Combinatorial Methods: How will They Integrate into Chemical Engineering?

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As entry into the 21st century approaches and the popular press continues to capitalize on the Y2K problem (or lack thereof!), it is appropriate to ask whether new paradigms are emerging in chemical engineering. If so, will they be able to transform the discipline for the better? Any survey of the recent literature will reveal the increased use of "combinatorial methods" in the 1990s. This is especially true in the areas of bioengineering (You and Arnold, 1996; Bornscheuer, 1998), chemical and biochemical synthesis (Wilson and Czarnik, 1997; Szostak, 1997), and more recently in materials synthesis (Xiang et al., 1995; Klein et al., 1998) and catalysis (Cole et al., 1996; Jandeleit et al., 1998; Schlögl, 1998; Senkan, 1998). Combinatorial methods seek to find an answer to a correctly posed question by creating a large set of inputs (called a library) that can be subjected to a particular test (screen), that if constructed appropriately, leads to a set of outputs that have been classified by the test. A proper testing protocol allows for the selection of the output candidates that best meet the criteria imposed by the screening process to address the question of interest. Such a system can be written mathematically as:

$$\boldsymbol{Ax} = \boldsymbol{by} + \boldsymbol{n}$$

where the vector $\boldsymbol{x}$ represents the set of inputs, the matrix $\boldsymbol{A}$ the screen, and the resultant vector $\boldsymbol{by}+\boldsymbol{n}$ the output. Ideally, the input and screen are chosen such that the coefficient $\boldsymbol{b}$ is large, the vector $\boldsymbol{y}=[1,0,...,0]^T$, and the vector $\boldsymbol{n}$ is some threshold level in the experiment. Normally, the screen does not provide a single answer, i.e., the vector $\boldsymbol{y}$ contains numerous nonzero entries. For systems of biological origin, the size of the input/output set can be enormous ($>10^8$), while for practical application to chemical synthesis, the values are more on the order of 10^3. Thus, the problems with combinatorial methods are to skillfully create the input set and the screen such that b is large and $\underline{y}$ contains a limited number of nonzero entries.

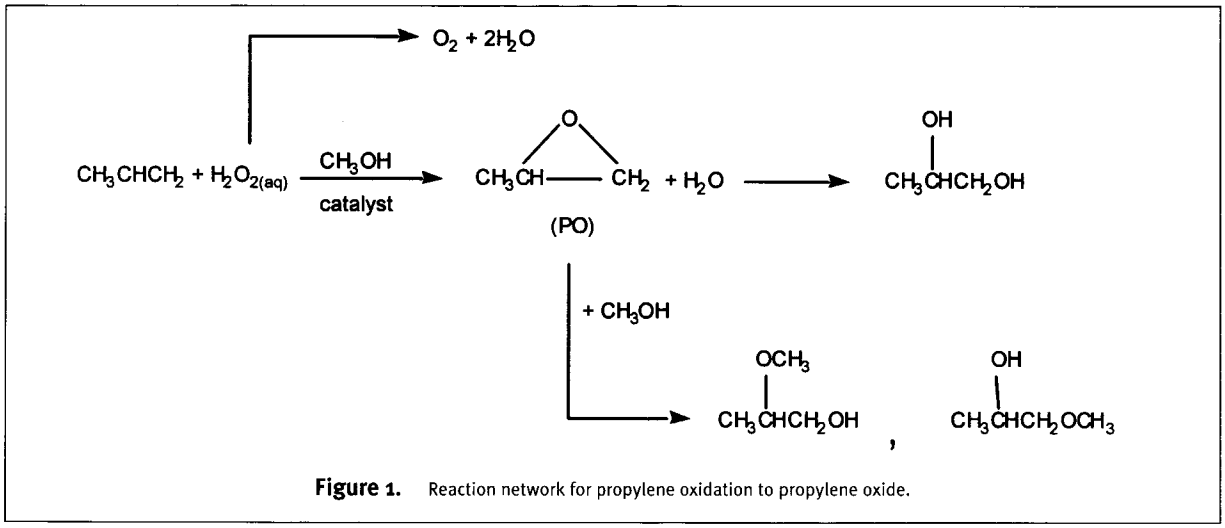

Figure 1. Reaction network for propylene oxidation to propylene oxide.

One could argue that combinatorial methods have been used throughout the 20th century in numerous fields of endeavor but have not employed the aforementioned jargon. Take, for example, Alvin Mittasch, who may have performed the first combinatorial catalytic chemistry when he tested (screened!) 6,500 materials for use as ammonia synthesis catalysts in the early 1900s (Boudart, 1999). What has changed over the century is the ability to automate and miniaturize physical manipulations that were performed previously by manual labor and to provide new testing methods including various spectroscopies. Today, the use of combinatorial methods is left to the creativity of the investigator. There is no doubt that this class of methodologies will be exploited further in future years in chemical engineering, and thus my aim here is to provide a cau-

tionary note concerning the "blind" use of these tools much in the same manner that the discipline approached the use of numerical software in the 1970s and 1980s. I would like to address several issues of concern when dealing with combinatorial methods.

Cautions and outlook

When using combinatorial methods, the following steps are utilized (adapted from Gordon, 1998):

1. library design
2. selection of components to create the library
3. creation of the library
4. screening of the library
5. identification of entries that show the greatest output from the screen
6. rationalization of results.

To delineate some of the features of this process, I will contrive a very small and simple example. Consider the reaction network shown in Figure 1. The epoxidation of propylene with aqueous H_2O_2 in methanol to give propylene oxide (PO) can be accomplished using a titanium-containing molecular sieve called TS-1. Additional unwanted reactions produce: PO ring opening products via nucleophilic attack by water and/or methanol; dioxygen from hydrogen peroxide. Although this reaction network is somewhat small, it provides challenges for designing a combinatorial approach to elucidate improved catalysts.

Step 1 is to design a library. For this case, numerous titanium-containing molecular sieves could be prepared. This type of library is already very directed (as opposed to random searching of numerous other element combinations). Thus, a point worthy of consideration when formulating a combinatorial method is how narrowly or broadly focused does the library design need to be to answer the question posed?

Step 2 is how to select components to create the library. Titanium-containing molecular sieves can be prepared via hydrothermal methods from alkoxides of titanium and silicon. Thus, one could search composition space using these two alkoxides (see Klein et al., 1998, for an illustration on how this could be achieved).

Step 3 is to create the library. Upon preparation of the library, such issues as homogeneity, size, and contamination are of extreme importance. Likewise, for the case illustrated here, multiple phases, e.g., a crystalline molecular sieve or an amorphous oxide, can form at the same composition. Thus, the investigator must be extremely careful in properly designing and implementing the "creation of the library" step. Techniques that allow for the preparation of library diversity such that each element of the library is a discrete entity are best suited for implementation.

To properly carry out ***Step 4***, great thought and creativity are helpful. Clearly, the answer received from a combinatorial method is that which is implemented in the screen. For example, the data in Table 1 are from TS-1 materials that have essentially the same composition. What makes these TS-1 materials different is the fraction of Ti that is not in the crystal and is available to convert H_2O_2 to dioxygen [increasing fractions of Ti outside the molecular sieve framework when going from (I) to (III)]. If the library of TS-1 materials behaved as described by the data in Table 1, then the "best" catalyst for the epoxidation reaction would depend on the screen used. If the screen measured olefin conversion, TS-1 (I) and TS-1 (III) would give the same result. For this system, H_2O_2 eff. is critically important. A screen for dioxygen production would yield the answer that TS-1 (II) and TS-1 (III) are equivalent even though TS-1 (II) clearly converts more of the olefin than TS-1 (III). Thus, it is obvious that "you get what you screen for" (You and Arnold, 1996). In this example, it is clear that the "best" screen would simultaneously assay for both PO and dioxygen.

Table 1. Reaction data for epoxidizing an olefin with aqueous H_2O_2 over TS-1 catalysts.*

	Olefin Conversion, %	H_2O_2 Eff., %
TS-1 (I)	6.3	67.0
TS-1 (II)	7.2	62.1
TS-1 (III)	6.0	61.9

*H_2O_2 Eff. defined as moles of epoxide formed per mole of H_2O_2 consumed x 100%. From Dartt et al. (1994).

Step 5 involves the identification of superior entries in the library. Characterizations necessary to identify the superior entries are greatly facilitated if the elements of the library are homogeneous.

Finally, in ***Step 6***, the results are rationalized. For the example illustrated, proper characterization would show that increasing amounts of titanium not in the molecular sieve crystal structure are detrimental to the catalyst performance by promoting the formation of dioxygen. Armed with this information, a new and more focused library design could hopefully be accomplished.

Assuming that the intelligent use of combinatorial methods can be accomplished, these tools are best used for systems that involve discrete entries so that homogeneity, characterization and scaleup issues are minimized. Likewise, processes that can establish equilibrated states such as binding, rather than kinetically controlled pathways such as catalysis, are more amenable and straightforward to analyze. This is not to say that kinetically controlled processes cannot be explored via combinatorial methods, it is that they are less likely to provide unambiguous results.

Another tool in the ever-expanding "toolbox"

While combinatorial methods provide a powerful paradigm for the partial solution to numerous problems, they can be applied only to a limited set of situations. Thus, they should be considered as another "tool" in the ever-expanding "toolbox" of our discipline. Additionally, these methods can provide large data sets to make it possible to understand complex problems that hopefully will lead to better "rational designs." Of importance here is the fact that combinatorial methods do not provide a deep understanding of the underlying chemical and physical phenomena of a process and are thus of little help in designing the scaleup necessary for development and commercialization steps.

I have raised what I believe are two important questions for our discipline as we are now confronting the general use of combinatorial methods. First, "blind" use is likely to provide misleading (or even wrong) results. Second, general disregard of other methodologies that have thus far failed in their search for "the pot of gold at the end of the rainbow" for a particular problem in preference to

combinatorial methods is not likely to have significant impact. The judicious use of combinatorial and noncombinatorial methodologies, however, should be of great help in solving numerous problems. These issues remind me of the "growing pains" the discipline went through when the numerical software "tools" became readily available in the 1970s and 1980s. Let's hope that the effective integration of combinatorial methods into chemical engineering readily occurs in the near future by learning lessons from our past.

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