Computer Aided Molecular Design for bio-sourced molecules. The IBSS Tool

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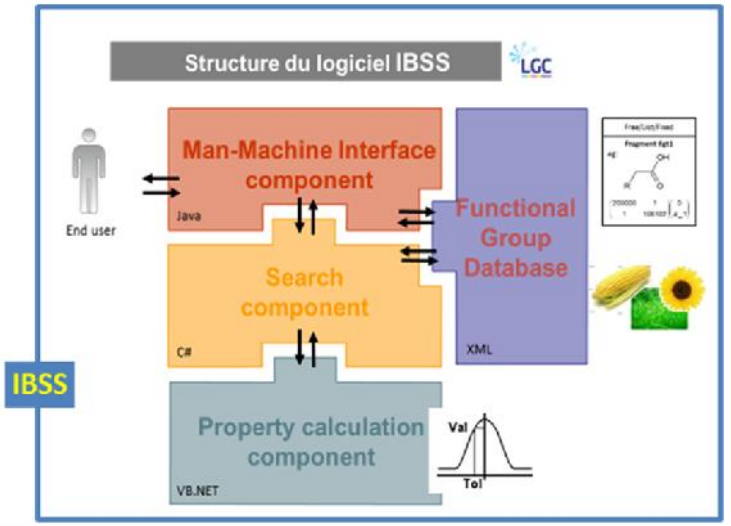
PSI Procédés et Systèmes Industriels

INBIOSYNSOLV (IBSS) IN CONTEXT

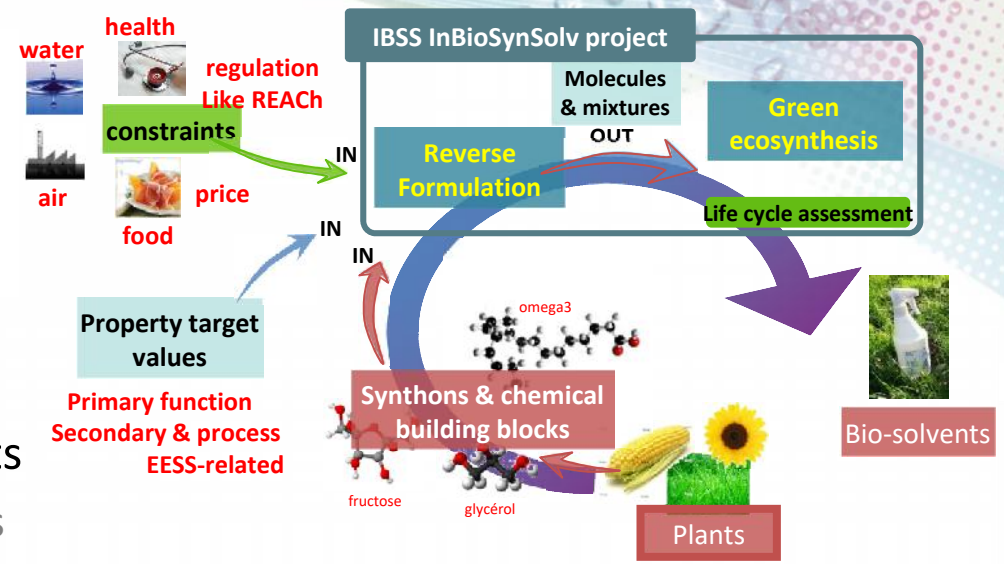


J. HEINTZ, J.P. BELAUD D, V. GERBAUD. Chemical enterprise model and decision-making framework for sustainable chemical product design. Computers in Industry Special Issue, 65(3), 505-520, 2014.

J. HEINTZ, J.P. BELAUD, N. PANDYA, M. TELES DOS SANTOS, V. GERBAUD. Computer aided product design tool for sustainable chemical product development. Comput. Chem. Eng., 71, 362–376, 2014.

Designing bio-based products

- **Motivation:**
  - Finding new molecules or substituting existing molecules by greener and safer ones

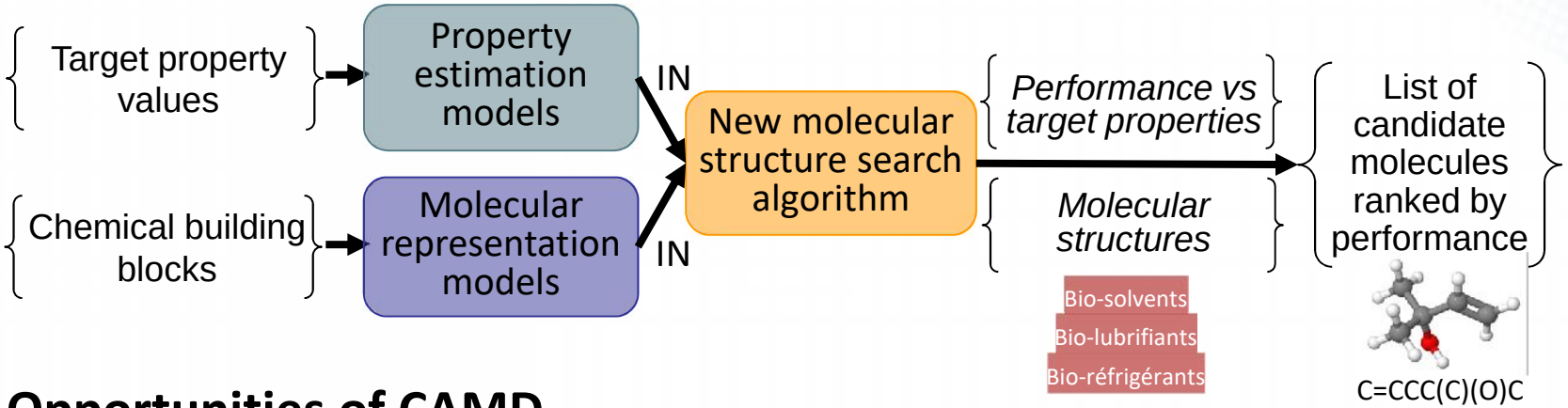


- **Challenges for substitution**
  - Multiple molecular requirements
    - Low price of chemical synthesis
    - Keep at least one key property (eg. solubilizing an active principle)
    - Keep process & usage properties (surface tension, viscosity, vapor pressure)
    - Improve EHS / Environment Health Safety properties
      - » *Improve market added value: "green product issued from renewable materials"*
  - Need of a screening method that will explore many chemical structures and match multiple properties at the same time.
    - > 30 millions molecules are registered but 10 000 are well described with properties
    - "trial and error" or "high-throughput experiments" methods are inefficient and costly and not adapted to multiple requirements

→ What about CAMD Computer Aided Molecular Design?

Computer Aided Molecular Design

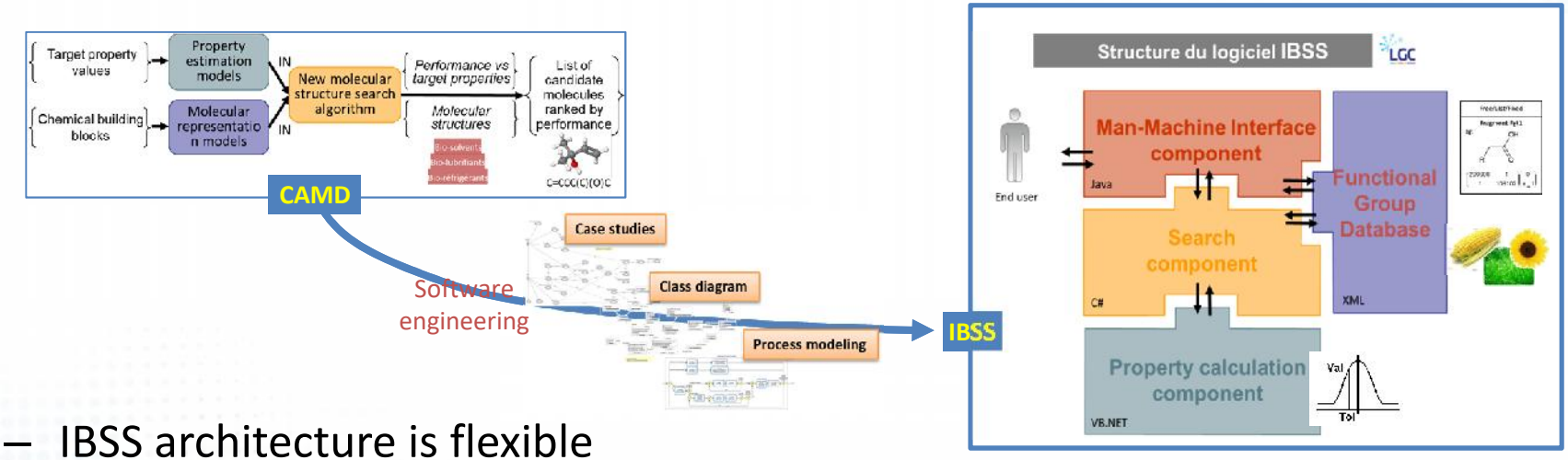
- **Computer Aided Molecular Design (Brignole & Gani, 1983)**



- **Opportunities of CAMD**
  - Can explore millions of chemical structures in a few hours
  - Can handle multiple properties at the same time
- **Limitations of CAMD**
  - CAMD remains a screening technique → needs further experimental validation
  - CAMD needs property prediction models related to molecular structures
    - Property prediction models : group contribution, QSAR, QSPR, …
    - Accuracy of prediction is unequal: from very good to approximate
      - ! Property models accuracy is never better than experimental measurements

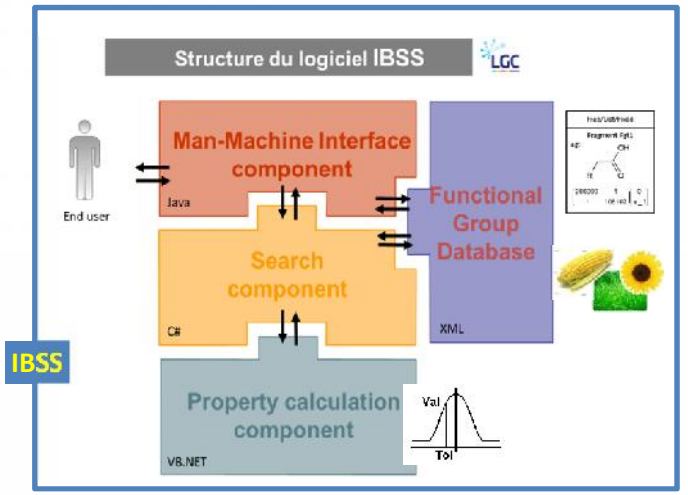
IBSS: InBioSynSolv Project (ANR CP2D 2009)

- **The IBSS software follows the CAMD concepts but is adapted to deal with mixtures where biobased synthons can be imposed**
  - A component-based software



  - IBSS architecture is flexible
    - New property models can be added into property library
    - New candidate synthons and other chemical building blocks can be added into the functional group database
  - As of today, IBSS is licenced by INPT University to the Toulouse SATT but it is not distributed so far by the Toulouse SATT.
    - Ask any of the authors for conditions of a further test.

INBIOSYNSOLV (IBSS) IN PRACTICE

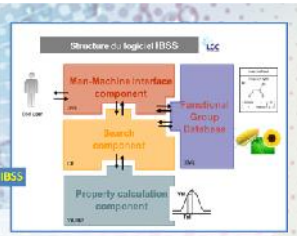


V. GERBAUD, TELES DOS SANTOS M., PANDYA N., AUBRY J.M. Computer aided framework for designing bio-based commodity molecules with enhanced properties. *Chem. Eng. Sci.*, 159, 177-193, **2017.**

L. MOITY, MOLINIER V., BENAZZOUZ A., JOOSSEN B., GERBAUD, V., AUBRY J.M. A "top-down" in silico approach for designing ad hoc bio-based solvents: Application to glycerol-derived solvents of nitrocellulose. Green Chem., 18, 3239-3249, 2016.

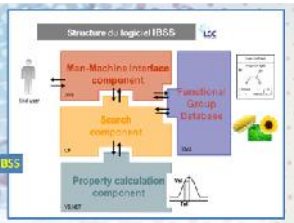
M. BERGEZ-LACOSTE, S. THIEBAUD-ROUX, P. DE CARO, J.F. FABRE, V. GERBAUD, Z. MOULOUNGUI. From chemical platform molecules to new biosolvents: Design engineering as substitution methodology. Biofuels, Bioproducts & Biorefining., 8, 438-441, 2014.

What is IBSS good for?

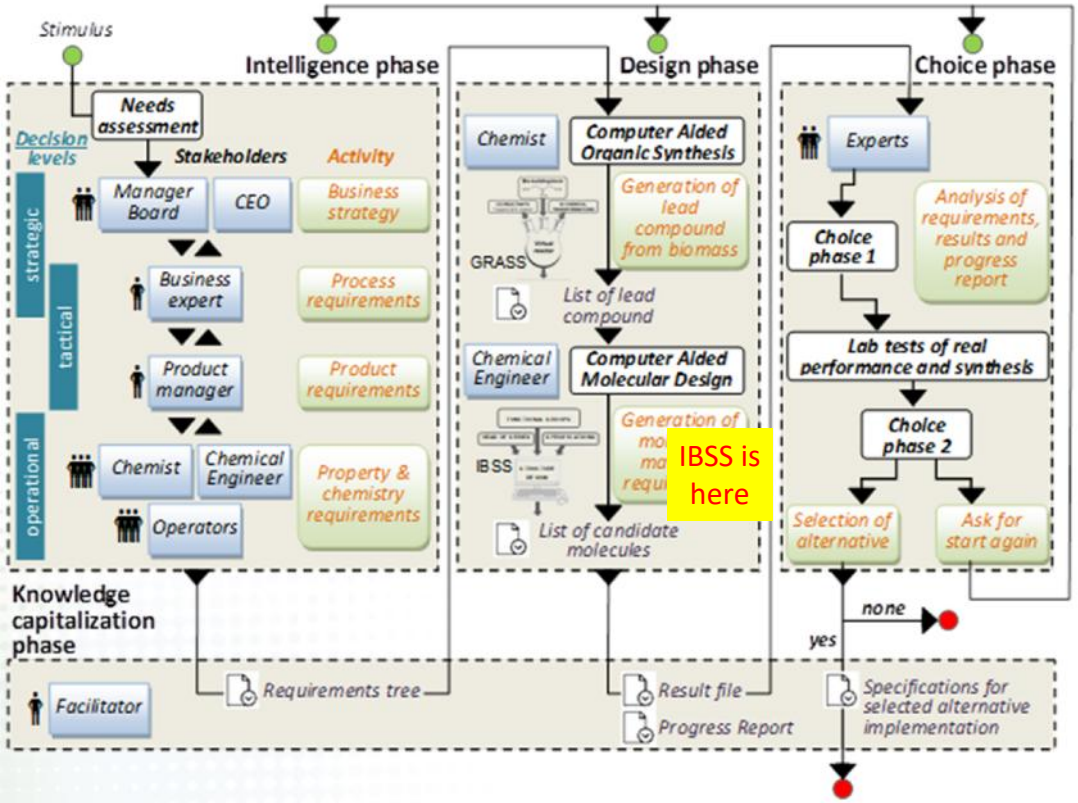


- **For design**
  - Designing molecules or mixtures that match multiple property targets aggregated in a performance function
    - → *explore the chemical world efficiently*
  - Designing molecules from any set of building blocks or biasing the design towards molecules that contain bio-sourced synthons
    - → *design biosourced molecules*
- **For property estimation**
  - Evaluate the performance of a list of molecules with respect to an objective function consisting of multiple property target values.
    - → *estimate never measured properties; compare property model with measured values*
  - Use property prediction models of different accuracy (and computer time) for the same property within a multilevel accuracy scheme
    - → *compare property models*
- **For screening**
  - Find how chemical group & functions impact the performance value (and rule out chemical functions that are the least interesting!)
    - → *get the ideal fingerprint of your future molecule*
  - Find if some chemicals in your company should undergo chemical improvements to match target properties.
    - → *Assess the opportunity to improve the company's portfolio value*

How to properly use IBSS



1. **Gather a panel of field experts for defining requirements and analyzing results**



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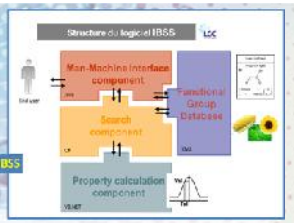
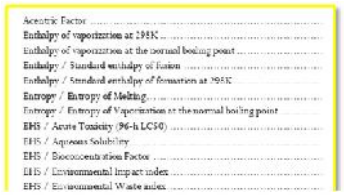
→ Define which properties are important and what are the target values

How to properly use IBSS



2. Run IBSS for screening chemicals with multiple properties

1. Select property prediction models from a library of 39 models



→ set target values (or range)

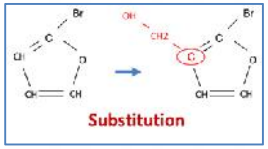
→ define property weights

→ define the performance objective function

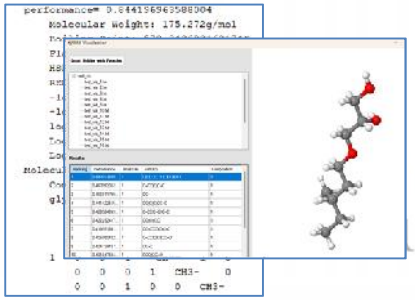
2. Select building blocks from the database

(> 100 chemical groups + > 300 biosourced synthons)

3. Run the search for new structures



4. Analyse results and select the best candidates worth more advanced inverstigation



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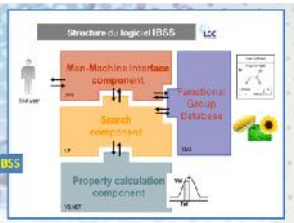

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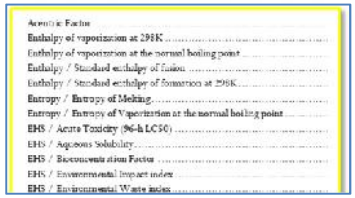


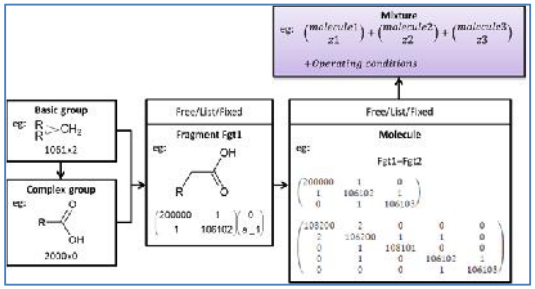
→ set target values (or range)

→ define property weights

→ define the performance objective function

2. Select building blocks from the database and tailor the structure

(> 100 chemical groups + > 300 biosourced synthons)



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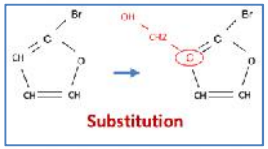

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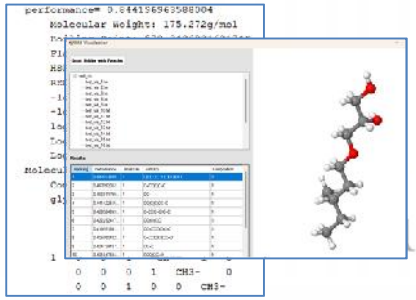

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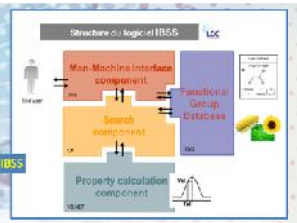


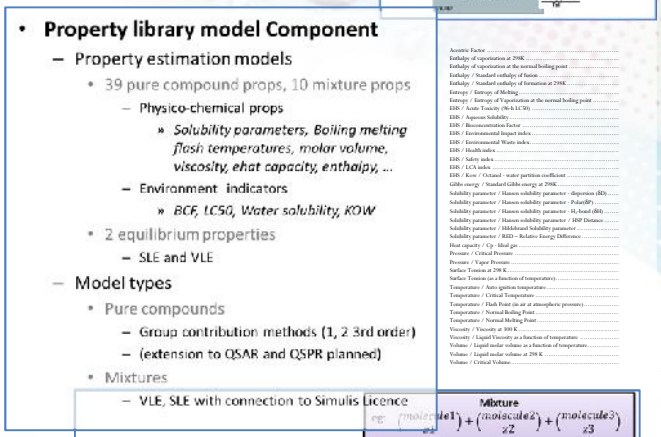
3. Post IBSS:

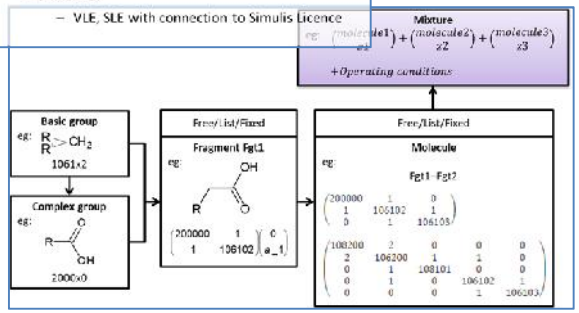
1. Because property prediction (and performance) evaluation can be inaccurate and mixture non linear effects are not accounted by simplest methods,
   - → It is recommended to use advanced prediction methods (eg. VLE thermodynamics calculation, COSMO-RS…) on a selected list of molecules that seem worth more investigation

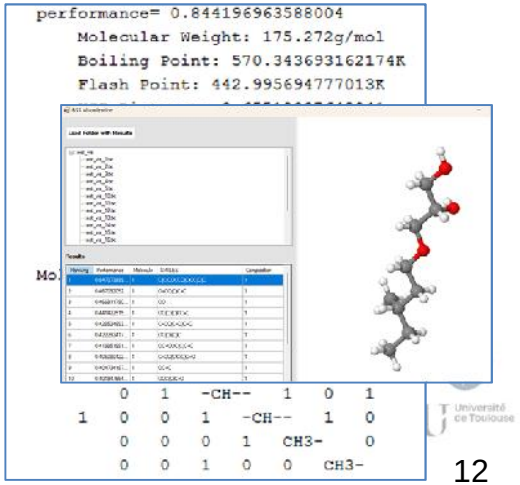
2. Perform experimental validation

IBSS User guide

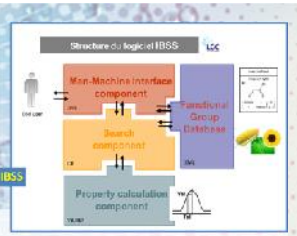
- **What the expert IBSS user can do:**
  - INPUT
    - Tailor the search algorithm parameters
    - Define (and save for later) chemical structures
      - Renewable synthons
      - Building block chemical groups
    - Define (and save for later) mixture parameters
      - Structure of the molecule or of the mixture
        - » *Are some molecules fixed? Are some fragments imposed in a molecules ? What are the list of building blocks to build the fragments?*
    - Define (and save for later) an objective function that is used for computing a performance value
  - OUTPUT
    - Retrieve a list of candidate molecule or mixture
      - Performance, composition, molecular structure, 3D
        - » *e.g.: a molecule improved from the in-house "glycerol29 synthon" with 9 property targets. Performance=84%*







Feedback on IBSS since 2009



- **Case studies**
  - Finding biosourced solvants with low EHS impacts for agroindustry active principles
    - 9 properties (solubilization, surface tension, ... 5 EHS factors)
      - » *Patent: (WO2014132178A2) Furfural derivatives as a vehicle*
  - Finding cooling mixture for airplanes
    - 6 properties working from -55°C to +55°C + nonflammable
      - » *Patents: Coolant mixtures for use in heat-exchange devices in the aerospace field (WO2017216493A1) /// Non-flammable or weakly flammable cooling mixtures, characterised by low relative volatility for two-phase heat-exchange systems (WO2017216492A1)*
  - Finding solvents for perfume industry
    - » *I. Rodriguez-Donis, V. Gerbaud, S. Lavoine, S. Thiebaux-Roux. Computer aided product design of alternative solvents based on phase equilibrium synergism in mixtures. Comptes rendus de Chimie, 21, 606-621, 2018.*
  - Finding greener solvents for photovoltaic panel production
    - » *Wang, J., Rodriguez-Donis, I., Thiebaud-Roux, S., Ibraikulov, O., Leclerc, N., Lévêque, P., Gerbaud, V., Kohlstädt, M., Heiser, T. Selection of green solvents for organic photovoltaics by reverse engineering. Mol. Syst. Des. Eng., 7, 182-195, 2022.*
  - Substituting hexane in metabolite extraction from biomass feedstock
    - » *Nehmeh, M., Rodriguez-Donis, I., Cavaco-Soares A., Evon, P. , Gerbaud, V., Thiebaud-Roux, Bio-refinery of oilseeds: oil extraction, secondary metabolites separation towards protein meal valorisation – A review. Processes, 10(5), 841, 2022.*

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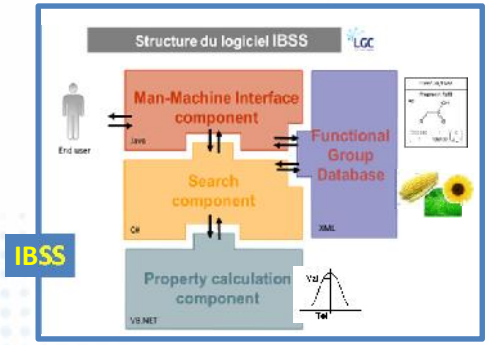
thank you



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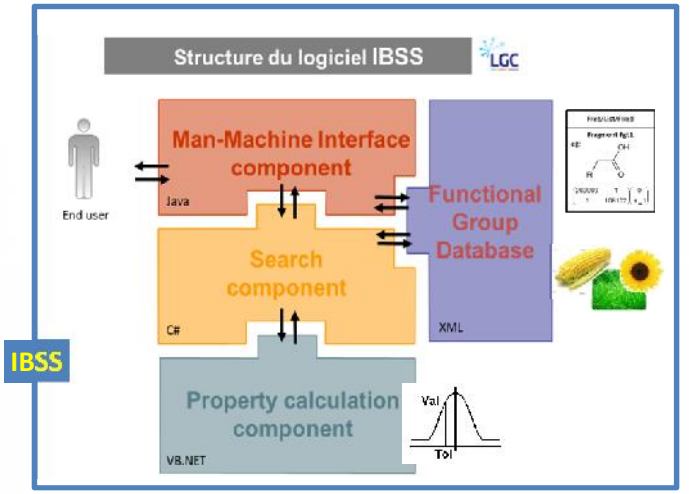
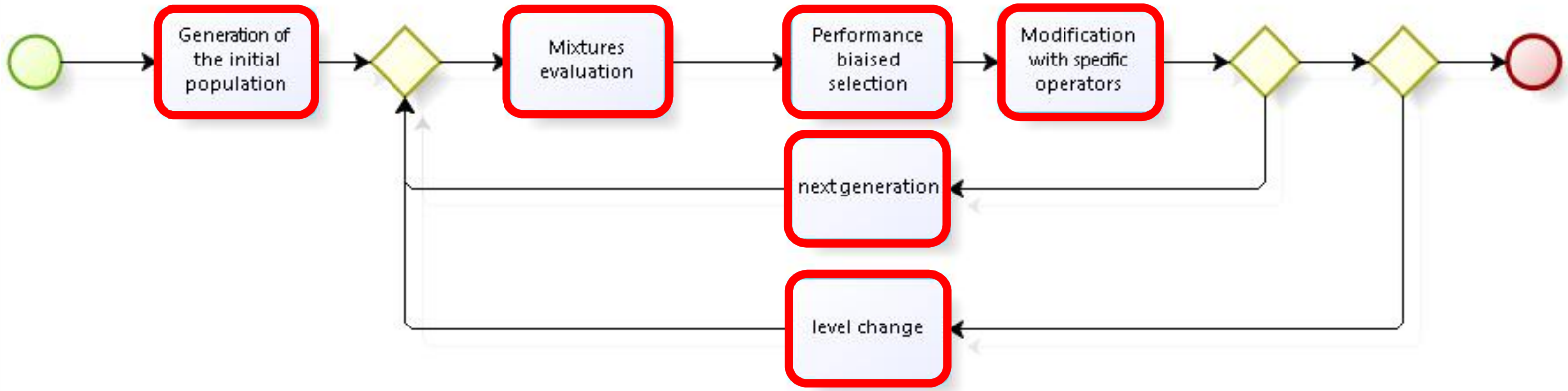
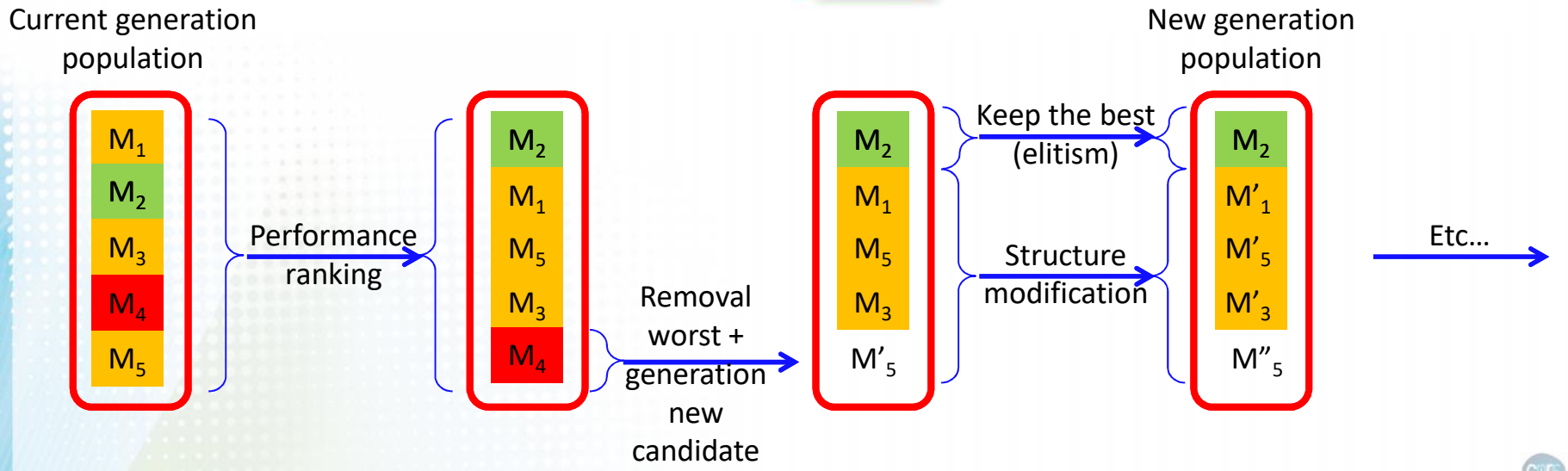
IBSS IN DETAILS



IBSS Computer Aided Mixture Design

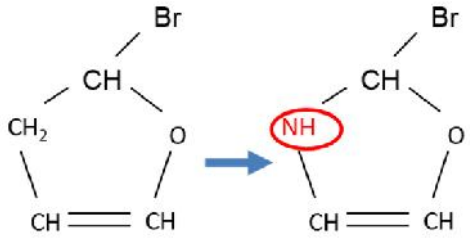
- **SEARCH Component**  **uses a Genetic algorithm**



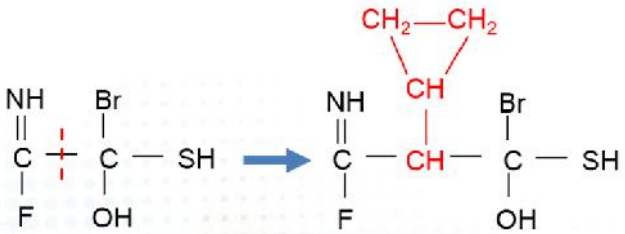


IBSS Computer Aided Mixture Design

- **Operators for modifying molecular structures**

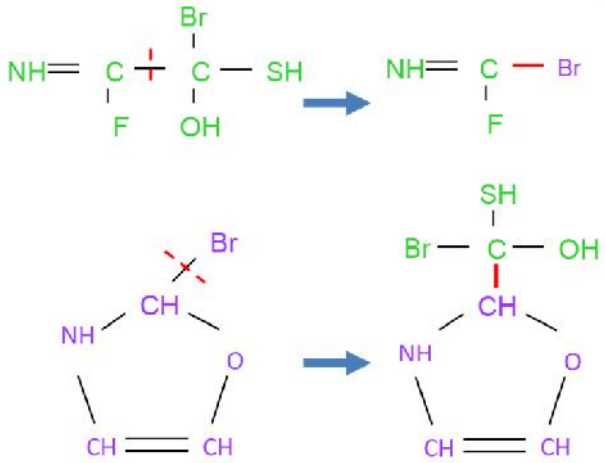


Mutation

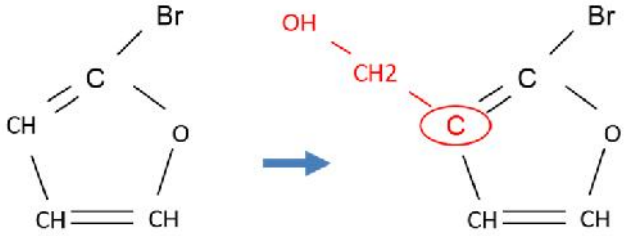


Insertion

Deletion



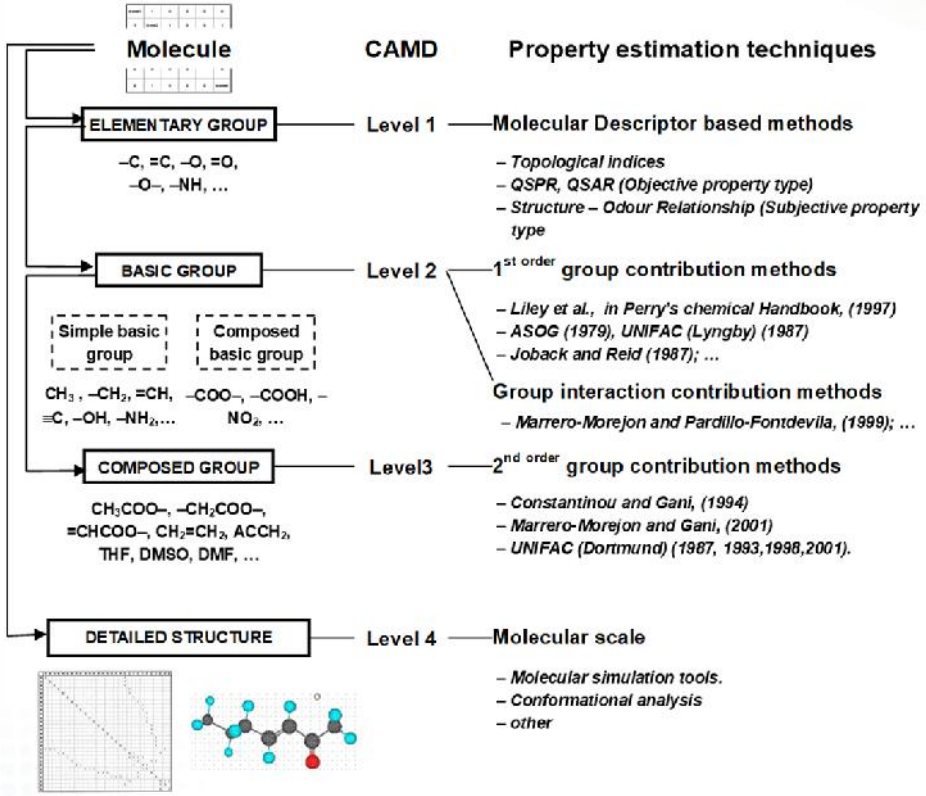
Crossover



Substitution

Review of poperty estimation models

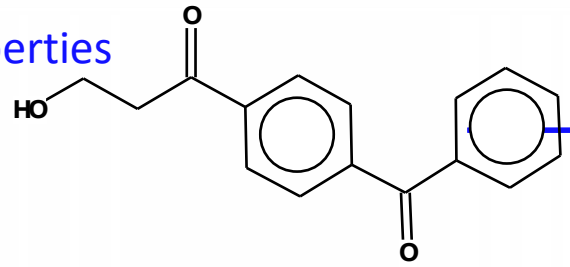
- **Pure compound**



- **Mixture models**
  - Linear mixing rule is rarely good but non linear models are rare!
  - Accurate mixture models require thermodynamic based models
    - Much more computer time demanding and often with dedicated solving strategy -> test in IBSS have concerned small scale problems only.

Molecular representation (ex. chemical groups)

properties



2D structure hypothesis

OCCC(=O)c1ccc(cc1)C(=O)c2ccccc2

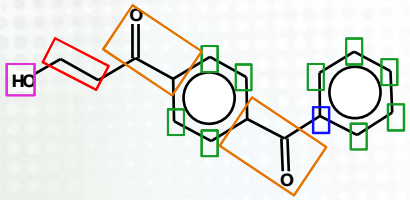
SMILES (*Simplified Molecular-Input Line-Entry System*)

- Prediction of properties f(X) from group contributions

$$f(X) = \sum_i N_i C_i + w \sum_j M_j D_j + z \sum_k E_k O_k$$

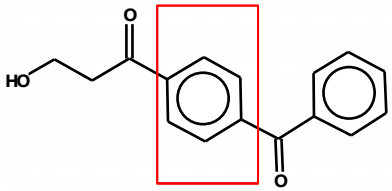
level 1

2 aC-CO
9 aCH
1 aC
1 OH
2 CH2



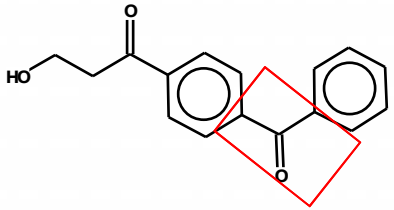
level 2

1 AROMRINGs1s4



level 3

1 aC-CO-aC (different rings)



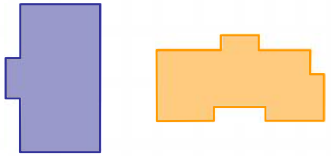
IBSS Computer Aided Mixture Design

- **Property library model Component**
  - Property estimation models
    - 39 pure compound props, 10 mixture props
      - Physico-chemical props
        - » *Solubility parameters, Boiling melting flash temperatures, molar volume, viscosity, ehat capacity, enthalpy, …*
      - Environment indicators
        - » *BCF, LC50, Water solubility, KOW*
    - 2 equilibrium properties
      - SLE and VLE
  - Model types
    - Pure compounds
      - Group contribution methods (1, 2 3rd order)
      - (extension to QSAR and QSPR planned)
    - Mixtures
      - VLE, SLE with connection to Simulis Licence

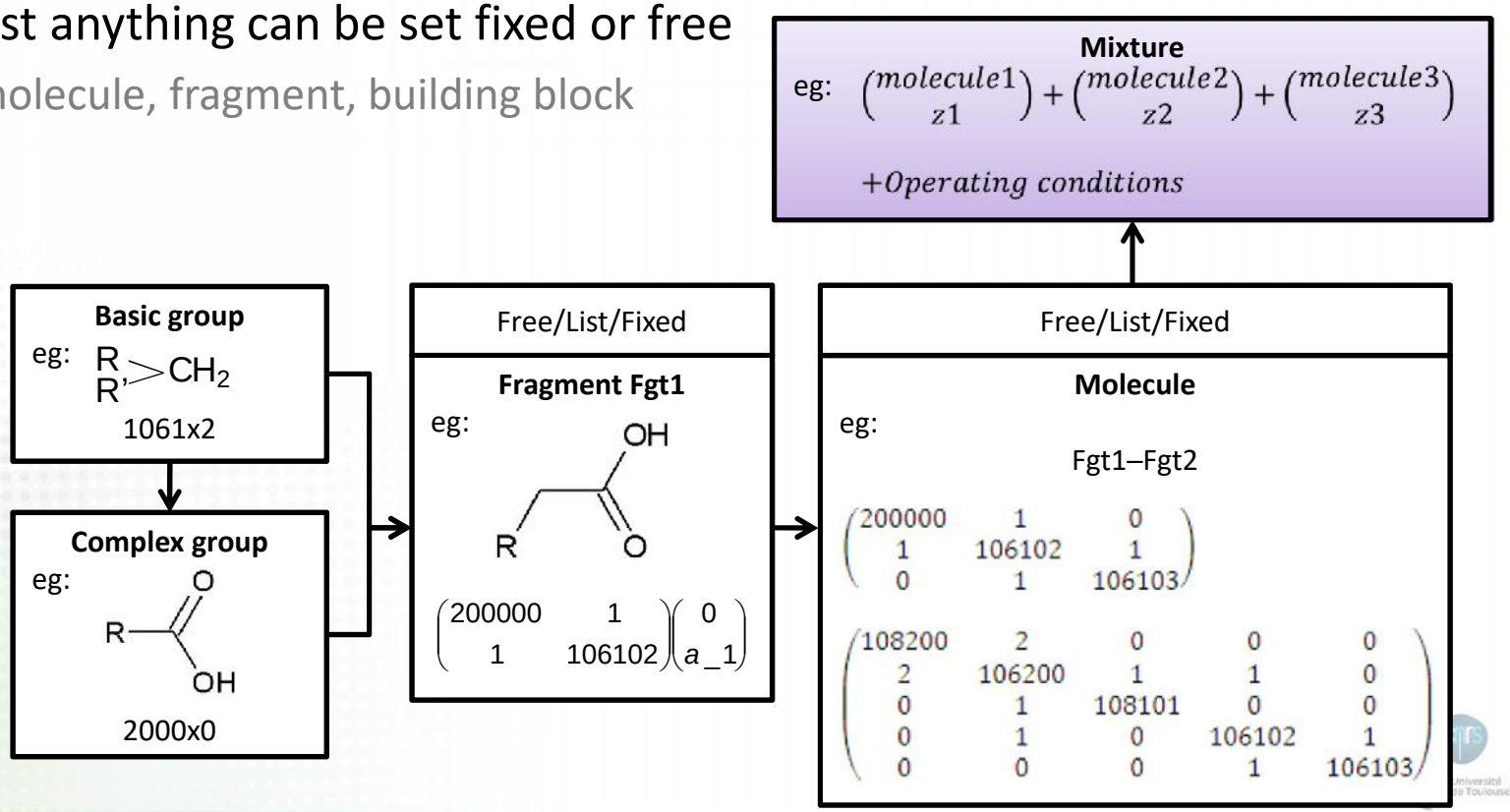
Acentric Factor
Enthalpy of vaporization at 298K
Enthalpy of vaporization at the normal boiling point
Enthalpy / Standard enthalpy of fusion
Enthalpy / Standard enthalpy of formation at 298K
Entropy / Entropy of Melting
Entropy / Entropy of Vaporization at the normal boiling point
EHS / Acute Toxicity (96-h LC50)
EHS / Aqueous Solubility
EHS / Bioconcentration Factor
EHS / Environmental Impact index
EHS / Environmental Waste index
EHS / Health index
EHS / Safety index
EHS / LCA index
EHS / Kow / Octanol - water partition coefficient
Gibbs energy / Standard Gibbs energy at 298K
Solubility parameter / Hansen solubility parameter - dispersion (δD)
Solubility parameter / Hansen solubility parameter - Polar(δP)
Solubility parameter / Hansen solubility parameter - H_2-bond (δH)
Solubility parameter / Hansen solubility parameter / HSP Distance
Solubility parameter / Hildebrand Solubility parameter
Solubility parameter / RED – Relative Energy Difference
Heat capacity / Cp - Ideal gas
Pressure / Critical Pressure
Pressure / Vapor Pressure
Surface Tension at 298 K
Surface Tension (as a function of temperature)
Temperature / Auto ignition temperature
Temperature / Critical Temperature
Temperature / Flash Point (in air at atmospheric pressure)
Temperature / Normal Boiling Point
Temperature / Normal Melting Point
Viscosity / Viscosity at 300 K
Viscosity / Liquid Viscosity as a function of temperature
Volume / Liquid molar volume as a function of temperature
Volume / Liquid molar volume at 298 K
Volume / Critical Volume

IBSS Computer Aided Mixture Design

- **Molecular representation scheme**
  - Developped to allow biased search towards bio sourced molecules
  - Software components concerned are:



  - Almost anything can be set fixed or free
    - molecule, fragment, building block



IBSS Computer Aided Mixture Design

- **Performance evaluation**
  - Components

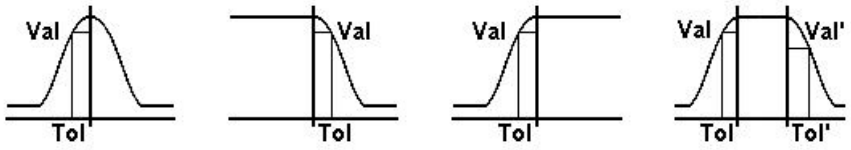
Property
Ex: viscosity,
Solvent power

Mixture estimation model
ex: Tamura et al. 1952

Pure compound estimation model
Ex: Conte et al., 2008

Target
Ex: ϵ [0.8;1.4] cp

Performance Function
ex: Gaussian type

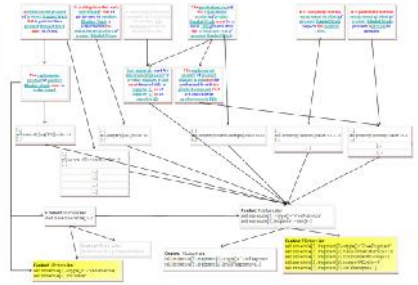


$$GloPerf = \frac{\sum_{p=1}^{np} w_p \cdot PropPerf_p}{\sum_{p=1}^{np} w_p}$$

$$GloPerf = \frac{\prod_{p=1}^{np} w_p \cdot PropPerf_p}{\sum_{p=1}^{np} w_p}$$

IBSS Computer Aided Mixture Design

- **IBSS flowchart and file types**



PDF

Final choice step

txt

IBSS software