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Experimental methods in chemical engineering: High throughput catalyst testing — HTCT

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Abstract

The conventional one-at-a-time strategy to evaluate catalysts is inefficient and resource intensive. Even a fractional factorial design takes weeks to control for temperature, pressure, composition, and stability. Furthermore, quantifying day-to-day variability and data quality exacerbates the time sink. High-throughput catalyst testing (HTCT) with as many as 64 parallel reactors reduces experimental time by two orders of magnitude and decreases the variance, as it is capable of quantifying random errors. This approach to heterogeneous catalyst development requires dosing each reactor precisely with the same flow and composition, controlling the temperature and identifying the isothermal zone, on-line analysis of the gas-phase, and a common back pressure regulator to maintain constant pressure. Silica capillary or microfluidic distribution chip manifolds split a common feed stream precisely (standard deviation <0.5%), thus guaranteeing reproducibility. With these systems, experimenters shift their focus from operating a single reactor to careful catalyst synthesis, sometimes delicate catalytic reactor loadings, and the handling, processing, and analysis of massive amounts of data. This review presents an overview of the main elements of HTCT, its applications, potential sources of uncertainty, and a set of best practises derived from scientific literature and research experience. A bibliometric analysis of articles Web of Science indexed from 2015–2020 grouped research into five clusters: (1) discovery, directed evolution, enzymes, and complexes; (2) electrocatalysis, reduction, adsorption, and nanoparticles; (3) hydrogen, oxidation, and stability; (4) DFT, combinatorial chemistry, and NH_3; and (5) graphene and carbon.

KEYWORDS

catalyst screening, catalyst testing, heterogeneous catalysis, high-throughput

1 | INTRODUCTION

Catalysis is a fundamental pillar of modern society that transforms raw materials into valuable chemicals efficiently. As much as 90% of all chemical processes apply catalysts in various markets such as food, pharmaceuticals, petrochemicals and fuels.[1] Furthermore, heterogeneous catalysis is expanding its role in emerging applications such as green chemistry, fuel cells, and biorefining.[2]

Developing and optimizing catalysts requires extensive experimental testing because of the large number of parameters that needs to be evaluated.[3] At the beginning of the twentieth century, BASF carried out 22 000 catalytic tests while developing their ammonia process.[4,5] Executing experiments one at a time restricts creativity and the capacity to quantify the variability encountered in day-to-day operations and thus data quality. High-throughput, or rather, miniaturized parallel catalyst testing, mitigates this to a certain extent; with more reactors, more ideas can be tested, automation reduces variability, and miniaturization minimizes investment and operating costs.

One of the biggest advantages of high-throughput catalyst testing (HTCT) is that it dramatically reduces the time required to develop or optimize a catalyst (Figure 1).[8] Demonstration facilities require teams of four technicians working around the clock, while parallel, automated HTCTs operate with 0.02 person-h^{-1}.[6] However, for some liquid or gas/liquid applications, the scale of HTCT systems is inconvenient because of their inability to supply enough samples for market development tests.[9]

The focus of academia and industry for HTCT has been to develop large catalyst libraries with few performance indicators (many catalysts are tested to confirm activity but ignore selectivity or co-products, i.e., low density information)[10] or to identify a large set of performance indicators for a few catalysts (high density information). By the 1980's, HTCT units consisted of six-parallel reactors to collect high-density information.[11,12] Designs improved with time to accommodate up to 64 highly automated reactors that were safer to operate, with improved analytical equipment and better quality data.

However, whereas testing capacity is the bottleneck for single reactors, HTCT is limited by synthesis and characterization of catalysts, as well as product characterization, i.e., product composition to calculate conversion, data processing, and analysis. HTCT requires intelligent planning and a well-thought-out design of experiments (DoE).[13] Data handling workflows must match with the capabilities of the HTCT equipment.

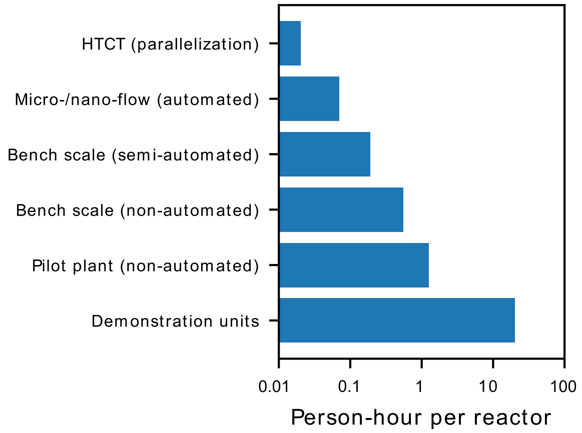

FIGURE 1 Relation between the person-hours spent per reactor and the type of testing unit[6,7]

This review is part of a series dedicated to documenting experimental methods in chemical engineering and focuses on high throughput testing of heterogeneous catalysts.[14] We discuss HTCT equipment and methods for gas–solid and gas–liquid–solid applications, data handling, and analysis, which are among the biggest challenges in HTCT programs. Finally, we include a set of guidelines and best practises, which also apply to single-reactor systems. Although the synthesis of materials and characterization of products are also highly relevant for HT technologies, these topics are out of the scope of this review but are available in the open literature.[10,13,15,16]

2 | DESCRIPTION

2.1 | Heterogeneous catalyst testing

To achieve the testing objectives, the kinetics and catalyst performance must be independent of mass and/or heat transfer resistances and other phenomena that may hinder the intrinsic catalytic behaviour. These resistances originate at fluid–solid interfaces (usually referred to as external transport), within the catalyst particles (typically called internal transport), and at tube walls (Figure 2). In addition, as with single catalyst testing units, the fluid dynamic behaviour must approach ideal plug flow (PFR) to interpret the data appropriately.[17] To ensure every reactor fulfils this criterion, the protocol includes testing boundary conditions, flow regime, and heat and mass transfer resistance.

2.2 | Fixed bed catalyst testing criteria

Fixed bed reactors are designed to approach the ideal plug flow regime. Rule of thumb criteria have been developed that are based on the ratio of the particle diameter, d_p, to bed diameter, D, and the number of particles making up the bed length, L_b.

2.2.1 | Reactor level

At the reactor level, the main aspects to consider are the axial dispersion, radial dispersion and wetting characteristics (trickle-flow reactor case), the flow velocity profile, and pressure drop across the catalyst bed.

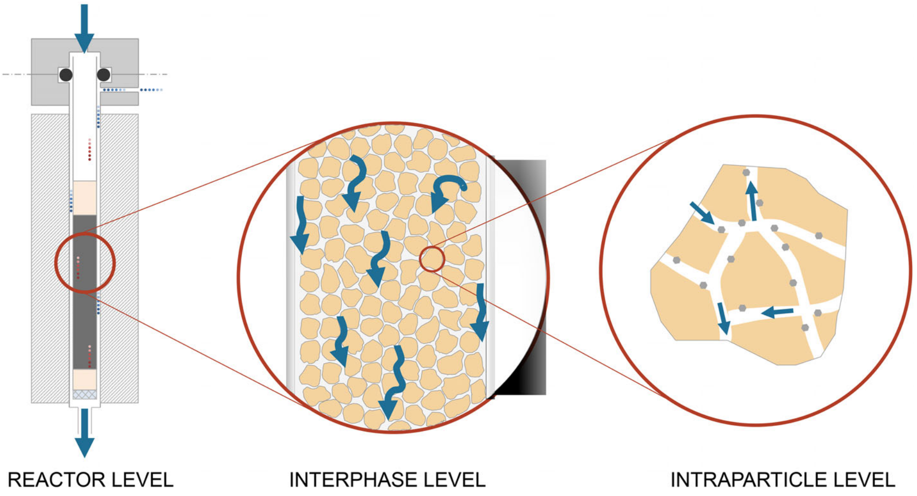

FIGURE 2 Three scales of transport phenomena

To neglect axial dispersion, $\mathcal{D}$, a minimum bed length, $L_{b,min}$, is required. The criterion shown in Equation (1) accounts for catalyst particle diameter, d_p, the degree of conversion, x, the order of the reaction (n), and a modified Bodenstein number, $N_{Bo,ax}$[18,19]:

$$\frac{L_{b,min}}{d_p} > \frac{8n}{N_{Bo,ax}} \ln\left(\frac{1}{1-x}\right) \tag{1}$$

In the case of trickle-bed reactors, the radial dispersion and wetting characteristics play an important role, especially when capillary forces dominate over gravity.[20] The criteria used to assess the role of these phenomena are shown in Equations (2) and (3), respectively.[9,20] Please note that $D_{e,rad}$ refers to the radial dispersion coefficients and the correlations of Delgado[21] could be use for its calculation:

$$\frac{r_v^{obs}(1-\epsilon_B)L_h^2}{D_{e,rad}c_s}\left(\frac{n+1}{2}\right) < 0.15 \tag{2}$$

$$\frac{\mu_L u}{\rho_L d_p^2 g} > 4\cdot 10^{-6} \tag{3}$$

The flow velocity profile should mimic that of a PFR. In order to minimize gas bypassing along the reactor wall due to high void fractions of the packing, known as wall effect, the ratio of the bed diameter, D to the particle diameter, d_p, should in general be greater than 10 (Equation (4)).[22] An exception to this equation is single-pellet-string reactors (SPSR), where it has been shown that $D/d_p < 3$ is actually beneficial.[7] A detailed residence time distribution study should accompany any test to better characterize the gas-phase hydrodynamics[23]:

$$\frac{D}{d_p} > 10 \tag{4}$$

To minimize axial concentration gradients (due to the change in pressure, $c = \frac{P}{RT}$, not reaction), the bed pressure drop, ΔP_b, must be less than 20% of the the total pressure, P_{tot} (Equation (5))[22]:

$$\frac{150\mu_g}{d_p^2}\frac{(1-\epsilon_B)^2}{\epsilon_B^3}u + \frac{1.75\rho_g}{d_p}\frac{(1-\epsilon_B)}{\epsilon_B^3}u^2 < 0.2\frac{P_{tot}}{L_b} \tag{5}$$

2.2.2 | Fluid–solid interphase and intraparticle levels

The mass and heat transfer limitations in the fluid–solid interphase can be neglected when the the following two criteria are met[22]:

$$\frac{r_v^{obs}}{a' k_f c_b} = N_{Ca} < \frac{0.05}{|n|} \tag{6}$$

$$\left(\frac{E_a}{RT_b}\right)\left|\frac{(-\Delta H_r)k_f c_b}{hT_b}\right| N_{Ca} < 0.05 \tag{7}$$

The left term of Equation (6), the Carberry number (N_{Ca}), is the ratio of the reaction rate observed to the maximum mass transfer rate from the bulk of the fluid phase to the external catalyst surface. This criterion considers that the effectiveness factor of the catalyst particles deviates less than 5% from unity. The effectiveness factor relates the reaction rate observed to the rate that would be obtained at bulk fluid phase conditions but it only applies to irreversible nth order reactions under isothermal conditions.[2]

The criterion in Equation (7) indicates if temperature gradients between the bulk fluid and the catalyst particle are negligible. It was also derived considering that the effectiveness factor for the catalyst particle deviates less than 5% from unity. As shown in Equation (7), the criterion relates the following: (i) the dimensionless activation energy, $E_a/(RT)$, which indicates how variations in temperature affect the reaction; (ii) the Prater number, $N_{\mathrm{Pra}} = ((-\Delta H_r)k_f c_b)/(hT_b)$, which relates the heat generated by the reaction to the heat transfer through the boundary layer between the catalyst and the bulk fluid phase; and (iii) the Carberry number, which provides a measure of the rate observed to the maximum rate of mass transfer.

In addition, the mass and heat transfer limitations within the catalyst particles are negligible when the criteria given by Equations (8) and (9) are fulfilled[22,24]:

$$\left(\frac{r_v^{\mathrm{obs}} L^2}{D_e c_s}\right)\left(\frac{n+1}{2}\right) < 0.15 \tag{8}$$

$$\left(\frac{E_a}{RT_b}\right)\left|\frac{(-\Delta H_r) D_e c_s}{\lambda_{e,p} T_b}\right|\left(\frac{r_v^{\mathrm{obs}} L^2}{D_e c_s}\right) < 0.1 \tag{9}$$

Equations (8) and (9) represent criteria to identify the presence of mass or heat transfer effects within the catalyst particle. These criteria consider that the effectiveness factor deviates less than 5% from unity. For Equation (8), the first term to the left in parentheses is the Wheeler–Weisz modulus that relates the reaction rate observed to the rate of mass transport due to diffusion. The effective diffusivity term accounts for molecular and Knudsen diffusivity, which is linked to the pore diameter and the mean free path of the molecules. The structure of Equation (9) is similar to Equation (7) as it contains the dimensionless activation energy, while the Wheeler–Weisz modulus replaces the Carberry number, and $((-\Delta H_r)D_e c_s)/(\lambda_{e,p}T_b)$ relates the rate of heat released or consumed by the reaction to the rate of heat transfer through the catalyst particles due to conduction.

The criteria requires the activation energy (E_a) or the heat of the reaction (ΔH_r), and system properties such as the heat (h) or mass transfer coefficients (k_f).

Diluting the bed with silicon carbide (SiC) distributes the heat of reaction over a larger surface area so the bed operates isothermally.[17] Isothermal behaviour is not a trivial topic. Even for laboratory reactors, large deviations from isothermicity can be observed, especially when the reactions involved are highly exothermic. For an example on temperature effects, please refer to the work of Yarulina et al.[25] on the methanol-to-hydrocarbon reactions over ZSM-5. On the other hand, excessive diluent could affect the observed reaction; thus, the criteria for the maximum fraction of diluent, b (on a volume basis), considers bed length and particle diameter:

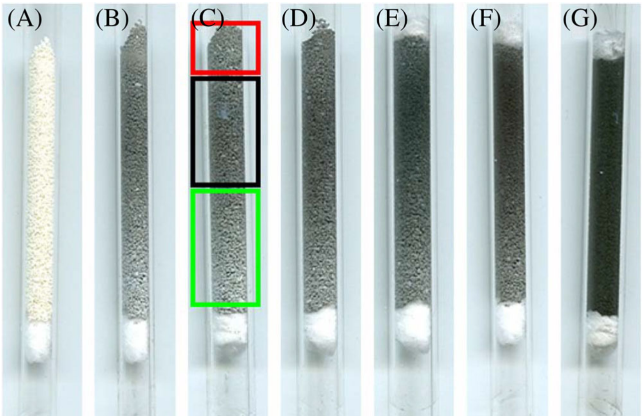

FIGURE 3 Methanol-to-olefins reaction in a 6 mm ID reactor. Coke continues to build up on the ZSM-5 catalyst over several hours. Letters a-g represent times of 0, 10, 20, 50, 110, 170, and 1310 min, respectively

$$\frac{2.5 b d_p}{(1-b)L_b} < 0.05 \tag{10}$$

However, even when these criteria are met, if the catalyst sinters or deactivates due to coke deposition or changes in the lattice structure, radial and axial gradients may confound the interpretation of the kinetic data (Figure 3).[26] For example, in the methanol-to-olefins process, coke continually builds on ZSM-5 zeolite over a period of 24 h, but the distribution is heterogeneous; it builds up at the entrance (darkest part of the catalyst bed) and spreads to the rest of the reactor with time. Coke blocks silicoaluminophosphate (SAPO) catalysts within minutes and so requires a frequent regeneration step. In the glycerol to acrolein reaction, coke forms on WO_3/TiO_2 over several hours (< 14 h). Acrolein preferentially reacts on the most active non-selective sites, which thereby reduces by-products.[27] Fluidized beds, on the other hand, operate isothermally, and the catalyst is backmixed, ensuring radial and axial homogeneity. However, they do require an entirely different set of design criteria with respect to particle properties and gas velocities.[28]

2.2.3 | Single-pellet-string reactor (SPSR)

The single-pellet-string-reactor (SPSR) is a special type of fixed-bed reactor where the average diameter of the catalyst particles is close to the internal diameter of the reactor, and catalyst particles are stacked on top of each other.[29] In this case, Equation (4) is invalid, as the typical ratio D/d_p is less than 3.[20] Despite this low ratio, SPSRs' mass transfer performance for gas/solid and gas/liquid/solid reactions is good.[20,29,30] In addition, in the case of gas/liquid flow, a Taylor flow pattern develops, which might account for the unexpected improvement of heat transfer properties.[20]

In two recent publications, Fernengel et al.[31,32] developed and proposed a SPSR design criterion that could be used to assess existing set-ups or to design new ones, and a modified equivalent diameter used with the Blake-Kozeny equation to accurately estimate the pressure drop.

The validity of the single-pellet-string approach has been demonstrated even for complex chemistries like hydrodesulphurization[30]; the results derived from a reactor at a scale less than 1 ml resembled a bench scale reactor of >200 ml.

Moulijn et al.[20] stated that "In catalyst testing a bonus for a single-pellet string reactor is the option to study the catalyst pellets as they are, thus, without crushing."

2.3 | HTCT equipment

HTCT has been a powerful tool in the discovery and development of new materials and catalysts for the industrial base chemicals and for the pharmaceutical industry.[13,33] Its main advantages include short development times, improved reproducibility, and a high success rate.[13] For these reasons, most major pharmaceutical companies, and many bulk and specialty chemicals companies like BASF, Dow, Clariant, ExxonMobil, and Bayer, among others, have built their own HTCT laboratories.[13,33] In addition, several companies offer HTCT equipment or services to help third parties accelerate their research and developmental programs. Here, we include a non-comprehensive list of companies that provide equipment and/or HT services[34]: Avantium, HTE, Xytel, AMTECH, Hel, Premex, Chemspeed, TeamCat, Integrated Lab solutions (ILS), Zeton, and RealCat, among others.

Many of these companies develop their own technologies to improve and further extend the capabilities of HTCT equipment. For this review, we have selected the Flowrence technology to exemplify generalities of HTCT units.

2.3.1 | Flowrence technology

An HTCT system is similar to a single reactor system; both consist of three main sections: (i) feed section, (ii) reaction section, and (iii) product section.

In principle, it is feasible to configure a high-throughput unit as a system of parallel individual reactors to allow for the maximum operating flexibility. This would result in a unit where each reactor has individual controllers in the feed, reaction, and product sections.[35] However, the cost grows almost proportionally with the number of parallel reactors (not economies of scale, but some economies related to experience).[36,37]

Therefore, the design of an HTCT system requires a balance between operating flexibility and costs, while maximizing data quality.

Avantium N.V. has developed a line of HTCT systems called Flowrence that are built following a general principle but are adaptable to meet the particular needs of each application.[30,38,39] A 16-reactor Flowrence unit (Figure 4), for example, has a common diluent gas section and a separate common mixed feed gas manifold. The gases feed to 16 inlet tubes together with a liquid injected through a single manifold. The reactor pressure is controlled downstream of the string catalyst bed and each effluent is selected to feed to a gas chromatograph (GC) for analysis. The effluent passes through a quench (one quench for each of the 16 lines) that is housed in a cooling tray held at 10–80°C to facilitate condensation.

Feed section

A manifold consisting of restrictors like silica capillaries or microfluidic distribution chips splits the feed stream precisely, which guarantees that the results are reproducible.[40–42] A microfluidic chip consists of one inlet, a number of etched channels with identical length and hydrodynamic diameter, each leading to one outlet. The microfluidic chip precisely splits the feed stream, with a relative standard deviation RSD of less than ±0.5% (depending on the operating conditions). Microfluidic distributors (splitter chips) in Flowrence systems apportion the feed to 16 reactors. From a cost and operational point of view, the splitter chip offer additional advantages as they are easy to use, much less expensive than 16 mass flow controllers, and less cumbersome to replace than capillaries. On the other hand, one needs to realize that using devices that work on a flow restriction principle implies that the feed source needs to be at a pressure that is, sometimes, 3–5 MPa higher than the inlet reactor pressure that is required.

Flow restrictors also distribute liquids. However, for certain applications, the pressure drop could be excessive (highly viscous fluids) or the nature of feed (e.g., vacuum gasoil [VGO] used in refinery catalyst testing applications) can lead to fouling of the restrictors, resulting in poor control due to changes in pressure drop over time. As a result, active control of the liquid feed is required. In this case, individual mass flow controllers may be appropriate. Flowrence systems combine the flow restriction principle with actual measurement of the feed flow, the active liquid distribution (ALD) system.[43,44]

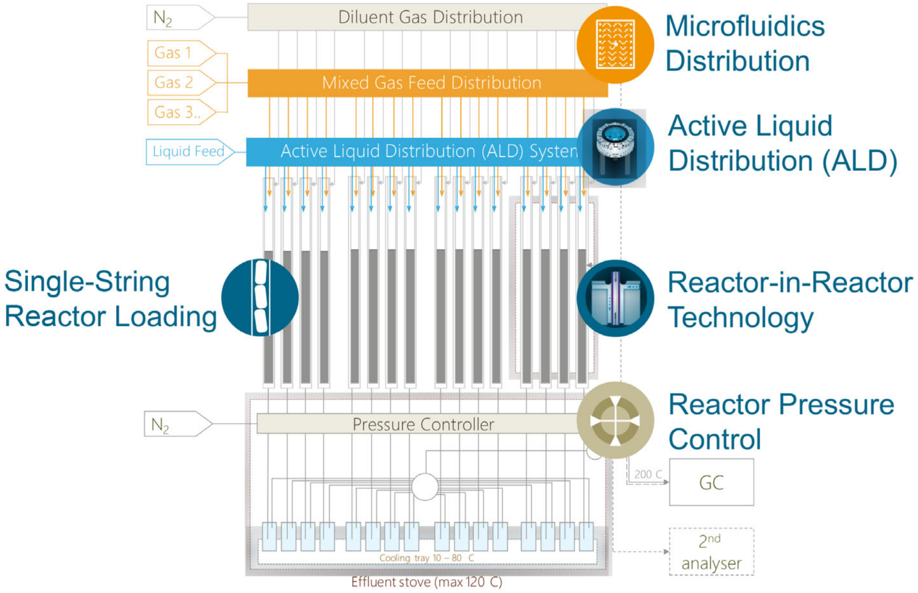

FIGURE 4 Schematic diagram of 16-reactor set-up. Figure prepared from Vilela[38]

Precise gas and liquid feeding to all reactors is the basis for closing mass balances precisely and accurately. In the case of units operating with microfluidics chips for the gas feed, and an ALD for the liquid feed, the overall mass balance is expected to better than ±2%. Together with the reactants, the feed section includes internal standards to calculate flow rates.

Reaction section

The reactors are located in heating blocks to maintain a uniform temperature distribution along the catalytic bed and a preheating zone to condition the feed to a set temperature.[16,30,35] Each heating block has individual temperature controllers that operate up to 950°C (Figure 4). The blocks also work as heat sinks; they either provide heat or remove it to facilitate isothermal operation. The patented tube-in-a-tube technology allows the use of thin-wall reactors made of quartz or stainless steel, with internal diameters varying from 2–5 mm, which can hold catalyst loadings from about 20 mg to a few grams, depending on the reactor characteristics, and can operate up to 20 MPa.[35,45,46] In the reactors, the catalytic bed must be located within the isothermal zone of the heating block.[35,42,46] A secondary advantage of this concept is the option to adopt a truly inert reactor, like quartz, to minimize material effects at high temperature and pressure. Heat effects are negligible when the heat transfer through the boundary layers or across the catalyst particles is much faster than the heat generated or consumed by the reaction.

Product section

The product section consists of a temperature-regulated chamber that ensures product handling and separation under controlled conditions. A manifold depressurizes the product streams and selects the reactor outlet stream to send to the analyzer.[6,22] A common back pressure regulator (BPR) maintains all reactors at the same pressure.[47] A BPR for each reactor increases precision and flexibility but costs more.[48,49] The Flowrence design includes a reactor-pressure-control (RPC) system that minimizes variability across parallel reactors, which is especially important for low-pressure applications. In the case of trickle-flow chemistry, an automated gas/liquid separator collects the liquid for each reactor, and the gas stream is sent to the selector valves for further on-line analysis. The collected liquid samples are sent to off-line analysis for data matching with the gas phase analysis (Figure 4).[30,35]

3 | APPLICATIONS

High-throughput catalyst screening (HTCS) as a part of HTCT has been widely used in the heterogeneous and homogeneous catalysis fields for synthesis, characterization, and screening techniques to accelerate the discovery and development processes. Researchers apply HTCS for chemical synthesis, polymers, electrochemistry, pharmaceutical, petrochemistry, and refining.[41,50]

Since 1996, Web of Science (WoS) has indexed 1011 articles containing high-throughput catalyst screening as the keywords in the the search criterion topic.[51] The WoS categories in which the research most frequently appears includes multidisciplinary chemistry with 310 occurrences followed by physical chemistry (278), applied chemistry (176), chemical engineering (114), and organic chemistry (102). The categories are intrinsically connected to research in chemical engineering.[52] The journals that published the most articles are among those with the highest impact factor in catalysis: *Angewandte Chemie-International Edition* (40 articles), *Catalysis Today* (37), *Chemistry-A European Journal* (32), *Applied Catalysis A-General* (27), *ACS Combinatorial Science* (25), *Journal Of The American Chemical Society* (25), and *Advanced Synthesis & Catalysis* (24). Over the last 10 years, the number of articles published per year has varied consistently between 30–40.

Since 2014, WoS has indexed 343 articles mentioning HTCS; the web-based program VOSViewer groups them into four major clusters (Figure 5).[53] The red cluster, with the most keywords (28), is centred around discovery, complexes, and directed evolution. The green cluster, on the opposite side of the map (which indicates that it has the least commonality with the red cluster), has 18 keywords that mostly deals with electrocatalysis, reduction, adsorption, and nanoparticles. These two clusters sandwich the blue and yellow clusters: design, oxidation and hydrogen dominate the blue cluster, while combinatorial chemistry, heterogeneous catalysis, and density functional theory are the major topics of the yellow cluster.

Nature Materials published the most cited article in HTCS, with 1870 citations, entitled "Computational High-Throughput Screening of Electrocatalytic Materials for Hydrogen Evolution."[54] This work describes a density functional theory (DFT)-based, high-throughput screening method to identify new electrocatalysts for the hydrogen evolution reaction (HER, green cluster). This method evaluated 700 binary surfaces to estimate their activity and selectivity for HER. Experimental data validated the DFT predictions and this work demonstrated the benefits of HTCS in accelerating the discovery of new and more efficient catalysts. *Angewandte Chemie International Edition* published the next three most cited articles,[55–57] dealing with combinatorial and evolution-based methods and libraries. Since 2014, the most cited articles appeared in *ACS Sustainable Chemistry & Engineering*: "Facile and One-Pot Access to Diverse and Densely Functionalized 2-Amino-3-cyano-4H-pyrans and Pyran-Annulated Heterocyclic Scaffolds via an Eco-Friendly Multicomponent Reaction at Room Temperature Using Urea as a Novel Organo-Catalyst" (182 citations)[58]; *Energy & Environmental Science*: "Towards a

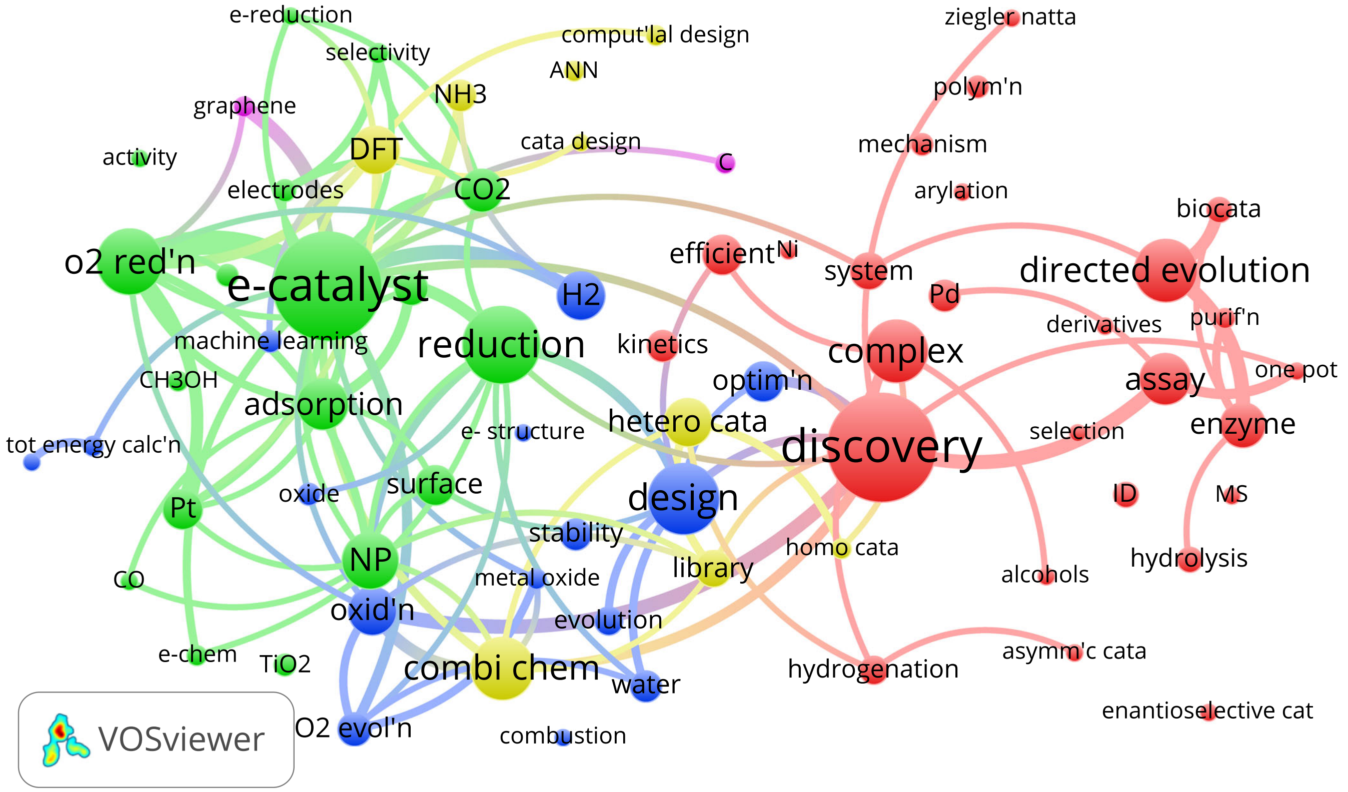

FIGURE 5 High-throughput catalyst screening bibliometric map of articles WoS indexed from 2014–2020.[51] The database comprises the 72 most often mentioned keywords. VOSViewer software groups keywords together in clusters that are related and gives them the same colour and places them in closer proximity. The size of the circles is proportional to the number of articles. The search included high-throughput catalyst screening with 343 total occurrences. The largest circle in the red cluster is discovery and the size corresponds to 38 articles (more than 10%). Electrocatalyst, the biggest circle among the green cluster, is also mentioned as a keyword in 38 articles. Design is the largest circle in the blue cluster with 25 articles, and combinatorial catalyst has 22 articles. The smallest circles represent 6 articles. The map excludes both catalysis and high throughput screening, which have 71 and 68 occurrences, respectively

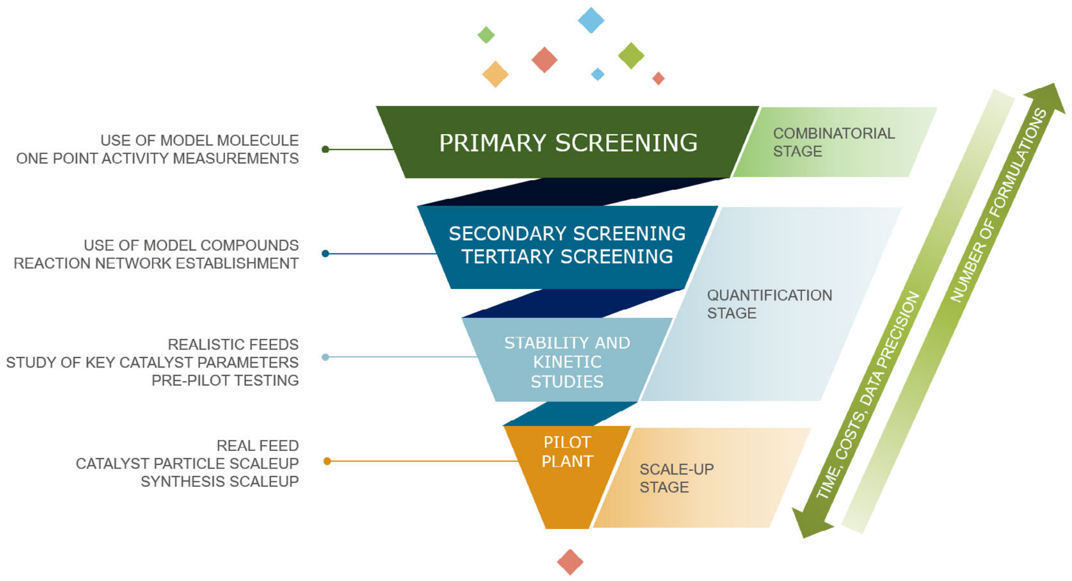

FIGURE 6 Schematic representation of the stages comprising a catalyst development program

TABLE 1 High-throughput catalyst testing (HTCT) applications in catalysis

Application	Objectives	Why HTCT?
Primary screening[61]	Catalyst and product discovery	Shorten discovery path Enlarge pool of ideas
Secondary and tertiary screening[62]	Catalyst formulation tuning Product composition definition Operating conditions optimization	Shorten catalyst formula optimization process Optimize process operating conditions
Catalyst comparison[38, 63]	Selection of optimal commercial catalyst	Compare catalyst at realistic conditions De-risk catalyst change out Decrease cost to select catalyst
Reaction kinetics[6, 62, 64]	Generation of data to model kinetics	Reduce time and cost
Process optimization[3, 6, 65]	Pre-pilot testing	Shorten timeline to optimized feed conditions Reduce risks by widening sample funnel
Deactivation/lifetime[66]	Pre-pilot testing	Reduce risks by widening sample funnel

Comprehensive Understanding of Visible-Light Photogeneration of Hydrogen from Water Using Cobalt (II) Polypyridyl Catalysts" (138 citations)[59]; and *Journal Of Physical Chemistry Letters*: "Machine-Learning-Augmented Chemisorption Model for CO_2 Electroreduction Catalyst Screening" (124 citations).[60]

3.1 | HTCT applications in heterogeneous catalysis

Heterogeneous catalysis adopted HTCT after it was first implemented in the pharmaceutical industry.[46] While several workflows to make heterogeneous catalysts exist, the three fundamental stages begin with discovery of new materials to scale-up of catalyst preparation procedures and industrial testing (Figure 6 and Table 1):

1. In the Combinatorial Stage, a large number of catalysts are prepared and their performances are assessed in short tests (primary screening). The main idea is to identify potential materials suitable for the application.
2. The Quantification Stage includes a more thorough evaluation of potentially interesting materials identified in the Combinatorial Stage. The focus is to optimize process parameters (secondary and tertiary screening), determine reaction kinetics, and perform stability studies. Although less samples are studied, the number of experimental conditions is larger.
3. In the Scale-up Stage, the testing program focuses on evaluating commercial size catalyst samples using real feeds at industrial relevant operating conditions, including unreacted feed recycle. In general, catalysts are tested in demonstration plants where reactor

scales are comparable to those of the final commercial unit. This step manufactures quantities large enough for customer qualification.[3]

If traditional methods of catalyst synthesis and testing are used, the developmental program becomes inefficient and costly,[3] mostly because they are performed sequentially, which requires long timescales. Therefore, the high-throughput synthesis and testing of catalysts becomes an attractive tool to accelerate the development process in all stages.

3.1.1 | Catalyst screening and discrimination

Probably the best-established application of HTCT, in the heterogeneous catalyst field, is catalyst screening and discrimination, which is often applied at different stages of technology development.

The primary screening aims at pre-selecting the most promising materials out of a vast and diverse pool of options that are available at the early catalyst developmental stage. Usually, at this stage, a simple single-point-activity testing is performed. The parallelization of tests, in the primary screening, significantly decreases the time required for identifying potential catalyst champions that ultimately reduces the time to market. While primary screening is widely used in drug discovery processes in the pharmaceutical industry,[33] it is the experience of the authors that primary screening has been largely abandoned in fixed-bed heterogeneous catalysis applications due to limitations of translating results to later development stages.

In the secondary screening, a group of selected catalysts is subject to more exhaustive testing. The experimental campaigns are elaborate with a wider and more realistic range of operating conditions, more comprehensive analytics, and higher data quality.[62] Although the pool of catalysts at this stage is much smaller compared to the primary screening, HTCT reduces the time to identify the optimal formulation and the most favourable process conditions.

Apart from developing new catalyst technologies, catalyst screening discriminates between commercially available catalysts. This is particularly relevant for established technologies, such as refinery processes, where the unbiased selection of the catalyst directly influences profitability. Users compare the performance of catalysts available on the market, under industrially relevant conditions, prior to loading the catalyst into the industrial reactor. A catalyst performance test supported by data-driven decisions minimizes risks associated to a catalyst exchange and leads to higher economic return.[63]

3.1.2 | Optimization of process parameters

The optimization of process parameters is typically performed for a limited number of promising candidates, which have been identified in the Secondary screening step. This optimization phase is also known as tertiary screening that not only covers process optimization, but also deals with aspects of operation like susceptibility to poisoning or the effect of fluid dynamics on the performance of the catalysts.[41] Parallel testing of multiple catalysts during process conditions optimization decreases the timeline for the search of optimal catalyst feed conditions combination for the identified leads. Moreover, availability of multiple reactors gives an opportunity to keep more catalyst samples from the screening stages, which ultimately reduces the risk of discarding more suitable catalyst candidates.

3.1.3 | Kinetic modelling and mechanistic studies

In recent years, HTCT has more frequently been used to accelerate kinetic studies, as a deeper insight into the underlying process can be obtained from these data. This knowledge helps establish a more robust catalyst activity ranking and estimates for scaling up processes or further optimization.[67]

Depending on the modelling objective and amount of data available, the kinetic model might contain more or less detail and, hence, will require a dataset of a different size. Comprehensive models require extensive detailed information on pressure, temperature, composition, product inhibition, and suspected poisons. Acquiring this data takes time, but HTCT reduces costs as it measures multiple conditions simultaneously, and duplication increases data significance.

3.1.4 | Catalyst deactivation and lifetime

Assessing deactivation rate (stability) is another major challenge while developing catalyst because it takes as much as 1000 h or more. Long-term catalyst lifetime studies are conventionally performed only at the latest stage of technology development when a single catalyst has been selected. In case of failure, time to market becomes longer or revenues drop in established processes. Parallel reactor units test multiple catalysts earlier in the development process when there are still other potential formulations available. Widening of the sample funnel during testing of this crucial parameter identifies promising candidates, which could have been excluded if only the initial activity was investigated. In addition, the chance of encountering a late stage failure if performance issues only display at longer times on stream is minimized by including more candidates than would be feasible using a classical one-at-a-time approach.

4 | UNCERTAINTIES AND LIMITATIONS OF HTCT

4.1 | Experimental errors

Experimental errors impact data quality and its interpretation, which is especially relevant when discriminating between catalysts with similar activity. High throughput-testing generates a sufficient amount of data to statistically discriminate performance between catalysts.[68] A common mistake while interpreting data, not limited to HTCT, is the misuse of the term's accuracy and precision of experimental measurements: accuracy is the measure of how close the experimental result is to the true or reference value while precision is the measure of how close the data points collected at the same conditions are to each other.[69,70] Repeatability considers experiments performed on the same equipment, by the same researcher, and following the same procedure. Reproducibility, on the other hand, implies the use of different equipment, researchers, and location. Conditions when experiments are repeated in the same laboratory and with the same equipment, but by a different researcher and within expanded span of time, can be referred to as intermediate precision conditions.[69]

The magnitude of error varies with chemistry, equipment, procedures, and operating and ambient conditions. For example, when temperature dominates the experimental error ($\Delta_T > \Delta_{\mathrm{otherfactors}}$),[70] the variance decreases with increasing temperature.[68,71] To properly characterize variability, replicates are required. This is one advantage of HTCT as replicates are performed in parallel, saving time and resources.[72] It takes seven measurements to achieve a 95% confidence level, Δ_T, equal to the standard deviation of the measurement, σ_T.[73] To achieve a 99.9% confidence interval requires 17 repeats (assuming the error is normally distributed):

$$n = 2.4 + 3.8\frac{s^2}{\Delta^2} \quad \forall n > 3,\ p < 0.05 \tag{11}$$

$$n = 3.6 + 6.6\frac{s^2}{\Delta^2} \quad \forall n > 5,\ p < 0.01 \tag{12}$$

$$n = 5.4 + 11\frac{s^2}{\Delta^2} \quad \forall n > 7,\ p < 0.001 \tag{13}$$

Statistical interpretation of the results depends on the nature of the experimental error. When it comes to HTCT, variability arises from catalyst sampling and loading, flow control and distribution, temperature, pressure, analytical method, mass balance control, and ambient conditions.

4.1.1 | Catalyst sampling and loading

The majority of HTCT systems adopt micro/miniaturized reactors.[36] Scaling down reactors introduces variance due to sampling a heterogeneous batch of catalyst (the sample representative).[19,74] Factors include how the catalyst pellets were made (size and shape of extrudates), structural properties, or impregnation quality for supported catalysts.[75] In reactors on the order of 100 g and more, established sampling procedures minimize the variability.[7] Single-string packing reactors require a non-biassed catalyst sampling procedure.[30]

Like large industrial reactors, bed packing is a factor for HTCT. At the catalyst activity screening stage, rather than pellets, powders are tested, so particle size distribution and particle size itself are factors. For fluidized bed reactors, we test the spray dried catalyst but screen the catalyst to maintain $60\ \mu\mathrm{m} < d_{\mathrm{p}} < 150\ \mu m$. For fixed bed catalysts, we test full-sized pellets in the later stage and when comparing commercial catalysts.

4.1.2 | Flow control and distribution

The accuracy of the flow distribution contributes to experimental error. As described above, there are passive distribution systems, like capillaries, and active ones, like mass flow controller and metering pumps, which are used to regulate the flow of gas and/or liquid feed to each reactor. New technologies based on microfluidic distribution systems improve both distribution and operability.[44] For first order reactions, neglecting other sources of variability, the variance of the conversion, σ_x^2, is inversely proportional to the square of catalyst mass, W, and kinetic rate constant, k, and proportional to the variance of the flow rate, σ_v^2[68]:

$$\sigma_x^2 = \left(\frac{1}{W^2}\right)\left(\frac{\sigma_v^2}{k^2}\right)(1-x)^2 ln^4(1-x) \tag{14}$$

4.1.3 | Temperature

Screening catalyst requires regulating temperature precisely and accurately. For a first order reaction and neglecting all other sources of variability, the conversion variance, σ_x^2, increases with T to the fourth power, to the second power with activation energy, and is proportional to the variance of temperature (σ_T)[68]:

$$\sigma_x^2 = [(1-x)ln(1-x)]^2\left(\sigma_T\frac{E_a^2}{T^4}\right) \tag{15}$$

To achieve an uncertainty of ±0.5% in the activation energy over Δ10 K requires measuring temperature to within ±0.03 K, which highlights the relevance of highly accurate and precise temperature control.[76]

4.1.4 | Pressure

HTCT systems are equipped with pressure regulating systems to reproduce commercial operation. The importance of high precision in the pressure control becomes more relevant in low-pressure applications. Pressure regulators rated at ±100 kPa induce errors of ±1% when operating at ±10 MPa, and the expected error increases proportionately at lower pressures.

4.1.5 | Analytical

Mass spectrometer (MS) and GC are the most common instruments to monitor the gas stream composition, while high pressure liquid chromatography (HPLC) is a robust method for liquid phase analysis. The choice depends on product composition, required sensitivity, reproducibility, and speed of analysis. An on-line MS samples the gas stream up to 20 Hz while micro-GCs sample at rates three orders of magnitude slower.

Frequent calibration (from several times a day to every hour) reduces the error related to drift in an MS.[77] Checking the calibration of a GC and HPLC at least once per week is appropriate. HPLC precision is much higher than that of a GC (with a precision on retention time of 0.1 min or <0.5%),[78] which in turn is better than that of an MS.

4.1.6 | Mass balance closure

Mass balance closure is a quality control benchmark that applies to each reactor and to the whole system. For multicomponent reactions with more than five co-products and byproducts, a mass balance of ±5% is a target. However, to discriminate between catalysts in an HTCT unit, the target should be much narrower if the catalysts under evaluation display similar behaviours. HTCT reduces variability by controlling conditions precisely but also through repeat runs.

Leaks in the system, undetected compounds, poor calibration of the analytical instruments, and faulty mass flow metres contribute to mass balance errors.[34] On-line MS facilitates real time mass balances as the data feed directly into databases. GC and HPLC analyses are slower but can also be automated to close mass balances more quickly and thereby detect and correct errors.

5 | EXPERIMENTAL DESIGN AND DATA MINING

5.1 | Design of experiments (DoE)

A robust experimental design has a clear goal and allows one to define the conditions where data must be collected to maximize the information obtained with the minimum number of experiments.[79] Multiple DOE protocols are possible "for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions."[80]

Full factorial designs are impractical even for HTCT and so we adopt fractional designs to decrease the load and time.[34] A DOE must account for nonlinear phenomena (like temperature) and interactions. HTCT explores additional experimental conditions without adding excessive time or effort to complete testing programs.

The four main categories of experimental design are comparative, screening, response surface, and sequential (or optimization). Comparative designs concentrate on a single factor. As such, they have little relevance to evaluation of catalyst. Screening designs (or statistics driven) discriminate between relevant factors and unimportant ones. The relevant factors are tested in the next level of testing with either a response surface or optimization design.

Traditional screening designs are full factorial with n levels and q factors which identify interactions and nonlinear effects, but at the expense of an enormous number of experiments (Figure 7). Catalyst testing programs consider as many as 10 factors like synthesis method, support type, metal loading, post-synthesis treatment, experimental temperature, pressure, and space-velocity (SV), which requires 2^{10} experiments for a linear system and 3^{10} for a non-linear system. Although HTCT explores a large amount of variables rapidly, it is impractical and costly to screen the entire space of variables.[81] However, when necessary, like in the ammonia synthesis case with 22 000 tests, HTCT reduces the time it takes.[4, 5] HTCT

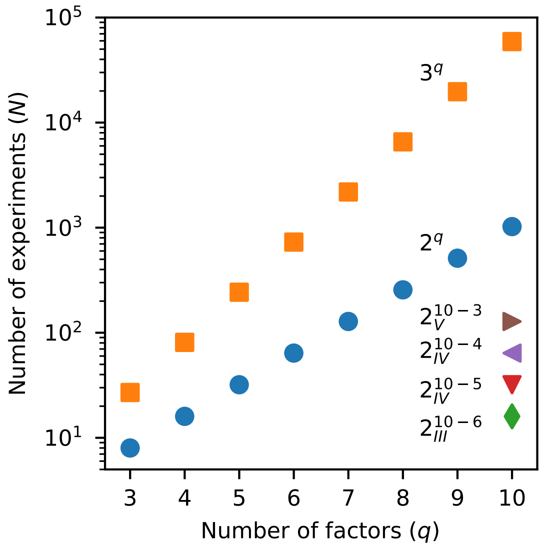

FIGURE 7 Number of experiments for 2-level full factorial designs, 3-level full factorial designs, and 2-p fractional factorial designs

complements intelligent planning and a DoE rather than replacing these two processes.[13]

A 10-factor, two-level fractional experimental design requires from 16–128 experiments, depending on the target design resolution. For a full factorial $n = 2^{10} = 1024$ (Figure 7).

Response surface designs identify interactions between factors and non-linearities. The correct interpretation of the resulting data should give clarity on the shape of the response surface that is being investigated. Factorial or composite designs are appropriate complements to response surface methods since they provide minimum-variance estimates of the parameters.[82,83] Response surface designs can also be multi-objective, where the desired outcome could maximize a variable, for example space–time-yield, while at the same time minimizing the selectivity of a specific by-product.

Sequential experimental designs chose the conditions of subsequent experiments based on the results of previous experiments.[84] This methodology is especially powerful to estimate kinetic parameters and to discriminate among kinetic models.

5.1.1 | Kinetic model discrimination

Consider that all combinations of experimental conditions can be represented in a grid. Each coordinate of the grid represents a combination of experimental factors: temperature, pressure, SV, and initial reactant concentration. Then, in each grid position, we evaluate a design criterion to determine the optimum grid position to be tested in the next experiment. This grid search approach is faster than optimization routines.[2]

Kinetic model design criteria are based on the maximum divergence between model predictions and data.[85] The set of experimental conditions that lead to the largest divergence is selected as the grid position to conduct the next set of experiments. HTCT calculates and check multiple grid positions simultaneously, which converges to optimal conditions more rapidly.

Although calculating the design criterion at each grid position might appear complicated, predefined algorithms simplify the task (computer-aided design). Informatics is the key to collect, process, and analyze data from a HTCT system, and to evaluate the design criterion that defines the next set of experimental conditions that are required to discriminate among plausible kinetic models and improve the kinetic parameter estimates.

5.1.2 | Catalyst design (information driven)

Information-driven catalyst designs are composed of two experimental phases. In the first phase, researchers identify the catalysts that provide the most information.[42] These catalysts are not necessarily the most active or selective, but we acquire mechanistic information from the experiments. In the second phase, catalysts' descriptors are characterized and translated into catalyst performance by means of, for example, a microkinetic model.[42] Since the catalyst performance is described at a fundamental level, the number of experiments can be limited to a range of conditions, while still allowing extrapolation to untested operating conditions.[34,42]

5.2 | Data mining and visualization

In general, the raw results of a catalytic test are signals from analytical instruments and measuring devices that represent only information and not knowledge. For example, the information obtained from an analytical instrument includes area under peak for a GC, and time and fragment intensities for an MS. We transform this information to knowledge by converting GC areas into concentrations and, subsequently, to molar flow rates based on the outlet flow rate of the reactors. A mass balance across the unit validates the coherency of this information.

Handling, processing, and interpreting data are some of the main challenges in HTCT. In traditional catalyst testing (one test at at time), researchers have more time to review and interpret results and plan additional tests.

The volume of experimental data generated by HTCT is overwhelming and data interpretation becomes a bottleneck. Therefore, data mining and visualization techniques are essential.

Data mining is the data-to-knowledge transformation process and is a branch of statistics.[81,86] Data only represents information and not knowledge.[87] Data (information) collected and computer models must be interpreted and understood. Data wrangling follows the execution of the experimental design (Figure 8). Wrangling involves tidying and transformation. Tidying means compiling and storing data from various sources in a consistent matter; each column is a variable and each row is an observation.[88] Transformation (modelling) comprises a couple of steps, including reducing the dimensionality of the data to simplify the analysis (principle component analysis, PCA).[34]

Another step consists of applying simple modelling tools like multiple linear regression (MLR) and partial least squares (PLS)[81] or complex tools like genetic algorithms (GA), artificial neural networks (ANN),[89] and classification trees (CT).[13,90] Some complex methods are like black boxes where the logic of cause and effect are masked by the algorithm, which is probably their biggest disadvantage: "Just because a program did not crash does not mean that the results are meaningful" (Table 2).[81]

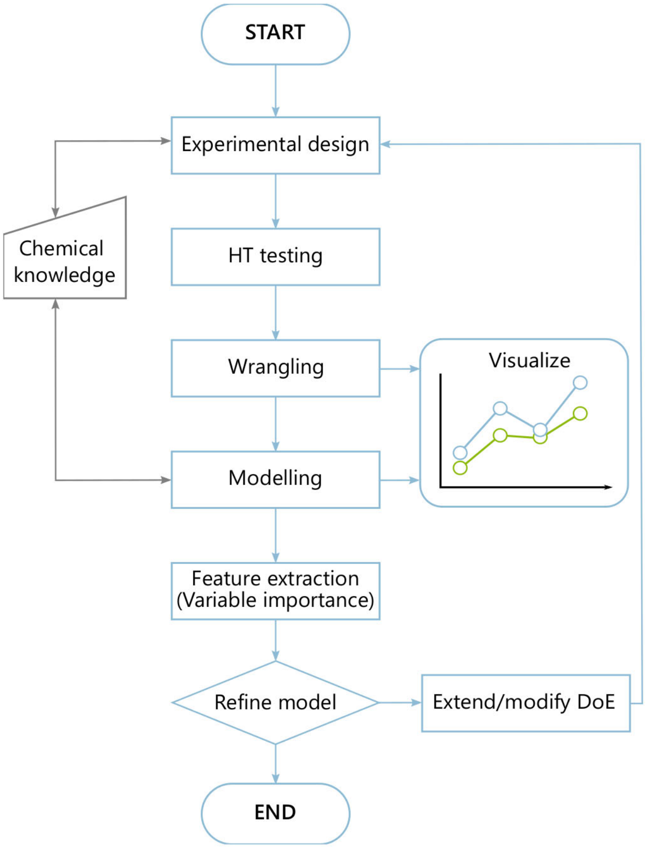

FIGURE 8 General data-mining approach. Adapted from Rothenberg,[81] Ohrenberg et al.,[86] and Caruthers et al.[87]

TABLE 2 Comparison of modelling tools (non-comprehensive)

	MLR	PLS	ANN	CT
Simple systems	+	+	−	−
Complex systems	−	−	+	+
Easy-to-follow logic	+	+	−	+

5.3 | DoE software, data visualization, and data mining

Informatics is the answer to analyzing the data generated by high-throughput testing. Software packages are available that execute DoE, data visualization, modelling, and/or data mining. Well-known commercial software include Minitab, Design-Expert, Statgraphics, and JMP. These packages have user-friendly interfaces that reduce the learning curve and facilitate data exploration and data mining.

They analyze data from a statistical point of view and, consequently, have little capability to estimate parameters or model data based on solving coupled partial differential-algebraic systems of equations. Software like MATLAB, R, and Python are platforms to solve these equations and handle large data sets. They have plotting capabilities that can be automated. On the other hand, the learning process is slower as the user interface is less intuitive.

There are also specialized software that focus on reaction engineering aspects such as reactor modelling, kinetic modelling and discrimination, parameter estimation, and optimal experimental design to improve parameters estimates. One example of this type of software, known by the authors, is Athena Visual Studio (https://athenavisual.com/), and potentially many others could also fall in this category.

So far, a single platform is incapable of designing experiments, processing large data sets, producing professional plots, and solving partial differential equations. As a consequence, researchers maintain various programs to derive knowledge from the information they gather.

6 | BEST PRACTISES IN HTCT

Smart planning and handling large data sets are among HTCT best practises beyond what is required for single reactor operation. The life cycle of a testing program includes initiation, planning and preparation, execution,

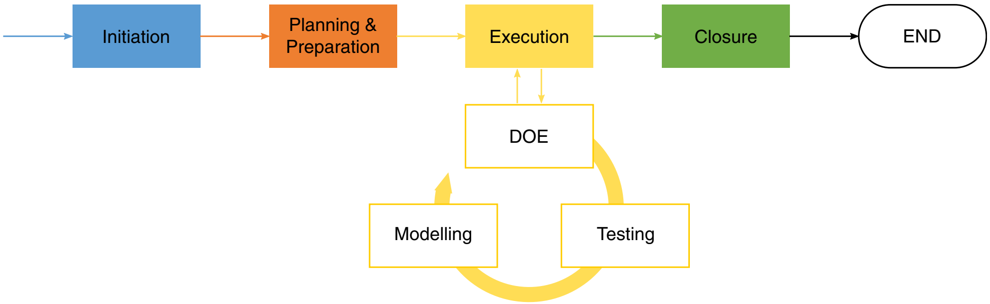

FIGURE 9 Global experimental program stages

and closure (Figure 9). The execution stage could be unidirectional, meaning that the set goal is achieved with the initial DoE design. It could also be cyclic, which would require continuous data analysis, processing, DoE, and catalyst testing activities. The latter is likely when the goal is to develop a new catalyst, or to discriminate between rival kinetic models (Figure 9).

Two real-life examples illustrate situations that researchers face developing an HTCT program (but the procedure also applies to single reactor testing). The first example, related to Fischer-Tropsch, deals with the initiation and planning stages.[39] The second example, on oxidative coupling of methane, concentrates on the execution phase.

6.1 | Initiation

The first steps in planning and executing an HTCT program, are to define the goal(s), specify the critical performance parameters, and assess if the goal(s) can be achieved with the available resources:

- The definition of the goal is typically related to the stage reached by the catalyst development program (Section 3). Using the Fischer-Tropsch case study, we see that the goal was clearly stated: the authors wanted to rank 30 ruthenium catalysts based on CO conversion and explore the reaction product composition.[39]
- Assess if the goal can be achieved in the high-throughput unit given the intrinsic constraints associated to the equipment. For example, if the threshold to discriminate between catalysts is $\Delta = 0.2\%$, is it achievable considering the intrinsic uncertainties related to the test? (Section 4).

6.2 | Planning and preparation

In this stage, researchers: (i) specify the experimental program (DoE); (ii) calculate critical conditions associated with pressure drop, heat and mass transfer, and catalyst bed length, among others; and (iii) prepare the test rig to execute the experimental program.

6.2.1 | The experimental program

Specifying the experimental program involves a set of decisions that would allow a safe, logical and well-thought-out sequence of experiments. Some key elements include:

- Safety is the first consideration before performing any test, which includes the chemistry itself (physical properties, toxicity, carcinogenicity of reactants and products), evaluation of the systems that are to be in place when performing the test, evaluation of various hazardous scenarios, and writing operating, start-up, and shut-down procedures.
- Prepare an experimental design (DoE) that is required to achieve the goals set in the previous stage. The DoE considers all relevant process variables. The Fischer-Tropsch case study included 30 catalysts operating at two pressures, three temperatures, with two catalyst particles sizes, packing the reactor with and without diluent, and a fixed SV and H_2/CO ratio.[39] The program lasted only 1 week compared to 14 months for a single-reactor conventional approach.[39]
- A well-planned DoE facilitates interpreting data, which could include data mining techniques and surface response models.
- If the individual outlet flow rate of each reactor cannot be measured directly, use one or several internal standards in the feed mixture. The number of internal standards depends on the number of detectors. (An MS samples all of the streams so each would have an internal standard.) We calculate the total and individual outlet and verify the mass and elemental balances across the unit.
- Whenever possible, include a blank reactor to monitor feed composition during the tests. Sampling the feed periodically confirms the fidelity of the analytical instrument or identifies changes in the feed composition.
- Maintain the same activation protocol followed by a pre-established stabilization time.

- Repeat standard conditions periodically to monitor the change in catalyst activity with time.

6.2.2 | Preliminary calculations

G. J. Quarderer said that "Four to six weeks in the lab can save you an hour in the library."[91] This statement stresses the relevance of the preparation to minimize unnecessary time-consuming laboratory work. Sometimes we can predict, with a high degree of confidence, what will happen during the test given a certain set of conditions. These predictions consist of well-known calculations that one can use to avoid issues during operation of the equipment and minimize the effects of heat and mass transport phenomena (Section 2). As a good practise, these key numbers calculate the following:

- • ΔP (Ergun equation for fixed beds).[92]
- The heat and mass transfer rates. Then, one must assess the criteria described in Section 2. If the criteria is not met, one could minimize heat and/or mass transfer limitations by executing one or more of the following actions:
- Dilute the bed with inert (Section 2).
- Operate narrower reactors to increase the superficial velocity, which improves convective heat and mass transport rates. Moreover, narrow reactors have higher surface-to-volume ratios, which increases heat transfer rate and lowers radial thermal gradients.
- Decrease d_p to increase the surface area available (better external mass transfer) and reduce the molecular diffusion distance (better internal mass transfer). When particle shape and size are goals of the test, this step is unnecessary. The constraint on d_p is up to $\Delta P < 0.2 P_{tot}$.
- The minimum bed height to achieve the desired conversion. This is associated with $\mathcal{D}$ and assumptions around ideal plug flow (Section 2).
- The expected concentration of reactants, products, and byproducts as a function of operating conditions to assess safety and analytical requirements.

Some of these actions are commonly applied in catalytic studies, especially when the chemistry is highly sensitive to heat and/or mass transport phenomena.[39]

6.2.3 | Commissioning

When a robust commissioning protocol is missing, issues may arise in the execution phase. Key points to check include:

- Test for leaks. Together with implications of safety (risk of explosion, exposure to hazardous gases), leaks introduce mass balance errors.
- Calibrate critical instruments on a regular basis against standards for pressure, temperature, flow, and composition.
- Identify where the reactor operates isothermally.[46]
- Verify that the distribution manifold feeds reactors evenly, particularly for passive distributors that use ΔP (capillaries or microfluidic chips).
- Document the verification of equipment and commission test results to trace the performance with time and record changes made to the testing facility. For analyzers, Shewhart control charts should be established to trace the precision and accuracy of the measurements. This graphical approach determines variability on a process and whether it is due to chance (common causes) or attributable to a change in the process (assignable cause).[93,94]
- Set-up informatics tools for the system, to collect, clean, and process data into a format that is easy to visualize. This step prepares data for the data-mining phase and applies to process and catalyst performance data.

6.3 | Execution

In the execution stage, the foreseen experimental plan is put into motion, and key activities focus on monitoring, controlling, and fine-tuning the workflow to maximize the value of the data generated:

- Verify ΔP. A high ΔP indicates plugging, that the d_p is too small (the particles might have commuted during the loading phase or due to a mechanical upset), or that the flow rate is higher than expected.
- Monitor the performance by analyzing process data (level, pressure, temperature, or flow variables). Smart plots help analyze large data sets as they evolve with time. For example, Figure 10 is a cell plot for an HTCT unit with 64 parallel reactors. The target, lower and upper specification limits, and the process values are displayed to rapidly identify deviations in the process by observing changes in the colour and intensity.[95]
- Evaluate the catalyst performance data (catalyst activity, conversion, selectivity, or yield) of a particular product continuously. To interpret data more efficiently we apply data visualization tools. For example, a single plot could demonstrate the relationship between the response variable (ethylene yield in case of oxidative coupling) as function of three and four factors (Figure 11).[39,79] The position of the symbol in the

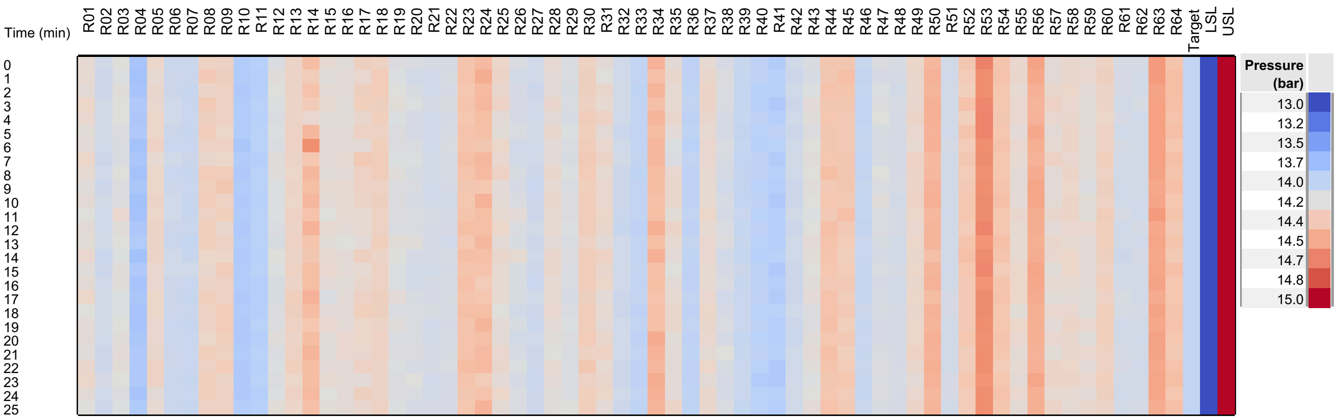

FIGURE 10 Exemplification of smart figures to assess process parameters. This figure allows, for example, qualitative inspections of a process parameter, such as temperature or pressure of flow. The target, lower and upper specification limits, and the process values given by colour allow for fast identification of deviations of the process, which would be characterized by dark blue or dark red cells

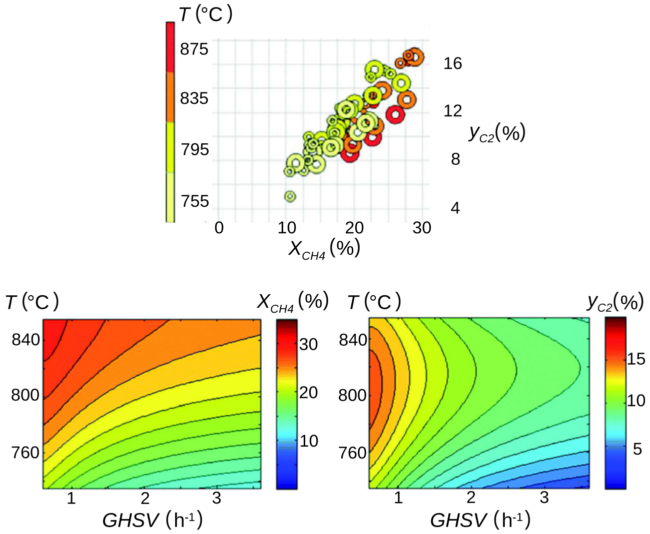

FIGURE 11 Comparison of multi-factors scatter plots versus contour plots to demonstrate catalyst performance data. Adapted from Ras and Rothenberg[79] with permission from the Royal Society of Chemistry

upper plot captures the effect of methane conversion, colour corresponds to temperature, and symbol size to pressure. The contour plots at the bottom of the figure require two plots to demonstrate the relationship between the factors T, GHSV, and the primary variables, methane conversion and ethylene yield. The plot relied on a regression model to generate the contours. An additional plot is required to account for the contribution of GHSV to conversion and selectivity in the scatter plot.

- Reassess the appropriateness of the experimental plan frequently. As an example, assume that a range of SV has been considered for the test. If conversion approaches equilibrium or 100%, discriminating between catalysts and generating a kinetic model is harder (almost impossible if x is close to 100% for the tests). To lower the degree of conversion, one could increase the SV, for example, by using higher feed flow rates (which may conflict with the ΔP constraint), or by loading less catalyst in the reactor. Another approach could involve lowering the reaction temperature (which may change the reaction mechanism).[96] Furthermore, stressing catalysts (operating at high conversion, like commercial conditions) produces unexpected byproducts and affects deactivation rates.[97] Adjusting conditions changes the design and compromises the statistical interpretation of the data, which invariably means more experiments will be required.

6.4 | Closure

This is the last phase of the experimental program and it focuses on finalizing the experimental campaign and results processing. Activities at this stage include:

- Preparing the deliverables facilitated by standardized structures; informatics tools generate plots and reports of the performance parameters (Section 5).
- Decommissioning the unit to maintain a safe and clean environment. In addition, issues related to solidification of materials, odours, or cross-contamination are minimized.
- Evaluating how the experimental program developed and assessment of opportunities for improvement in future tests.

7 | CONCLUSIONS AND OUTLOOK

HTCT has become indispensable for catalysis research and development. It reduces time and effort to develop a catalyst by several orders of magnitude while minimizing the variance in the data. Companies and universities widely use HTCT. It has become a new standard for materials screening and it is applied at every stage of a catalyst development program, including process optimization and material lifetime studies. However, to take advantage of this powerful methodology, researchers must become aware of the basic principles of catalyst testing, high-throughput experimentation, its nuances, and potential challenges that arise for each specific application. Careful and intelligent planning of the experimental program becomes a key factor to the success of an HTCT program. Researchers must avoid the pitfall of completing large numbers of unplanned tests only because an HTCT system is available. DoE, minimizing mass and heat transfer resistances, applying best practises to select and load solids, and attention to analytical protocols are steps that improve the chances on generating high-quality, meaningful data. The shear volume of data (information) HTCT parallel reactor systems generate can be overwhelming, so the bottleneck in development becomes processing the data and analysis rather than generating the data. To accelerate data analysis to create knowledge requires data mining and smart visualization techniques.

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NOMENCLATURE

b	Inert fraction of the bed ($m^3{}_{dil}m^{-3}{}_{dil+cat}$)
c	Concentration (mol m^{-3})
c_b	Concentration in the bulk phase (mol m^{-3})
c_s	Concentration at the surface of the catalyst (mol m^{-3})
$\mathcal{D}$	Axial dispersion (m^2s^{-1})
d_p	Equivalent spherical diameter of catalyst particle (m)
D	Reactor diameter (m)
D_e	Intraparticle effective diffusivity (m^2s^{-1})
$D_{e,rad}$	Effective radial dispersion (m^2s^{-1})
E_a	Activation energy (J mol^{-1})
g	Gravity constant (m s^{-2})
h_w	Heat transfer coefficient at the wall
ΔH_r	Enthalpy of the reaction (J mol^{-1})
k_f	Mass transfer coefficient (fluid-to-solid) (mol s^{-1})
L	Characteristic catalyst length (m)
L_b	Catalyst bed length (m)
L_h	Ratio of liquid hold-up to effective gas–liquid interfacial area
n	Reaction order
n	Number of experiments
P_{tot}	Total pressure
q	Number of levels for a factorial DoE
r_v^{obs}	Observed reaction rate per volume (mol $s^{-1}m^{-3}$)
R	Universal gas constant (J $mol^{-1}K^{-1}$)
s	Sample standard deviation
T_w	Reactor wall temperature (K)
t	Student's t statistic
u	Superficial velocity (ms^{-1})
x	Fractional conversion
z	Axial distance (m)

Dimensionless numbers

$N_{Bi,w}$	Biot number at the reactor wall ($=h_w d_p/\lambda_{eff}$)
$N_{Bo,ax}$	Bodenstein number ($=ud_p/D_{ax}$)
N_{Ca}	Carberry number (Equation (6))
N_{Pe}	Peclet number ($=uL_b/\mathcal{D}$)
N_{Pra}	Prater number ($=(-\Delta H_r k_f C_b)/(hT_b)$)

Greek Letters

α	Confidence level
Δ	Confidence interval ($t(\alpha,n-1)\sigma/\sqrt{n}$)
ϵ_b	Bed voidage
κ	Number characterizing the flow profile
$\lambda_{eff,b}$	Bulk effective thermal conductivity (J $m^{-1}s^{-1}K^{-1}$)
$\lambda_{eff,p}$	Particle effective thermal conductivity (J $m^{-1}s^{-1}K^{-1}$)
μ_g	Dynamic gas viscosity (Pa s)
μ_L	Dynamic liquid viscosity (Pa s)
ρ_g	Gas density (kg m^{-3})
ρ_L	Liquid density (kg m^{-3})
σ	Standard deviation

PEER REVIEW

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