predicted by the ANN (in silico evaluation) and second, stochastic selection of the catalysts takes into account their predicted catalytic performance (*fitness*). Finally, this new *real* generation is experimentally evaluated and the optimization cycle is repeated until a convergence criterion is satisfied. The application of this intelligent approach allowed the identification of two types of Ti-silicate mesoporous catalysts with enhanced epoxidation activity and selectivity, while minimizing the number of experiments required.

As a final point, the use of *virtual* or *computational* screening as an alternative to experimental screening should be mentioned. This approach, based on ab initio or density functional theory (DFT) calculations, amongst others, would allow the design of large libraries of catalysts on the basis of *first principles* and their evaluation using computational means. Although computational screening is a reality in drug discovery [89], only a few attempts have been reported in the field of heterogeneous catalysis [90–92]. To date, the use of computational screening is largely restricted to simple ideal processes, and it is still difficult to obtain reaction rates from computational calculations when the reaction involves many elementary processes, or when many atoms participate in the reaction. One example of this approach reported by Barteau et al. [90] used the computational screening to study ethane epoxidation catalysts, predicting a catalyst (Cu/Ag alloy) with better selectivity for ethylene oxide than the traditional monometallic silver catalysts.

3. Conclusions

From an industrial point of view, combinatorial techniques applied to heterogeneous catalysis accelerate the discovery and optimization of new catalytic materials, and therefore reduce the time required for industrial exploitation. Moreover, this methodology allows investment recovery in a shorter time, as well as an increase in the time available for catalyst exploitation under the patent exclusivity period.

From an academic/scientist point of view, combinatorial techniques do not merely consist of carrying out hundreds of experiments, they are a set of tools that allow an increase in the number of intelligently designed experiments by more than one order of magnitude. Therefore, this approach allows an increase in the number of variables to be studied simultaneously, something that was impossible without the use of high-throughput techniques. The large number of predesigned experiments allows complete kinetic studies to be performed with many catalysts, as well as comparison of their behavior on the basis of true values for the kinetic rate and adsorption constants, activation energy and heat of adsorption.

Using this approach, we should not only increase the rate of discovery of new catalysts, but also test theories and reach new designs based on first principles.

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