Integrated Chemical Product-Process Design: CAPE Perspectives

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Introduction

Problem Definition

Process Design

- Raw material
- Operating condition?

Product Design

- Molecule or mixture?
- Atoms or molecules

Product Application Design

- Product
- Application process?

Integrate Process-Product & Application

- Performance
- Equipment parameters?
- Product functions?
- Products
- Product properties

Molecule or mixture synthesis?

Application conditions?

Equipment parameters?

Atoms or molecules
Introduction

Examples of Product-Process Integration

- Petroleum blends & petroleum products: Routinely solved!
- Polymers & blends: Can be solved!
- Specialty chemicals (including drugs, ....): Process role?
Introduction

Examples of Product-Process Integration

For products such as drugs, pesticides, food, … delivery and application is important & needs to be validated.

- **Product Design**: Atoms or molecules
- **Product**: molecule/mixture?
- **Product properties**: Molecule or mixture synthesis?
- **Product functions**: Application conditions?
- **Application**: process?
- **Performance**: Equipment parameters?
- **Production process needs to be reliable – first time right is important**
### Introduction

#### Current Status

<table>
<thead>
<tr>
<th>Product-Process Characteristics</th>
<th>Chemicals &amp; chemical products</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-value</strong></td>
<td><strong>High-value</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Product type</strong></td>
<td>Reactive agents, solvents, process fluids, ….</td>
<td>Active ingredients; additives, …</td>
</tr>
<tr>
<td><strong>Consumer products</strong></td>
<td><strong>Consumers products</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Process design</strong></td>
<td>Economically efficient</td>
<td>Operationally reliable</td>
</tr>
<tr>
<td><strong>Application process</strong></td>
<td>Easy to validate</td>
<td>Difficult to validate</td>
</tr>
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</table>

- CAPE/PSE have routinely solved integrated product-process design problems for low value chemical products
- CAPE/PSE is very well equipped to solve the integrated product-process design problems for high value chemical products
Overview of Presentation

• Different types of design problems
  - Product Design Problem
  - Molecule Design Problem
  - Process Design Problem
  - Product-Process Evaluation

• Challenges & opportunities

• Issues & Needs

• Framework for an integrated approach

• Conclusions
Different Product Design Problems

1. Design of Molecule and/or Mixture

Given, a set of target properties $\theta$, find molecules or mixtures that match the target properties. CAMD & CAM$^b$D

solvents, fluids, ...  

drugs, pesticides, aroma, ....

Low Value High
Large Production rate Small
Easy Finding candidates Difficult
Different Product Design Problems

1. Design of Molecule and/or Mixture

CAMD & CAM$^b$D: Example

From a list of 250 solvents, find those that can be used as an oil-paint additive characterized by 25%- , 50%- & 75%- evaporation rate, solubility, viscosity and surface tension. Form the feasible set, find the optimal cost solvent mixture.

- Synthesis method for mixtures
- Property models for solvents
- Evaporation models for solvents
- Cost = $f(C_i, x_i)$

*Note: Mixture design similar to oil-blend (petroleum, edible oil, ....), polymer blend, formulations, ....*
1. Design of Molecule and/or Mixture

Given, a set of target properties $\theta$, find molecules or mixtures that match the target properties CAMD & CAM$^b$D

Issues & Needs

- Generate feasible candidates (synthesis method & tool)
- Estimate target properties (predictive property models)
- Evaluate performance (application process models)

Achenie et al, Computer Aided Molecular Design: Theory & Practice, CACE-12, 2003
2. Product-Process Evaluation

Given, a list of feasible candidates (product and/or process), the objective is to identify/select the most appropriate product-process based on a set of performance criteria.

For product design, this problem is similar to CAMD but without the generation step; also, similar to CAM\textsuperscript{b}D where additives are added to a product to significantly enhance the performance of the product.

**Examples**

- Select the optimal combination of pesticide and surfactants that match the needs of specific plants
- Select the optimal combination of drug/pesticide, solvent and polymeric microcapsule for controlled release of the product
- Increase the yield of a product by hybrid process operation
2. Product-Process Evaluation

**Simple Example:** From the derivatives of Barbituric acid, identify the candidate that is required in the smallest amount \( C \) to produce a 1:1 complex with protein (binding to bovine serum albumin) – calculated as a function of *octanol-water partition coefficient* of the candidate compounds: 

\[
\log_{10}(1/C) = 0.58 \log_{10}P + 0.239
\]

- Synthesis tool for isomer generation
- Property model for \( \log_{10}P \)
- Verify solubility in water

**Note:** How is the *backbone* (barbituric acid) identified and how is the relation (drug activity) between \( C \) vs \( \log_{10}P \) found?
2. Product-Process Evaluation

Process Analytical Technology – PAT

To ensure final product quality!

Estimate critical scientific & regulatory parameters early!

A. S. Hussain, CDER, FDA, 2002
Different Product Design Problems

2. Product-Process Evaluation

Process Analytical Technology – PAT
To ensure final product quality!

Estimate critical scientific regulatory parameter early!

Tablet Manufacturing (D. Radspinner, 2004)

Tablet Manufacturing (D. Radspinner, Sanofi-Aventis, 2004)
Different Product Design Problems

3. Design of Product-centric Process

Problem Characteristics

- Products are consumer products such as soap, detergents, fragrances, food, skin-care …
- Complex chemical systems involved
- Life of the product is getting shorter
- Volume/cost relationship needs to be improved by selling more
- Low-cost chemical routes are needed (better catalysts, faster reactions, increased yields, …)

Issues & Needs

Algorithm for generation of process flowsheet or batch recipe

Process-operation models for verification by simulation

Property models for product/process analysis
Product properties:
Consists of air-bubble, fat, water crystals in a sugar matrix
Texture is function of the sizes of air-bubble, fat droplet & water crystal

Process properties:
Contains batch & continuous operational steps
Same production-line may produce other products
Cleaned every day
Large scale production with accurate control of product texture

M. Meeuse, Unilever, 2005 (see also, paper in the ESCAPE-15 proceedings, 2005)
Schematic representation of ice cream structure

Air bubbles

Ice crystals

Sugar matrix

Structured 3D fat network

M. Meeuse, Unilever, 2005
3. Design of Product-centric Process

- 14 million molecular compounds have been synthesized
- About 100 thousand can be found in the market
- Only a small fraction can be found in nature
- Most of them will need to be conceived, designed, synthesized & manufactured!

Charpentier, Chem Eng Sci, 2004

**Design Problem:** Given, the identity of a product & its quality needs, raw materials that could be used, determine the process that can produce it (reliably, efficiently and sustainably)
3. Design of Product-centric Process

Example: Manufacture of Carnosic acid by recovering it from popular herbs (Harjo et al 2004)
Product-centric Process Development*

- The key to success is first identify the desired end-use properties of a product and then to control product quality by controlling the microstructure formation.
- Different scales of size, time & complexity.
- Collect sufficient data to enable systematic study leading to the development of appropriate mathematical models.

* Considering structured products

Charpentier, Chem Eng Sci, 2004
Polymer Based Microcapsules

- Suitability and optimal concentrations of raw materials
  - Polymer (P)
  - Active ingredient (AI)
  - Surfactant (M)
  - Solvents (S)
- Process design
- Optimization of operating conditions
- Design of sustain-release capabilities

G. Tse et al., J. Controlled Release, 1999
Polymer Based Microcapsules

- Polymer phase (P+S+AI): GC-FLORY $\gamma_{A,P}$
- Aqueous phase (W+AI): UNIFAC $\gamma_{A,W}$
- Micelle phase (M+AI): GC-FLORY $\gamma_{A,M}$

- Equilibrium factors:
  \[ K_{i/j}^A = \frac{x_i^j}{x_j^i} \approx \frac{\gamma_{A,i}^{\infty}}{\gamma_{A,j}^{\infty}} \]

- Material balance:
  \[ y_{i,F}(1+\sum_{l=1}^{F-1} \beta_l(K_{i,l}-1)) = z_i \]

- Mol fractions:
  \[ \sum_{i=1}^{C} \frac{K_{y}^i - 1}{1 + \sum_{l=1}^{F-1} \beta_l(K_{i,l}-1)} = 0, j = 1, 2, \ldots, F-1 \]

J. Abildskov & I. Kouskoumvekaki, PEC05-41, 2005
Polymer Based Microcapsules

AI loading in polymer

Emulsification-solvent evaporation method
Controlled release through Microcapsules

Definition of microcapsule:

Core: AI solid/liquid, pure/solution (or dispersion) + additives (solvent, emulsifier,...)

Coating: polymer membrane (rate-controlling) porous/non-porous

Release medium

K_{m-d}, K_{m-r}, D

Time course of concentration from conventional application (—) Controlled release application (—–)
Challenges and Opportunities – 4a

Pesticide Uptake in a Leaf

Internal Structure of Leaf

Multilayer Uptake Model

Droplet Evaporation Model

Energy Contribution

Cuticle
Epidermis

Wax
Cuticle
Plant Compartment containing epidermis and the layers beneath.

C14
C15
C16
C17
hwax
heuticle

r(t>0) r(t=0)
Diagrammatic representation of Equations used for Active Ingredient & Surfactant in the Model

\[
\frac{dM_{AI}}{dt} = -\frac{D_{AI} * S * (C1 - C0)}{h_{wax}} + Vd * \frac{dC_{dAI}}{dt}
\]

\[
\frac{dC_{dAI}}{dt} = 1000 \left( \frac{MW_{adj}}{MW_{AI}} \right) \left( \frac{S_{adj} - S_{water}}{\rho_{adj} * Vd} \right) \left( Vd * \frac{dC_{adj}}{dt} + \frac{dM_{adj}}{dt} \right)
\]

\[
\frac{dC1}{dt} = (D_{AI1} * B / h_{wax}^2) * (C2 - 2C1 + C0)
\]

\[
\frac{dC_{adj1}}{dt} = (D_{adj1} * B / h_{wax}^2) * (C_{adj2} - 2 * C_{adj1} + C_{adj0})
\]

\[
\frac{dC16}{dt} = ((D_{AI16} * B / h_{cut}^2) * (C17 - C16)) - ((D_{AI15} * B / h_{wax} * h_{cut}) * (KwCAI * C16 - C15))
\]

\[
\frac{dC17}{dt} = (D_{AI17} * B / h_{cut}^2) * (C18 - 2 * C17 + C16)
\]

\[
CpAI = C30 / KcpAI
\]
Challenges and Opportunities - 5

Design of Polymer

GIVEN: Target properties of polymer

TARGET: Find feasible alternative structures of polymer that fulfill 'Target' properties

Design of Membrane Based Separation Process

GIVEN: Mixture and desired degree of separation

Find a suitable polymer

TARGET: Design the separation

Polymeric-membrane based gas separation

Simultaneous design of polymer & separation process
Issues & Needs -1

Tools to handle scales & complexity

Polymerization of olefins on supported catalysts – consider different length scales

Charpentier, Chem Eng Sci, 2004

Problems highlighted under challenges & opportunities can be solved if the necessary methods & tools are available
Tools to handle scales & complexity

Needed: methods & tools for development of models
The need for integration

- Provide capability to create & manipulate product-process models
- Provide simulation techniques & supporting processing techniques to allow simulations of product and process performance
- Provide capability to simulate & evaluate many design alternatives in parallel to fast trade-off evaluations
- Provide integrated plug & play toolset for modelling and simulation of life-cycle factors for generic products

IMTI, Report, 2000
Integration of Product-Product Design

Chemical Product-Process Design

- Molecular Structure?
- Mixture Composition?
- Product Design
  - Property Models
  - Product Models

- Process Flowsheet?
  - Process Synthesis/Design Tools
  - Simulation Engine

- Process Design
  - Process Performance?
  - Product Performance?
  - Process-Product Evaluation

- Product Application Model
  - Process Analysis Tools
Types of Models & their Connection

Process Analysis Tools

Process Models

Balance Equations
\[ \frac{dx}{dt} = f(x, y, p, d, t) \]

Constraint Equations
\[ 0 = g_2(x, y, p, d) \]

Constitutive Equations/Phenomena Models
\[ 0 = g_1(x, y) - \theta \]

Product Model

Product Application Model

Conceptual variables - cannot be measured directly

Intensive variables - can be measured

T, P, x; \( \bar{N} \), species
Types of Models & their Connection

Oslo Evaporative Crystallizer (process model)

Solubility versus temperature (constitutive model)

Integration of process model with various constitutive models gives us a model of wide application range.
Table 1. Data-flow for each design problem

<table>
<thead>
<tr>
<th>Input Data</th>
<th>Problem Type</th>
<th>Output Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Building blocks for molecules; target properties and their upper/lower bounds and/or goal values</td>
<td>Molecular Design (CAMD)</td>
<td>Feasible molecular structures and their corresponding properties</td>
</tr>
<tr>
<td>List of candidate compounds to be used in the mixture, target properties and their upper/lower bounds and/or goal values at specified conditions of temperature and/or pressure</td>
<td>Mixture Design (CAMD)</td>
<td>List of feasible mixtures (compounds and their compositions) and their corresponding properties</td>
</tr>
<tr>
<td>Desired process specifications (input streams, product specifications, process constraints, etc.)</td>
<td>Process Design/Synthesis (PD)</td>
<td>Process flowsheet (list of operations, equipments, their sequence and their design parameters)</td>
</tr>
<tr>
<td>Desired separation process specifications (input streams, product specifications, process constraints, etc.) and desired (target) solvent properties</td>
<td>Process-Solvent Design</td>
<td>Process flowsheet (list of operations, equipments, their sequence and their design parameters) plus list of candidate solvents</td>
</tr>
<tr>
<td>Details of the molecular or formulated product (molecular structure or list of molecules and their composition and their state) and their expected function</td>
<td>Product Evaluation</td>
<td>Performance criteria</td>
</tr>
<tr>
<td>Details of the process flowsheet and the process (design) specifications</td>
<td>Process Evaluation</td>
<td>Performance criteria, sustainability metrics</td>
</tr>
</tbody>
</table>
### Available methods & tools

Table 2. List of methods/algorithms and tools/software that may be used for each problem (design) type.

<table>
<thead>
<tr>
<th>Problem Type</th>
<th>Method/Algorithm</th>
<th>Tools/Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular &amp; Mixture Design (CAMD)</td>
<td>Molecular structure generation; Property prediction &amp; database; Screening and/or optimization</td>
<td>ProCAMD</td>
</tr>
<tr>
<td>Process Design/Synthesis (PD)</td>
<td>Process synthesis/design; Process simulation/optimization; Process analysis</td>
<td>ICAS (PDS, ICAS-sim, PA)</td>
</tr>
<tr>
<td>Process-Solvent Design</td>
<td>CAMD-methods/tools; Process synthesis/design; Process simulation/optimization; Process analysis</td>
<td>ICAS (ProPred, ProCAMD, PDS, ICAS-sim, PA)</td>
</tr>
<tr>
<td>Product Evaluation</td>
<td>Property prediction &amp; database; Product performance evaluation model; Model equation solver</td>
<td>ICAS (ProPred, ICAS-utility, MoT)</td>
</tr>
<tr>
<td>Process Evaluation</td>
<td>Process synthesis/design; Process simulation/optimization; Process analysis</td>
<td>ICAS (ICAS-sim, ICAS-utility, MoT, PA)</td>
</tr>
</tbody>
</table>
Simultaneous product-process design

Group contribution approach for synthesis/design of molecules as well as process flowsheets

Atomic-groups are used to design molecules while process-groups are used to design flowsheets

Loic d’Anterroches, 2005
Conclusions & Future Work

• For CAPE/PSE methods to work, models are necessary
  – If appropriate models are available, almost all problems can be solved

• CAPE/PSE have solved product-process problems involving low-value simple chemical products

• High-value chemical products or product centric process design problems involve complex chemical systems
  – The limiting factors for these problems are availability of data and appropriate models
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- Prof. Ka Ng (ChERD, 82(A11), 1494-1504, 2004)
- IMBT (First product correct: Visions & goals for the 21st century manufacturing enterprise, Integrated Manufacturing Technology Initiative, Report, 2000, USA)