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# Combining operando spectroscopy with experimental design, signal processing and advanced chemometrics
# State-of-the-art and a glimpse of the future

Marc Garland

*Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore 627833, Singapore*

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ABSTRACT

The present contribution reviews the operando spectroscopy programme in the area of homogeneous catalysis that exists at the Institute of Chemical and Engineering Sciences (ICES). This review first considers the importance of experimental design and then addresses a number of signal processing issues. Band-target entropy minimization (BTEM), an algorithm designed for pure component spectral estimation, is the most important signal processing tool discussed. A homogeneous catalytic example using BTEM analysis, as well as other quantitative and kinetic analyses is shown. In addition to spectroscopic measurements, other in situ sensor measurements and their analyses are also discussed. The determination of individual physico-chemical properties of the constituents present allows insight into solute–solute interactions, etc. This review is based on a plenary lecture presented at Operando III.

## 1. Introduction

Modern organic syntheses rely to a large extent on metal-mediated strategies, both stoichiometric and catalytic [1,2]. Homogeneous catalysis using transition metal complexes as catalyst precursors is widely used in academia as well as industry to obtain increased rates of reaction, but equally importantly, to control chemo-, regio-, and stereo-selectivities. Homogeneous catalytic strategies are particularly attractive due to their increased atom economy [3].

The use of operando spectroscopic techniques has greatly increased understanding of homogeneous catalysis at the molecular level. Indeed, vibrational spectroscopies such as FTIR and Raman as well as NMR, are used to identify new transient and non-isolatable organometallic species which are present during the catalysis [4,5]. Subsequently, some but not all of these new species, can frequently be implicated as possible intermediates in the catalytic transformations. Operando spectroscopic techniques have also provided a means to better evaluate the time-dependent rates of formation of the primary and secondary organic products. The ability to identify species, and in some cases to evaluate concentrations and rates, has had a considerable and positive impact on better mechanistic understanding of homogeneous catalysis.

The amount of spectroscopic data acquired during a catalytic run or during a set of catalytic runs can be enormous, and the proper interpretation of these spectra presents a serious hurdle. Moreover, there is normally a considerable amount of information imbedded within these data sets, which are not extractible by conventional means.

The present contribution focuses on the signal processing techniques and other chemometric methods, currently being used at the Institute of Chemical and Engineering Science (ICES). In particular, three goals are discussed at considerable length (1) pure component spectral reconstruction of the constituents present (even down to ppm and sub-ppm concentration levels) (2) the subsequent use of these spectral estimates in order to obtain reliable quantitative information, such as concentrations and rates and (3) the development of kinetic expressions. Examples using vibrational spectroscopy are presented. It is emphasized that experimental design is extremely important, and the normal ways of conducting experiments in homogeneous catalysis are often not really adequate for further detailed numerical analysis.

## 2. Results and discussion

### 2.1. Experimental design

Batch recycle systems are the typical experimental set-up used for spectroscopic homogeneous catalytic studies at ICES. These systems consist of (1) a small batch reactor (2) a hermetically sealed pump (either a gear pump or membrane pump) (3) a recycle transfer line (4) appropriate spectroscopic cells (5) an injection/sampling block and (6) the spectrometers and sensors. A generic block representation is shown in Fig. 1. Details of the in-house

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E-mail address: marc_garland@ices.a-star.edu.sg.

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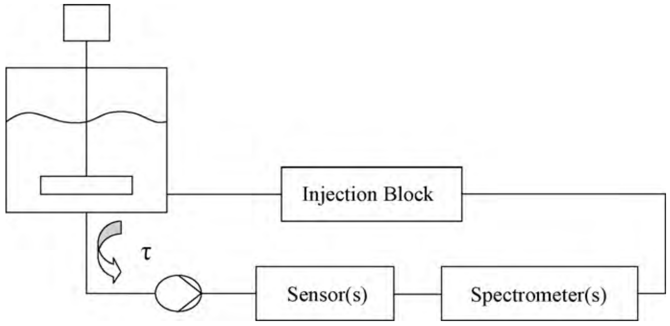

**Fig. 1.** A flexible experimental configuration for in situ spectroscopic studies of homogeneous catalytic systems. The characteristic recycle time is denoted by $\tau$.

constructed reactors, spectroscopic cells and injection/sampling block are provided elsewhere [6]. Although we have used a wide range of spectrometers for in situ measurements, FTIR and Raman are the two most commonly used at ICES.

There are a variety of mass transfer issues that need to be addressed in spectroscopic homogeneous catalytic studies [7]. These include, but are not restricted to, the gas–liquid mass transfer characteristics, the liquid phase mixing time and recycle time $\tau$. For well-designed systems, it is possible to saturate the liquid phase and achieve a well-mixed liquid phase in circa 2 min. Furthermore, the recycle time $\tau$ can often be reduced to circa 2 min as well. Taken together, these issues indicate that representative measurements can be made at most sensors and spectrometers circa 3–4 min after reaction startup, or circa 3–4 min after the further addition (perturbation) of a reagent. In other words, after this period, the liquid in the sensor or spectrometer is compositionally similar to the liquid in the reactor [6]. For typical homogeneous catalytic syntheses with reactions times on the order of many hours, the above mass transfer considerations are usually sufficient.

The injection block featured in Fig. 1 is a rather important aspect of the overall experimental set-up. Indeed, the injection block permits the easy injection of constituents (i.e. metal complex, ligand, substrate and solvent) either in a pulsed mode through HPLC type valves or in continuous mode through high-pressure syringe pumps. Perturbations of reactants and solvent during the course of a reaction are quite useful from a design-of-experiments viewpoint. Multiple perturbations allow the researcher to survey a larger range of experimental compositions rapidly. In addition, and from a signal processing viewpoint, the information content of such a large set of spectroscopic measures, with considerable variation in the signal intensities is more useful (vide infra).

### 2.2. Signal processing

Depending on the qualitative and quantitative expectations from the spectroscopic study, various signal processing techniques may be appropriate. Some of the simplest signal processing procedures may include denoising (where spline and other 1D filters are the most commonly used) [8], baseline correction via optimal subtraction of the solvent (or even other reagents) [9], etc. A review of signal processing issues associated with homogeneous catalysis is available [10].

A considerably more advanced signal processing approach involves the determination of the pure component spectra of individual constituents present in the multi-component spectroscopic measurements. The determination of high-quality pure component spectra from homogeneous catalytic studies can greatly facilitate the determination of the primary organometallic species present during the catalysis. In the case of vibrational spectroscopies, the obtained spectral estimates can be readily compared to DFT spectral predictions in order to confirm the chemical identify of the new and non-isolatable species [11,12]. For example, a large set of new possible species can often be imagined which might be consistent with the chemistry being studied and the various spectral estimates. DFT can then be used to obtain the associated set of optimized geometries as well as to predict the corresponding vibrational spectra. At this point, the spectral estimates and the DFT predicted spectra are compared, and some assignments can be made. This procedure is then repeated until all spectral estimates can be assigned to a structure [13].

Some of the more traditional self-modelling curve resolution algorithms include SIMPLISMA, IPCA, and OPA-ALS [14–16]. Most of these require an *a priori* estimate of the number of observable species present and are most suitable for obtaining spectral estimates of the major constituents present in a mixture. Our group at ICES developed an alternative approach which does not require an *a priori* estimate of the number of observable species present and which is particularly suitable for recovering the pure component spectral estimates of minor species. The band-target entropy minimization (BTEM) algorithm, which searches for spectral patterns possessing the least information entropy, generates one spectrum at a time [17,18]. This is done repeatedly until no further spectra can be recovered. It has been used to recover the pure component spectra of trace components such as the elusive species $HRh(CO)_4$ and all-terminal $Rh_4(CO)_{12}$ which are only present at the ppm level [19,20]. BTEM has been used repeatedly for the study of homogeneous catalytic systems [21–26]. Fig. 2 shows the three steps involved in BTEM, namely, data

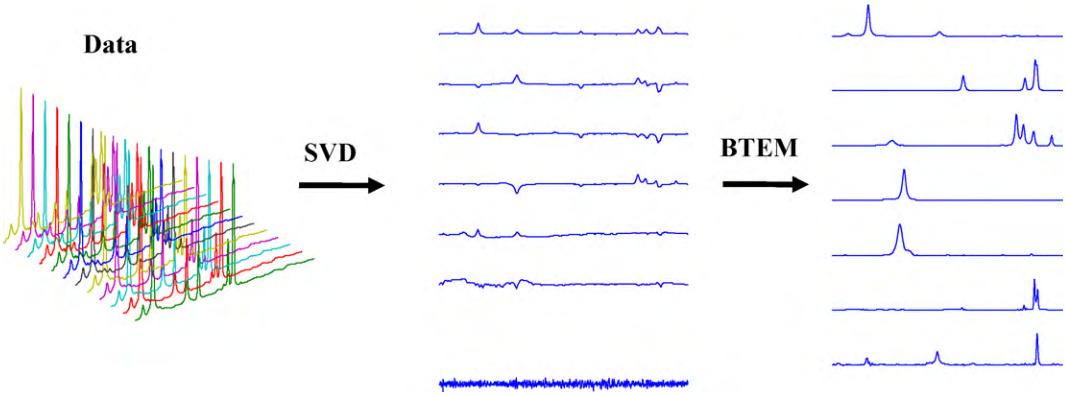

**Fig. 2.** An example of BTEM analysis from an unmodified rhodium catalyzed alkene hydroformylation reaction using mid-FTIR data. Hundreds of spectra were measured, the first circa 50 basis vectors are used, and circa a dozen pure component spectra are obtained (only a few of the liquid phase solutes are shown on the right hand side). A few of the pure component spectral estimates correspond to rhodium organometallics. All of the organometallics are at a mean concentration of circa 30 ppm and below during the experiments.

acquisition (normally 100's or 1000's of spectra), singular value decomposition to obtain the basis vectors and denoise the data, and BTEM analysis.

Although the BTEM algorithm has been successfully tested on MS [27], 1D and 2D NMR [28,29], UV–vis [30], 2D fluorescence [31], PXRD [32] and thermal emission data [33], it is primarily used at ICES for the analysis of FTIR and Raman measurements [34]. It can be noted that BTEM analysis is now being successfully used by a number of other groups in order to analyze MS [35,36] and Raman spectroscopic data [37,38] from non-catalytic systems.

### 2.3. Quantitative analysis and kinetics

A first step in the quantitative analysis of FTIR and Raman spectra is the generation of dimensionless Lambert–Beer–Bouguer expressions [39]. This is readily accomplished by using an internal standard – often chosen to be the solvent. In this manner, complications due to volumetric changes (i.e. during the dissolution of gases, change in solution volume due to reaction, etc.) are eliminated.

The second step is internal calibration, in other words, the determination of the properly scaled absorptivities of all observable components. This is achieved using (i) the dimensionless Lambert–Beer–Brouger expressions (ii) the normalized pure component spectral estimates obtained from BTEM analysis and (iii) the recorded moles of components introduced to the reactor [40]. If many perturbations are performed, or if many batch experiments are performed, then there are numerous mass balances that can be written and these are particularly useful constraints. The simultaneous solution of all the equations provides the properly scaled absorptivities and hence the corresponding concentrations. In this manner, it is possible to accurately evaluate the concentration of new organometallics/intermediates that exist during the catalysis even though they may not be isolatable. Fig. 3 shows typical concentrations profiles obtained from an unmodified rhodium catalyzed hydroformylation reaction.

The aforementioned quantitative analysis can be readily extended to determine the number of observable reactions, the stoichiometries of each observable reaction, and the corresponding extents of reaction [40]. For the unmodified rhodium catalyzed hydroformation there are two independent and observable reactions, namely, the transformation $Rh_4(CO)_{12}$ to $RCORh(CO)_4$ and the transformation of alkene to aldehyde [21,22,41]. Since both the extents of reaction and the concentrations are available at all reaction times it is a rather straightforward procedure to model each reaction. The resulting kinetic expressions are shown in Eqs. (1) and (2). Eq. (2) clearly shows that $RCORh(CO)_4$ is an intermediate since its concentration correlates with product formation.

$$\frac{d[RCORh(CO)_4]}{dt} = k_1[H_2]\,[CO]^2[Rh_4(CO)_{12}] \quad (1)$$

$$\frac{d[RCHO]}{dt} = k_2[H_2]\,[CO]^{-1}[RCORh(CO)_4] \quad (2)$$

Our group has used the above-mentioned approach and FTIR to study numerous rhodium and bimetallic alkene hydroformylations. In the monometallic case, only (i) $RCORh(CO)_4$ or (ii) $RCORh(CO)_4$ and $HRh(CO)_4$ have thus far been observed as intermediates during hydroformylations. Nevertheless, these observations together with Eq. (2) support the classic mechanistic description for alkene hydroformylation which is shown in Fig. 4. Other rhodium organometallics, such as $Rh_6(CO)_{16}$ have been observed during rhodium catalyzed hydroformylations as well, however, their concentrations do not correlate with product formation and hence, they are not intermediates in the catalysis.

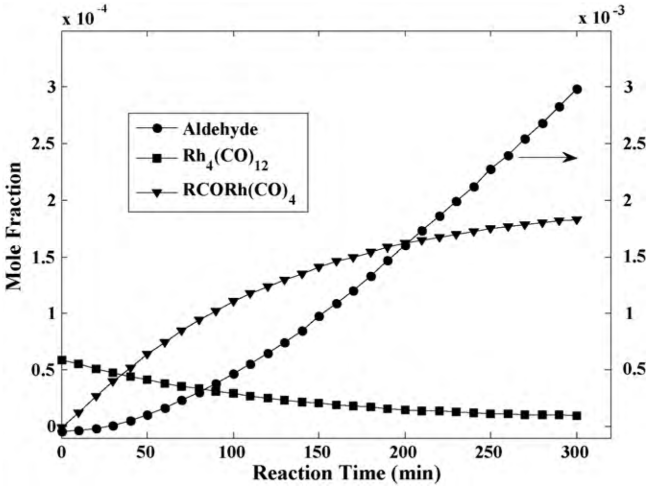

**Fig. 3.** The concentration profiles of the precursor $Rh_4(CO)_{12}$, the non-isolatable intermediate $RCORh(CO)_4$ and the organic product RCHO from the hydroformylation of 3,3 dimethylbut-1-ene at 298 K, 2.0 MPa CO and 2.0 MPa $H_2$.

### 2.4. The nested inverse problems

The progress achieved in the areas of signal processing and numerical analysis forms the basis for the operando spectroscopy and homogeneous catalysis programme at ICES. The connectivity of these numerical tools is best represented by Fig. 5 where the box summarizes the issues already discussed.

The numbers 0–4 represent the various levels of analysis. The zero level corresponds to the experimental inputs. These include the matrix of moles used in the syntheses $\mathbf{N}^0$ as well as the matrix of spectroscopic data $\mathbf{A}$. The first step is BTEM analysis to determine the number of observable species $S_{obs}$ present and their corresponding matrix of normalized pure component spectra $\mathbf{a}'$. Level 2 is obtained after algebraic system identification [40], and this provides the matrix of all mole $\mathbf{N}$, the matrix of properly scaled absorptivities $\mathbf{a}$, the number of observable reactions $R_{obs}$, the matrix of reaction stoichiometries $\nu$ and the matrix of extent of reaction $\xi$. When these quantities are known, simple regressions provide the kinetic expressions (level 3).

### 2.5. Future opportunities

More recently, our group has begun to develop some numerical tools needed to transform bulk sensor measurements (i.e. density, capacitance, heat flux, etc.) of multi-component reactive systems into solute physico-chemical parameters (partial molar volumes, dipole moments, etc.) and thermo-physical parameters (i.e. heats of reaction). The ability to determine individual physico-chemical and thermo-physical parameters could provide considerable new insight into homogeneous catalytic reactions. For example, the determination of solute dipole moments could help to confirm the solution geometry of organometallic intermediates and the determination of volumes of interaction could help to identify association between solutes (molecular recognition).

Using non-reactive multi-component systems and stoichiometric reactions as model systems, it has been possible to achieve the goals shown at level 4 in Fig. 5. Combining a variety of sensor measurements as input $\mathbf{B}$ (i.e. from densitometers, refractometers, capacitance cells, calorimeters) with the results of levels 1 and 2

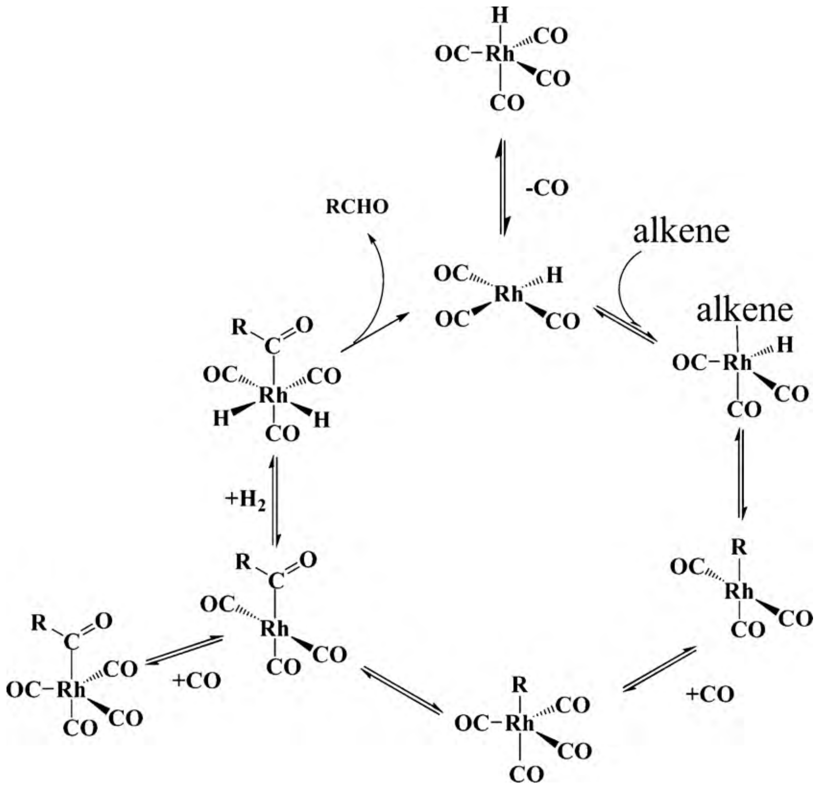

**Fig. 4.** The widely accepted mechanism for unmodified rhodium catalyzed hydroformylation. In many situations (i) $RCORh(CO)_4$ or (ii) $RCORh(CO)_4$ and $HRh(CO)_4$ are in observable exchange with the cycle under normal catalytic conditions.

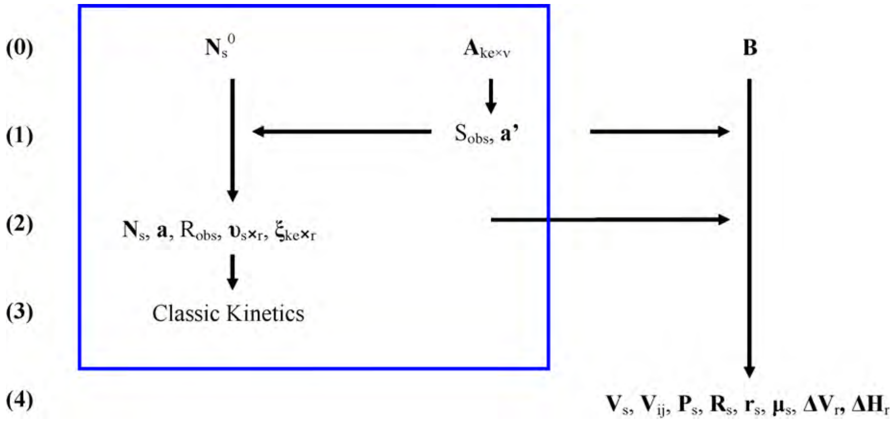

**Fig. 5.** The connectivity of numerical tools used in the operando spectroscopy and homogeneous catalysis programme at ICES.

analysis has allowed the determination of (1) solute partial molar volumes $V_s$ [42–45], (2) solute volumes of interaction $\Delta V_{ij}$ [42,44], solute polarizabilities $P$ [45,46], solute partial molar refractions $R$ [45], effective solute radii $r$ [45], solute dipole moments $\mu$ [46,47], reaction volumes $\Delta V_r$ [43], and heats of reaction $\Delta H_r$ [48]. The next step will be to apply these tools to homogeneous catalytic reactions.

## 3. Conclusions

The present review has shown that the combination of in situ measurements with advanced numerical tools provides a rather unique approach to studying homogeneous catalytic systems and provides considerable new insight. Additional new numerical tools have been developed to transform bulk sensor measurements into important physico-chemical and thermo-physical characterization parameters, and they will be applied to homogeneous catalytic systems in the near future.

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