Computer-Aided Methods & Tools for the Pharmaceutical Industry

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Statements from Industry

We develop and provide customized computer-aided solutions in process/product development, planning and operations to assist our company (pharmaceutical and specialty chemical products) to introduce new products to the market faster with lower initial cost of goods while improving cost effectiveness of their development and manufacturing groups - CAPEC member company

One of the key challenges facing pharmaceutical companies is to reduce the time to market and cost of goods of their products whilst continuing to comply and exceed stringent regulatory conditions - CAPEC member company

Need to make design decisions in the early stages of the process (design) lifecycle so that aspects of energy conservation, environment, waste, etc., can be incorporated - CAPEC member company, …

Our (CAPEC) role is to provide the methods & tools so that the above can be accomplished!

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The Challenge

The objective (challenge) is to identify the important fruits (products), the optimal path to reach them, the feasibility of the process, .....
## Dimension of the problem: Number of isomers

<table>
<thead>
<tr>
<th>$C_n$</th>
<th>$C_nH_{2n+1}OH$</th>
<th>$C_nH_{2n+2}$</th>
<th>$C_nH_{2n}$</th>
<th>$C_nH_{2n-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>8</td>
<td>39</td>
<td>18</td>
<td>66</td>
<td>32</td>
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<td>12</td>
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</tr>
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<td>16</td>
<td>48865</td>
<td>10359</td>
<td>93650</td>
<td>38422</td>
</tr>
<tr>
<td>20</td>
<td>2156010</td>
<td>366319</td>
<td>4224993</td>
<td>1678969</td>
</tr>
</tbody>
</table>

How many of these compounds are known? Can we afford to ignore this knowledge when developing new products and/or new processes?
Need for models

Model

Information (knowledge, data)

Simulation

Problem

Design

Production

Planning

Analysis

System

Process/Product

Operation

Environment

Business

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Research Programs in CAPEC

- Control & Operation
- Process Integration
- Process Models
- Property/Phenomena Models
- Synthesis/Design/Analysis
- Tools Integration

- Pollution & Waste
- Product
- Safety & Hazards
- Numerical Tools
- Databases

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Activities in CAPE Problems

Choosing among Process Alternatives Feasibility Study

Thermodynamic Model Selection

Parameter fitting for the Thermodynamic Model

Simulation Design Calculation Optimization

Properties of unknown molecules
Equilibrium Analysis
Model Selection Guide
Regression Input
Regression Result
Process Conditions
Properties Values

TMS
Thermodynamic Model Selection

TML
Thermodynamics Model Library

Propred
3.5

Pure component properties prediction

Pure properties Export / Import

CAPEC Thermophysical Properties Database
- Pure component properties and parameters
- Mixture properties and parameters
- Experimental data
Correlation & Prediction of Properties

- Group contribution approach for pure component and mixture properties
- Applications in specialty chemicals, fine chemicals, pharmaceuticals
- Electrolyte systems modeled
- Maintenance of library modules & model parameter tables
- CAPEC database of pure component and mixture properties (including solvents)
- Integrated computer aided methods & tools

Property Estimation

Step 1:
Problem analysis

Step 2:
Generation/creation of property model

Step 3:
Parameter Estimation

Step 4:
Validation of Property Model
New Group Contribution Method

<table>
<thead>
<tr>
<th>Property (X)</th>
<th>Left-hand side of Eq. 1 [Function ( f(X) )]</th>
<th>Right-hand side of Eq. 1 (Group- Contribution Terms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Melting Point ((Tm))</td>
<td>( \exp(Tm/Tm0) )</td>
<td>( \Sigma_i N_i Tm1i + \Sigma_j M_j Tm2j + \Sigma_k O_k Tm3k )</td>
</tr>
<tr>
<td>Normal Boiling Point ((Tb))</td>
<td>( \exp(Tb/Tb0) )</td>
<td>( \Sigma_i N_i Tb1i + \Sigma_j M_j Tb2j + \Sigma_k O_k Tb3k )</td>
</tr>
<tr>
<td>Critical Temperature ((Tc))</td>
<td>( \exp(Tc/Tc0) )</td>
<td>( \Sigma_i N_i Tc1i + \Sigma_j M_j Tc2j + \Sigma_k O_k Tc3k )</td>
</tr>
<tr>
<td>Critical Pressure ((Pc))</td>
<td>((Pc-Pc1)^{0.5}) - (Pc2)</td>
<td>( \Sigma_i N_i Pc1i + \Sigma_j M_j Pc2j + \Sigma_k O_k Pc3k )</td>
</tr>
<tr>
<td>Critical Volume ((Vc))</td>
<td>(Vc-Vc0)</td>
<td>( \Sigma_i N_i Vc1i + \Sigma_j M_j Vc2j + \Sigma_k O_k Vc3k )</td>
</tr>
<tr>
<td>Standard Gibbs Energy at 298 K ((Gf))</td>
<td>(Gf-Gf0)</td>
<td>( \Sigma_i N_i Gf1i + \Sigma_j M_j Gf2j + \Sigma_k O_k Gf3k )</td>
</tr>
<tr>
<td>Standard Enthalpy of Formation at 298 K ((Hf))</td>
<td>(Hf-Hf0)</td>
<td>( \Sigma_i N_i Hf1i + \Sigma_j M_j Hf2j + \Sigma_k O_k Hf3k )</td>
</tr>
<tr>
<td>Standard Enthalpy of Vaporization at 298 K ((Hv))</td>
<td>(Hv-Hv0)</td>
<td>( \Sigma_i N_i Hv1i + \Sigma_j M_j Hv2j )</td>
</tr>
<tr>
<td>Standard Enthalpy of Fusion ((Hfus))</td>
<td>(Hfus-Hfus0)</td>
<td>( \Sigma_i N_i Hfus1i + \Sigma_j M_j Hfus2j + \Sigma_k O_k Hfus3k )</td>
</tr>
</tbody>
</table>
Analyze the solubility of Fentanyl

- Generate data (using ProPred)
- Insert generated data into database
- Perform solid-liquid phase diagrams
Separation Boundaries: Distillation

VLE system

VLLE system

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Separation Boundaries: Crystallization
Process & Product Modeling

- Modeling of micro-organisms
- Modeling of fermentation processes
- Modeling of hybrid distillation operations and other non-conventional separation processes
- Modeling of fixed-bed reactor systems
- Special purpose models (e.g., uptake of pesticides, drugs, ...)
- **Computer aided process modeling toolbox**

*Models are the basis for all further work. Once the process/operation model has been established, it is analyzed, solved, combined, manipulated, etc., in other projects for development of algorithms for synthesis, design, control; for better understanding of process & product; for inventory, ....*


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What is computer aided modeling?

- Problem definition
- System characteristics
- Problem data
- Model construction
- Model solution
- Model verification
- Model calibration & validation
Model Construction Steps

- Derive the model equations
- Analyze model equations
- Translate the model equations to a solvable form; create library for use with a simulator or for on-line solution

A computer aided system assists the user in performing the above tasks
Model construction, generation & reuse,

Define Boundary  Describe System  Identify Building Block

Extract equations from library

* Balance Equations
* Constraint Equations
* Constitutive Equations

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Application of the modeling tool-box

- Process or Model
- Model library in simulator
- Connect model object to external applications
- Create own customized simulator
- Modeling Tool-box (MoT in ICAS)
- Calculator or solver
Construction of an operation & design model

Reaction: \( A \rightarrow B \)

Maximum conversion of 50% A at \( T = 340 \, \text{K} \)

Extract B from reactor with a solvent!

Solvent ID and effects need to be modeled

1. Charge Feed (open F1 & close F2)
2. Close F1
3. Heat until temperature = 340 K
4. Control temperature at 340 K
5. Charge solvent by opening F3
6. Extract B by opening F4
7. .......
Process/Product Synthesis & Design

Generate new process/product alternatives

Process ?

Raw Materials

Generate better alternatives for an existing process/product

Products?

mixture

reactor

separation

purge

Raw Materials

Products

Determine

* Optimal process/product
* Process/product/operation alternatives
* Design of control system
* Operating conditions

How? Make decisions based on the available knowledge (data) and/or calculations using the appropriate methods & tools
How do we use models in process design?

Simulation ► Constitutive Model ► Process Model

Design parameters

Raw material

T, P, X, compounds

Properties

Results

Product

Synthesis & Design

Iterative (trial & error) approach

Forward Problem: Service Role for Process & Phenomena Model
Current Approaches: Limited Search Space

* Choice of a constitutive model implicitly defines the search space

* Do we know enough to derive a single model?

* Can we solve simulation and/or optimization problems with multiple constitutive models representing the same variable?
More efficient method of solution

Simulation

Process Model

Constitutive Model

Synthesis & Design

Iterative approach

Design targets & feasibility

Results

Properties

T, P, X, compounds

Raw material

Design parameters

Forward Problem: Service & Advice Role for Constitutive Model(s)

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Integrated Process and Product Design

**Molecular Design**
- Discrete Decisions (e.g. type of compound, number of functional groups)
- Continuous Decisions (e.g. operating conditions)

**Process Design**
- Discrete Decisions (e.g. structural modifications)
- Continuous Decisions (e.g. operating conditions)

**INTERFACE**
Constitutive equations, e.g. property relations

**REQUIRED**
A framework for tracking properties

Given set of molecular groups to be screened (building blocks)

Designed components (e.g. raw materials, MSA's)

Constraints on property values obtained by targeting optimum process performance

Desired process performance (e.g. recovery, yield, cost)
Problem Definition: Reverse Problems

Reverse Simulation Problem: Given, Inputs & Outputs, calculate property clusters (design targets)

Reverse Property Calculation Problem: Given, Property (design targets), determine molecules, mixtures and/or conditions (T, P, x)
Other examples of reverse problem

Consider the reverse problem of simulation – given the design variables, solve the process model equations to determine the corresponding property values.

Mass Exchanger

Product + waste

Solvent

Product

Solvent + waste

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An example of product design

<table>
<thead>
<tr>
<th>Structure</th>
</tr>
</thead>
</table>
| ![Molecular structure of Morphine](image)

<table>
<thead>
<tr>
<th>Name</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_m (K)</td>
<td>528</td>
</tr>
<tr>
<td>δ (MPa)</td>
<td>26.3</td>
</tr>
</tbody>
</table>

**Figure 1**: Molecular structure and properties of morphine

**Define the product needs and then identify the molecules that match these needs!**

- Can we find better solvents than benzene, toluene or cyclohexane?
- Can we “design” drugs/chemical products with desirable properties?

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CAMD Framework

- Solutions of CAMD problems are iterative.
- Problem formulation controls the success.
- Essential qualities vs. (un)desirable qualities.
- Connectivity with external tools, data and methods.
Example: Design of solvent for Phenol

Benzene is used as a solvent for dissolving Phenol. Because of environmental considerations, it is desirable to replace Benzene.

Specifications:
- Should dissolve Phenol at ambient temperature conditions at least as well as Benzene.
- Have physical properties similar to Benzene.
- A stripper column is used to regenerate Water used for equipment cleaning between batches.
- Not pose the same environmental problems as Benzene.

Methyl sec-Butyl Ether

Structure

Solvation energy
-3.863 kcal/mol  
-7.081 kcal/mol

SLE Diagram for Phenol/Solvent system

Methyl sec-Butyl Ether (estimated $T_{\text{fusion}}$)

Benzene (estimated $T_{\text{fusion}}$)

Benzene (experimental $T_{\text{fusion}}$)
"I want acyclic alcohols, ketones, aldehydes and ethers with solvent properties similar to Benzene"

A set of building blocks: CH3, CH2, CH, C, OH, CH3CO, CH2CO, CHO, CH3O, CH2O, CH-O

A set of numerical constraints

Refined property estimation. Ability to estimate additional properties or use alternative methods. Rescreening against constraints.

Feasible alternatives found but do we have a sustainable process to manufacture it?

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Order the driving force diagrams in terms of $f_{ij \mid \text{max}}$; configure the distillation train in terms of $f_{ij \mid \text{max}}$; design each distillation column in terms intersection on $D_yD_x$ line.
Visualization of Synthesis & Design

- System: H₂O - (l)Asparagine - Alanine - Serine
- Products: (l)Asparagine, Alanine, Serine
- Solubility description:
  Solubility product-
  (l)Asparagine, Alanine, Serine
- Number of chemical species: 12
- Phase diagram type: quaternary
- Thermodynamic model:
  Electrolyte NRTL

Simultaneous problem solution and visualization for batch & continuous operations/processes

**Example: Flowsheet synthesis/design**

**Flowsheet Synthesis**

The operator based reduced models derived from the original mass balance models are linear, thereby making them applicable to simple graphical techniques.

**Visual Simulation**

Composition free design calculations, but the compositions can be back calculated directly since the flowsheet satisfies fundamental balances.
Examples: Blending/mixing Problem

Composition free reduced model

\[ C_{1m} = c_1 C_{11} + c_2 C_{12} \]
\[ C_{2m} = c_1 C_{21} + c_2 C_{22} \]
\[ C_{3m} = 1 - C_{1m} + C_{2m} \]
Industrial Collaboration: Examples

- Computer Aided Molecular Design - solvents, process fluids, product qualities, ...
- Modeling & analysis of electrolyte systems
- Optimization of a crystallization process
- Modeling, simulation & control of complex distillation operations
- Synthesis of batch operations (process route selection)
- Properties of new products (CAPEC Database) & molecule structure generation
- Reaction system analysis - alternative reaction paths
- Solubility of complex (new) chemicals & downstream separation
Process/Product Development in Industry

THE KEY DECISION POINT

Research route

Generate route options

Outline f/s & costs

Selection criteria

SHE impact

Market requirements (quality; tox)

Activity

VPC / margin

Capital

ROUTE SELECTION

Early formulation

Product specification

market forecast

business targets

Design, f/s,
cost estimate

Field trials; registration

Decision to invest

Ongoing development

Process development

Smith manufacture

FF&P development

FF & P = formulation, fill and pack

Outline f/s & costs

Process development

Ongoing development

Research Results of KT
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CAPEC Member Companies

- Current membership: 22 companies (+ IMP, Mexico)
- Access to research reports, databases & software
- Specialized collaborative research projects & exchange visits/training
- Annual discussion meeting