# Simultaneous Process and Molecular Design—A Property Based Approach

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*DOI 10.1002/aic.11141*
*Published online March 13, 2007 in Wiley InterScience (www.interscience.wiley.com).*

*Property clustering techniques and group contribution methods are combined to enable simultaneous consideration of process performance requirements and molecular property constraints. Using this methodology, the process design problem is solved to identify the property targets corresponding to the desired process performance. A significant advantage of the developed methodology is that for problems that can be satisfactorily described by only three properties, the process and molecular design problems can be simultaneously solved visually on a ternary diagram, regardless of how many molecular fragments are included in the search space. On the ternary cluster diagram, the target properties are represented as individual points if given as discrete values, or as a region if given as intervals. The structure and identity of candidate components is then identified by combining or "mixing" molecular fragments until the resulting properties match the targets.* © 2007 American Institute of Chemical Engineers *AIChE J,* 53: 1232–1239, 2007

*Keywords: property integration, group contribution, process and molecular design*

## Introduction

The terms product synthesis and design designate problems involving identification and selection of compounds or mixtures that are capable of performing certain tasks or possess certain physical properties. Since the properties of the compound or mixture dictate whether or not the design is useful, the basis for solution approaches in this area should be based on the properties themselves. However, the performance requirements for the desired component are usually dictated by the process, and, thus, the identification of the desired component properties should be driven by the desired process performance. Numerous contributions have been made in the areas of molecular synthesis and computer aided molecular design (CAMD), see for example, Harper and Gani,[1] Marcoulaki and Kokossis,[2] however, in order to utilize these techniques the desired component properties must be specified ahead of design. Doing so may lead to suboptimal designs, as the property targets for a new compound inherently will be dictated by the process, where it is to be employed. With molecular design techniques, the desired target properties are required input to the solution algorithm. Once again these decisions are made ahead of design, and are usually based on qualitative process knowledge and/or experience, hence, again risking a suboptimal design. Thus, there is a critical need for systematic methodologies capable of addressing both problems simultaneously, that is, identify the target properties of a new compound from the process design problem and, subsequently, synthesize molecular structures that match the targets.

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## Property Integration Framework

Introduction of the property integration framework by Shelley and El-Halwagi [3] allows for representation of process

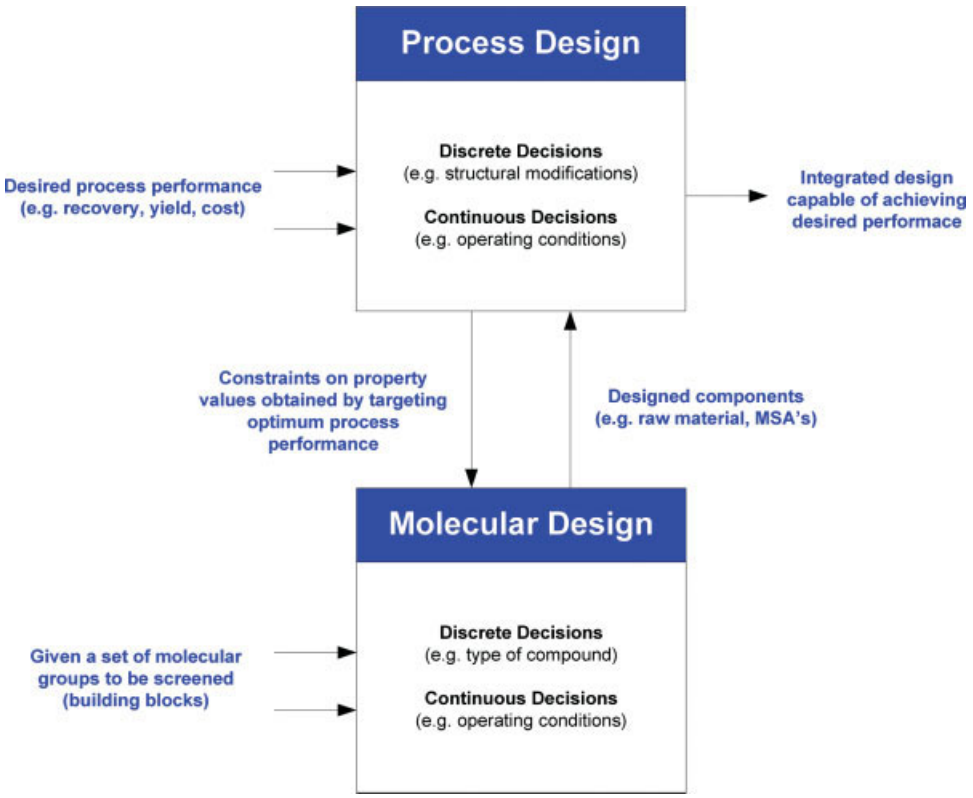


**Figure 1. Simultaneous approach to solving process and molecular design problems.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and products from a properties perspective. Utilizing this methodology enables identification of the desired component properties by targeting optimum process performance without committing to any component during the solution step. [4] For systems that can be described by only three properties, visualization of the problem, as well as identification of the solution is achieved using a ternary diagram. The identified property targets can then be used as inputs for solving a molecular design problem, which returns the corresponding components (see Figure 1).

To provide a unifying methodology for handling process and molecular design problems, the property integration framework is extended to include group contribution methods (GCM), which allow for prediction of physical properties from structural information. Initially the methods were based on the first-order groups,[5] however, work by Constantinou and Gani[6] and by Marrero and Gani[7] extended the methods to include second and third-order groups to increase the accuracy of the predicted properties. For this first unified framework only first-order GC methods are considered, but higher-order estimation will be included later.

By combining property clustering techniques and first-order group contribution methods (GCM), a systematic methodology is obtained that facilitates simultaneous consideration of property performance requirements of the designed component, as well as process and molecular constraints.

### *Property operators*

The basis for the property clustering technique is the use of property operators. Property clusters are conserved surrogate properties that are functions of nonconserved properties. They are obtained by mapping property relationships into a low-dimensional domain, thus, allowing for visualization of the problem.[3] Although the operators themselves may be highly nonlinear, they are tailored to possess linear mixing rules, for example, density does not exhibit a linear mixing rule, however, the reciprocal value of density follows a linear mixing rule.[8,9] It is clear that the operator expressions will invariably be different for molecular fragments and process streams, however, as they represent that same property, it is possible to visualize them in similar fashion (recall that visualization is only feasible for systems that can be described just by three properties). Extending this technique to include GCM for molecular design, introduces molecular property operators. Like the original process operators, their formulation must be such that it still allows for simple linear additive rules of the groups, which can be described by the following

$$\psi_j^M(P_j) = \sum_{g=1}^{N_g} n_g \cdot P_{jg} \tag{1}$$

In Eq. 1, $\psi_j^{\mathrm{M}}(P_j)$ is the molecular property operator of the $j^{\mathrm{th}}$ property. The molecular property operator describes the functional relationship of group contribution property

equations in a manner so that the RHS of the equations is always in the form of a summation of the number of each group ($n_g$) multiplied by the contribution to property $j$ from group $g$ ($P_{jg}$). Some properties are not predicted directly from GCM, but are estimated as functions of other properties that can be predicted using GCM, for example, vapor pressure (VP) cannot be estimated directly, however, it can be estimated from the boiling point, which is a property described by GCM, as shown in Eqs. 2 and 3.[10]

$$\log VP = 5.58 - 2.7\left(\frac{T_{bp}}{T}\right)^{1.7} \tag{2}$$

$$\psi^M(T_{bp}) = \exp\left(\frac{T}{t_{bo}}\right) = \sum_{g=1}^{N_g} n_g \cdot t_{b_g} \tag{3}$$

Where, $T$ and $t_{bo}$ are the chosen condensing temperature and the group contribution boiling-temperature constants, respectively.

Notice that the property operator can be very complex, but molecular formulation on the ternary diagram is still simple, because the property operators are forced to obey simple linear additive rules.[3,8,9]

Since the properties can have various functional forms and units, the molecular property operators like process property operators are normalized into dimensionless form by dividing by a reference operator. This reference is appropriately chosen such that the resulting dimensionless properties are all of the same order of magnitude. The normalized property operator is given as

$$\Omega_{ji}^M = \frac{\psi_j^M(P_{ji})}{\psi_j^{ref}(P_{ji})} \tag{4}$$

An Augmented Property index $\text{AUP}^{\text{M}}$ for each molecule (M) is defined as the summation of all the NP dimensionless property operators, ($\Omega^M$)

$$\text{AUP}^{\text{M}} = \sum_{j=1}^{NP} \Omega_j^M \tag{5}$$

The property cluster $C_j$ for property j is defined as the ratio of the $\Omega^M$ and $\text{AUP}^{\text{M}}$

$$C_j = \frac{\Omega_j^M}{\text{AUP}^{\text{M}}} \tag{6}$$

### *Visualization of the problem*

The conversion of property data to cluster values for process design has been developed by Eden et al.[8] Similarly the conversion of molecular property data to cluster values follows the outline in Table 1.

**Table 1. Calculation of Cluster$^{\text{M}}$ Values from GCM Predicted Property Data**

| Step | Description | Equation |
|---|---|---|
| 1 | Calculate molecular property operators | 1 |
| 2 | Calculate dimensionless molecular property values | 4 |
| 3 | Calculate molecular AUP indices | 5 |
| 4 | Calculate ternary cluster values for each formulation | 6 |
| 5 | Plot the points on the ternary cluster diagram | – |

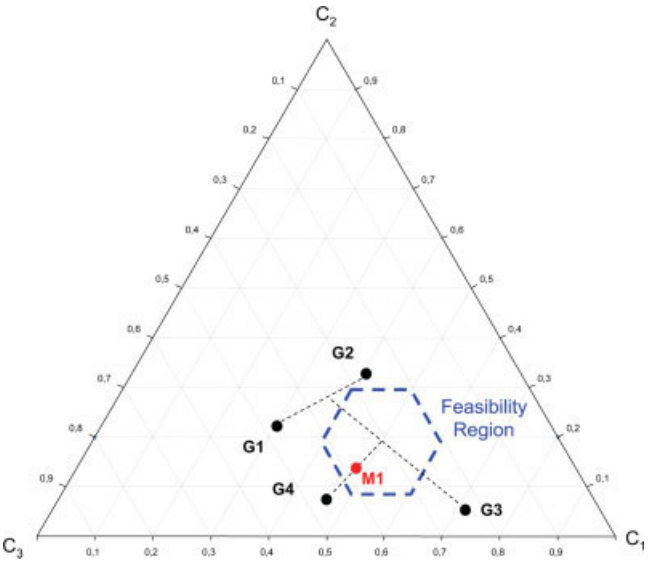


**Figure 2. Example of visual molecular synthesis.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The primary visualization tool from the mass integration framework is the source-sink mapping.[11] This tool is utilized in the molecular synthesis framework. In the original cluster formulation for process design (described by three properties), mixing of two sources is a straight line on the ternary diagram, that is, the mixing operation can be optimized using lever-arm analysis. Analogously, combining or "mixing" two molecular fragments in the molecular cluster domain, follows a straight line (an illustrative example is given in Figure 2). Design and optimization rules have been developed for property based process design problems,[8,9,12] and in the following similar rules are presented for property based molecular design problems.[13]

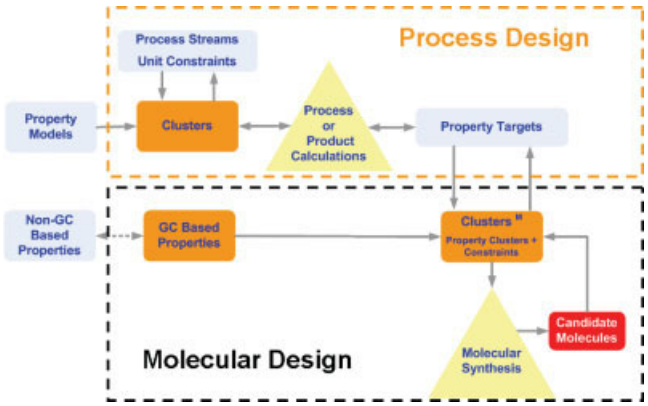


**Figure 3. Outline of simultaneous approach to process and molecular design.**

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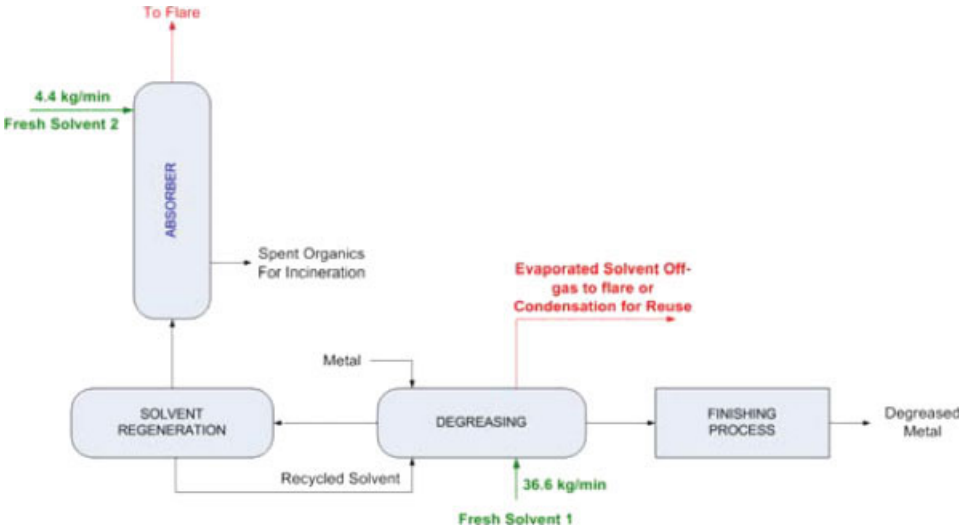


**Figure 4. Representation of original metal degreasing process.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Rule 1**. Two groups, G1 and G2, are added linearly on the ternary diagram, where the visualization arm $\beta_1$, describes the location of G1-G2 molecule.

$$\beta_1 = \frac{n_1 \cdot AUP_1}{n_1 \cdot AUP_1 + n_2 \cdot AUP_2} \tag{7}$$

**Rule 2.** More groups can be added as long as the free bond number (FBN) is not zero

$$FBN = \left[\sum_{g=1}^{N_g} n_g \cdot FBN_g\right] - 2 \cdot \left[\sum_{g=1}^{N_g} n_g - 1\right] - 2 \cdot NO_{Rings} \tag{8}$$

FBN is the free molecular bond number of the formulation, $n_g$ is the number of occurrences of group $g$, $FBN_g$ is the unique free-bond number associated with group $g$, and $NO_{Rings}$ is the number of rings in the formulation.

**Rule 3.** Location of the final formulation is independent of the order of group addition.

**Rule 4**. For completeness, the final formulation must not have any free bonds, that is, FBN has to be equal to zero.

Given a completed molecular formulation, three conditions must be satisfied for the designed molecule to be a valid solution to the process and molecular-design problem. Rules 5 and 6 are the necessary conditions, while Rule 7 is the sufficient condition.

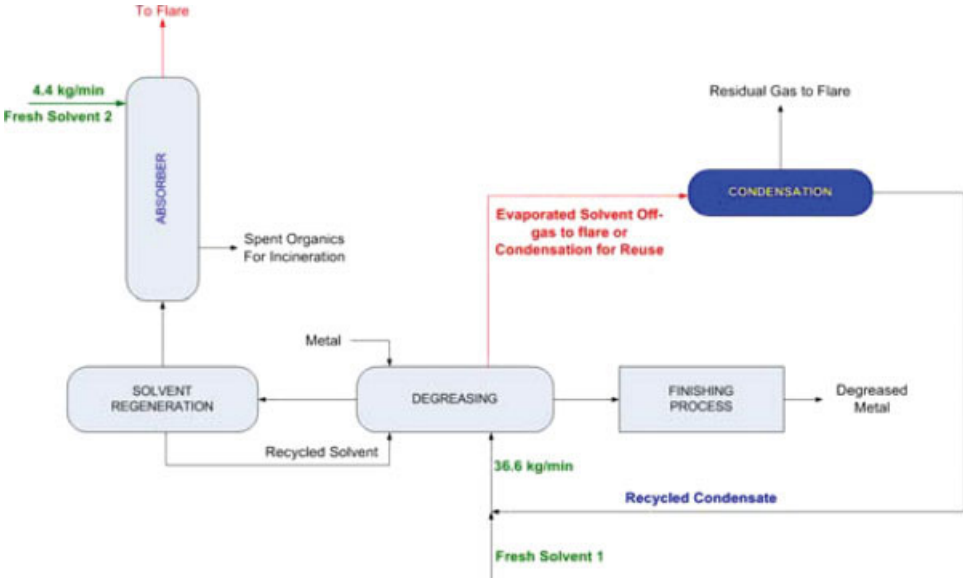


**Figure 5. Representation of metal degreasing process after property integration.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Table 2. Feed Constraint to the Degreaser**

| Property | Lower Bound | Upper Bound |
|---|---|---|
| S (%) | 0.00 | 1.00 |
| $V_m$ ($cm^3$/mol) | 90.09 | 487.80 |
| VP (mmHg) | 1596.00 | 3040.00 |
| $T_b$ (K) | 430.94 | 463.89 |
| Flow rate (kg/min) | 36.6 | 36.8 |

**Rule 5**. The cluster value of the formulation must be contained within the feasibility region of the sink on the ternary molecular cluster diagram.

**Rule 6**. The AUP value of the designed molecule must be within the range of the target. If the AUP value falls outside the range of the sink, the designed molecule is not a feasible solution.

**Rule 7**. For the designed molecule to match the target properties, the AUP value of the molecule has to match the AUP value of the sink at the same cluster location. In the case where the design problem included non-GC properties, those properties must be back calculated for the designed molecule using the appropriate corresponding GC property, and those values have to match the target non-GC property.

### *Feasibility region boundaries*

Constraints placed on both process and molecular-design problems are represented by a feasibility region on the ternary diagram. These property values are mapped as a feasibility region defined by six unique points, according to the findings of El-Halwagi et al. [9] and they are summarized in rule 8.

**Rule 8**: *Expressing property constraints as a Feasibility Region*

- The boundary of the true feasibility region can be accurately represented by no more than six linear segments.
- When extended, the linear segments of the boundary of the true feasibility region constitute three convex hulls (cones) with their heads lying on the three vertices of the ternary-cluster diagram.
- The six points defining the boundary of the true feasibility region are determined *a priori,* and are characterized by the following values of dimensionless operators

$$\left(\Omega_1^{\min},\Omega_2^{\min},\Omega_3^{\max}\right)\left(\Omega_1^{\min},\Omega_2^{\max},\Omega_3^{\max}\right)\left(\Omega_1^{\min},\Omega_2^{\max},\Omega_3^{\min}\right)$$
$$\left(\Omega_1^{\max},\Omega_2^{\max},\Omega_3^{\min}\right)\left(\Omega_1^{\max},\Omega_2^{\min},\Omega_3^{\min}\right)\left(\Omega_1^{\max},\Omega_2^{\min},\Omega_3^{\max}\right)$$

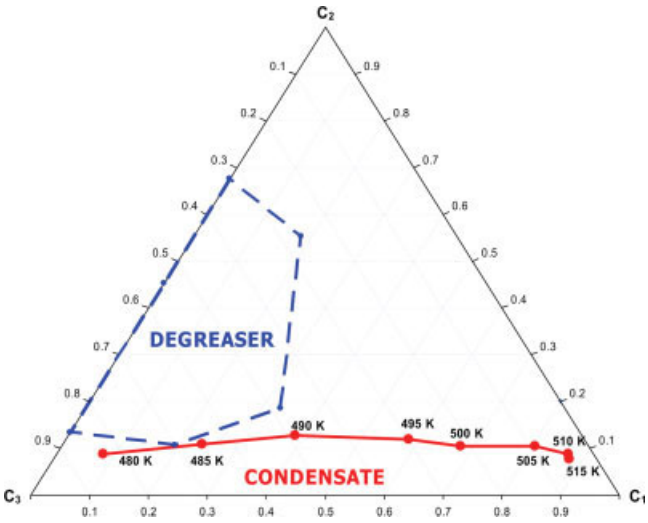


**Figure 6. Ternary representation of metal degreaser problem in process design.**

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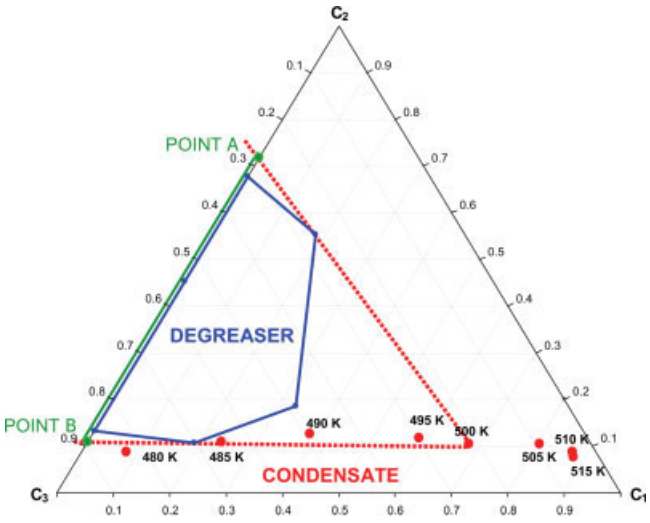


**Figure 7. Identifying property targets of the fresh solvent needed to maximize condensate recycle.**

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Now that the process and molecular design problems are both described in terms of clusters, a unifying framework exists for simultaneous solution of property driven design problems. In addition, the clustering technique reduces the dimensionality of both problems, thus, for systems that can be described by just three properties, it is possible to visually identify the solutions, which is a significant advantage of this approach. The integrated clustering methodology for the simultaneous solution of process and molecular design is summarized in Figure 3.

## Degreaser Case Study

A case study is discussed here to show the merits of using the simultaneous approach to solving process and molecular design problems via GCM and property clusters. Figure 4 illustrates a metal degreasing facility, with an absorber and degreaser. The process fresh resources are in the form of two organic solvent streams.[3] The off-gas volatile organic com-

**Table 3. Corresponding Property Values for Cluster Values Obtained from Process Design**

| | S (%) | VP (mmHg) | $V_m$ ($cm^3$/mol) |
|---|---|---|---|
| Point A | 0.00 | 1825.4 | 720.8 |
| Point B | 0.00 | 3878.7 | 102.1 |

**Table 4. Property Constraints Placed on Fresh Solvent Synthesis Obtained from Process Design**

| Property | Lower Bound | Upper Bound |
|---|---|---|
| $H_v$ (kJ/kg) | 50.00 | 100.00 |
| VP (mmHg) | 1825.40 | 3878.70 |
| $V_m$ ($cm^3$/mol) | 90.10 | 720.80 |
| $T_{bp}$ (K) | 418.01 | 457.16 |

pounds (VOCs) are a byproduct from the degreasing unit, and the current treatment of this stream is flaring. The problem with such a treatment as it leads to economic loss and environmental pollution.[14]

In this case study, the objective is to explore the possibility of condensing the off gas VOCs, to (1) minimize the use of fresh solvent, and (2) to simultaneously identify candidate alternative solvents for the degreaser (See Figure 5). Three properties are examined to determine the suitability of a given organic process fluid for use in the degreaser:

- Sulfur content (S)—for corrosion consideration, expressed as weight percent.
- Molar volume ($V_m$)—for hydrodynamic and pumping aspects.
- Vapor pressure (VP)—for volatility, makeup and regeneration.

The solvents that will be synthesized will be pure component fluids; hence, the sulfur content of these streams will be zero.

### *Process design*

The constraints on the inlet streams to the degreaser are given in Table 2.

The process operator mixing rules needed to describe the system are described by the following equations

$$S_M = \sum_{s=1}^{Ns} x_s \cdot S_s, \qquad S^{ref} = 0.5 \text{ wt } \% \tag{9}$$

$$V_{m_M} = \sum_{s=1}^{Ns} x_s \cdot V_{m_s}, \qquad V_m^{ref} = 80 \text{ cm}^3/\text{mol} \tag{10}$$

$$VP_M^{1.44} = \sum_{s=1}^{Ns} x_s \cdot VP_s^{1.44}, \qquad VP^{1.44,ref} = 760 \text{ mmHg} \tag{11}$$

Samples of the off-gas were taken, and then condensed at various temperatures ranging from 400–550 K, providing measurements of the three properties, as well as the flow rate of the condensate.[3] The data for the degreaser unit and for the condensate of the VOCs, are converted to cluster values according to cluster methodology developed by Eden et al.[8], see Figure 6. The degreaser property constraints are translated as a feasibility region according to the results highlighted in the *Visualization of the problem* Section.

Now that the problem has been mapped to the property domain and visualized on the ternary diagram, some constraints are placed on the process: the condensate temperature is set to 500K, and the fresh synthesized solvents are sulfur free. By fixing the condensation temperature at 500K the locus of possible solvents is bound by straight lines between the condensate and points A and B (see Figure 7) Using lever arm analysis, between the degreaser feasibility region and the condensate recycle stream, point A and point B are now identified on Figure 7. This adheres to the first constraint. Applying the second constraint on the process (no sulfur in fresh solvent), shows that the cluster solution to the degreaser problem corresponds to all points between points A and B on the $C_2$-$C_3$ axis.

### *Molecular design—fresh solvent synthesis*

Once all the constraints have been taken into account, and the property targets for molecular formulations have been set by process design, the second phase of this case study begins.

The cluster values associated with points A and B from the clustering diagram in Figure 7, are translated to physical property values using the methodology developed by Shelley and El-Halwagi[3] and Eden et al.[8] These property targets obtained from solving our process design problem are now the upper and lower property constraints placed on the solvent/molecular design problem, see Table 3.

The zero sulfur constraint placed on the problem provides an extra degree of freedom. So a heat of vaporization constraint is now placed on the fresh solvent problem. Now the properties used to describe the problem are heat of vaporization ($H_v$), boiling temperature ($T_b$) and molar volume ($V_m$). Notice that boiling temperature is used instead of vapor pressure since there is no direct group contribution method for predicting vapor pressure.[15] However, according to Eq. 2 vapor pressure is a function of boiling temperature. Hence, the vapor pressure property constraints are converted to boiling temperature upper and lower limits. All of the property constraints on the molecular design problem are now shown in Table 4.

**Table 5. Summarizes Property Operators Needed for Molecular Synthesis**

| Property | LHS of Equation $\Psi_j^M$ | RHS of Equation 1st order GC Expression | Reference Values |
|---|---|---|---|
| Standard heat of vaporization | $\Delta H_v - h_{vo}$ | $\sum_{g=1}^{N_g} n_g \cdot h_{v1}$ | 20 |
| Molar volume | $V_m - d$ | $\sum_{g=1}^{N_g} n_g \cdot v_1$ | 100 |
| Normal boiling temperature | $\exp\left(\frac{T}{t_{bo}}\right)$ | $\sum_{g=1}^{N_g} n_g \cdot t_{b1}$ | 7 |

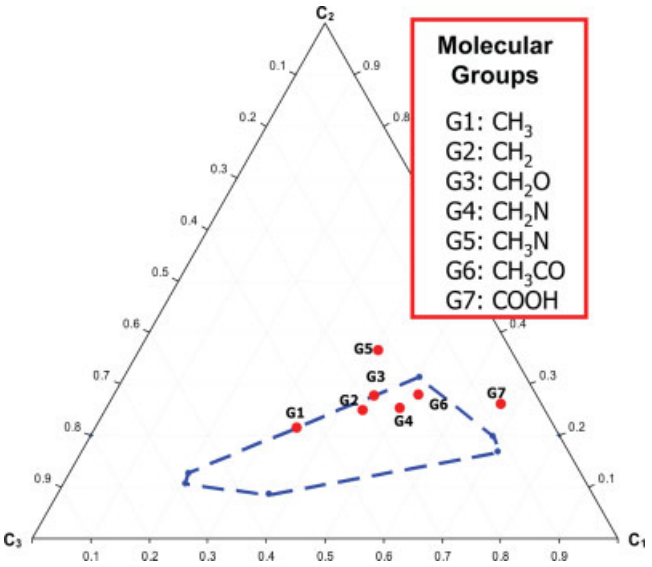


**Figure 8. Ternary diagram used to represent molecular synthesis problem.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

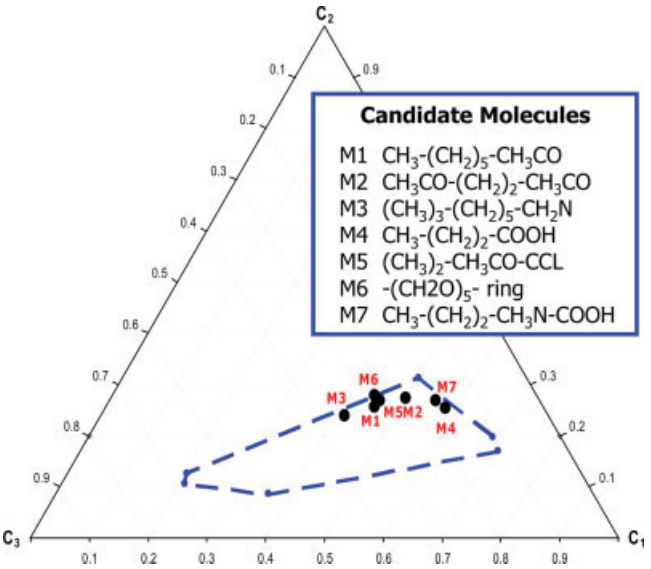


**Figure 9. Candidate formulated molecules.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The physical properties are predicted using the following first-order group contribution equations[6,16]

$$\Delta H_v = h_{vo} + \sum_i n_i \cdot h_{v1_i} \tag{12}$$

$$V_m = d + \sum n_i \cdot v_{1_i} \tag{13}$$

$$T_{bo} = t_{bo} \cdot \ln \sum_i n_i \cdot t_{b1} \tag{14}$$

The property operators derived from the earlier equations and their reference values are summarized in Table 5. Notice that RHS of the equation allows for the linear additive rules.

The problem is visualized by converting the property targets to cluster values following the methodology described in Table 1. The targeted properties are represented by a feasibility region, which has been identified as outlined in the *Feasibility region bounderies* section. The resulting ternary diagram is shown in Figure 8, where the dotted lines represent the feasibility region in the molecular design domain.

The design problem also states that the molecules to be designed can be made up of eight chemical groups. Carboxyl, methyl, and amine groups are among the selection. All the groups used in the molecular synthesis problem are shown in Figure 8, and were chosen to highlight the visual aspects of this clustering technique. The selection of building blocks is considered a pre-design step. Any other constraints on the molecular design problem can be imposed at this point.

Translating health and environmental concerns to the level of molecular synthesis can be achieved via exclusion or inclusion of certain molecular groups, such as chloro compounds and amines, or by excluding the formation of cyclical compounds. The latter is translated to the design problem by simply expressing the $NO_{Rings}$ to be zero.

Notice that even though some of the property operators formulated earlier are very complex, molecular synthesis on the ternary diagram is still simple because these operators are forced to obey simple linear additive rules. Seven candidates, M1–M7, are formulated for this solvent design problem (see Figure 9). However, the validity of the formulations is satisfied only after satisfying conditions summarized by Rules 4–8 in the *Expressing property constraints as a feasibility region* section. The cluster values of the designed molecules, M1–M7, are checked to make sure that they lie within that of the sink. The values of the augmented property index of the designed molecule must lie within the AUP range of the sink; in the degreaser case study the AUP of the sink ranged from 4.22–12.65, see Table 6. It is seen that molecules M5 and M6 fail to satisfy this condition.

The final necessary and sufficient condition is the property values of the new formulations must lie within the upper and lower constraints placed on the molecular-design problem, which includes the non-GC property constraints. The property values for the new formulations are back calculated using the methodology outlined earlier in the *Property operators* section. Molecule M3 fails to satisfy the property condition in the molecular domain; and although M7 satisfies the three GC properties, $H_v$, $V_m$ and $T_b$, it fails to satisfy the non-GC property for vapor pressure.

Consequently, M1, M2, and M4 are the final valid formulations. After searching the ICAS database,[17] M1, M2 and

**Table 6. Molecular Candidate AUP and Property Value**

| Formulation | AUP | $T_b$ (K) | $H_v$ (kJ/mol) | $V_m$ ($cm^3$/mol) | VP (mmHg) |
|---|---|---|---|---|---|
| M1 | 5.06 | 450.58 | 53.19 | 156.85 | 2078.98 |
| M2 | 4.71 | 448.54 | 54.13 | 118.03 | 2163.90 |
| M3 | 5.11 | 437.29 | 49.35 | 189.41 | 2692.07 |
| M4 | 4.86 | 438.97 | 63.29 | 93.39 | 2606.12 |
| M5 | 4.02 | 413.20 | 43.88 | 121.14 | 4241.48 |
| M6 | 4.19 | 428.11 | 44.22 | 127.66 | 3208.12 |
| M7 | 5.71 | 485.01 | 70.24 | 112.52 | 1037.99 |

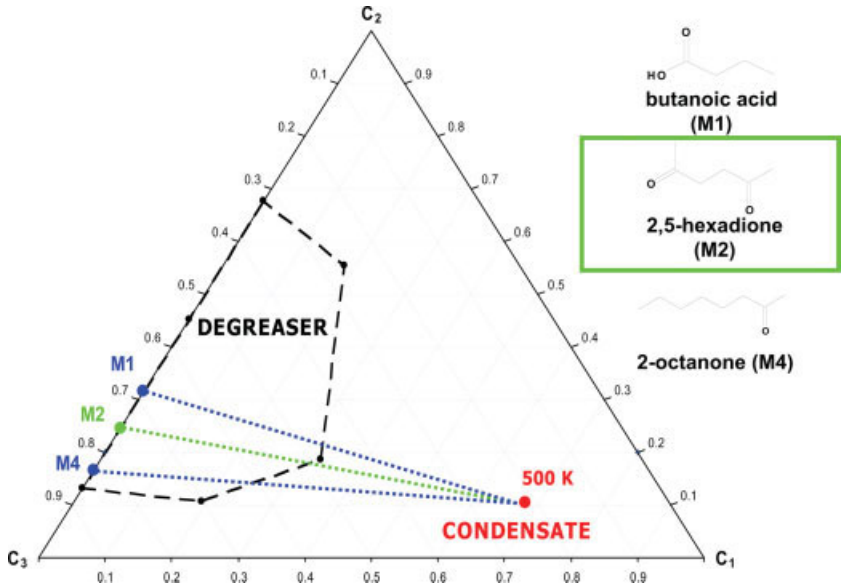


**Figure 10. Candidate molecular solutions obtained to satisfy optimized process design targets.**

[Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

M4 correspond to 2-octanone, 2,5-hexanedione, and butanoic acid respectively. The valid molecular structures are shown in Figure 10. The three candidates are mapped back to the process design framework to identify the formulation that will maximize recycle of condensate at 500K. Using lever arm analysis, 19.36 kg/min of fresh solvent 2,5-hexadione will allow for maximum condensate flow rate of 17.44 kg/min.

## Conclusions

In this work, a systematic property based framework for simultaneous solution of process and molecular design problems has been presented. The recently introduced property integration framework has been extended to include group contribution methods for molecular design. Using property clusters, the process design problem is solved to identify the property targets corresponding to desired process performance. The molecular design problem is solved to generate structures that match these targets.

A significant result of the developed methodology is that for problems that can be satisfactorily described by just three properties, the process and molecular design problems are solved visually and simultaneously on a ternary diagram, regardless of how many molecularly fragments are included in the search space. However, algebraic and optimization based approaches can easily extend the application range to include more properties.

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*Manuscript received Aug. 31, 2006, and revision received Jan. 26, 2007.*