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Development of a methodology for the sustainability evaluation of industrial pharmaceutical processes

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Introduction

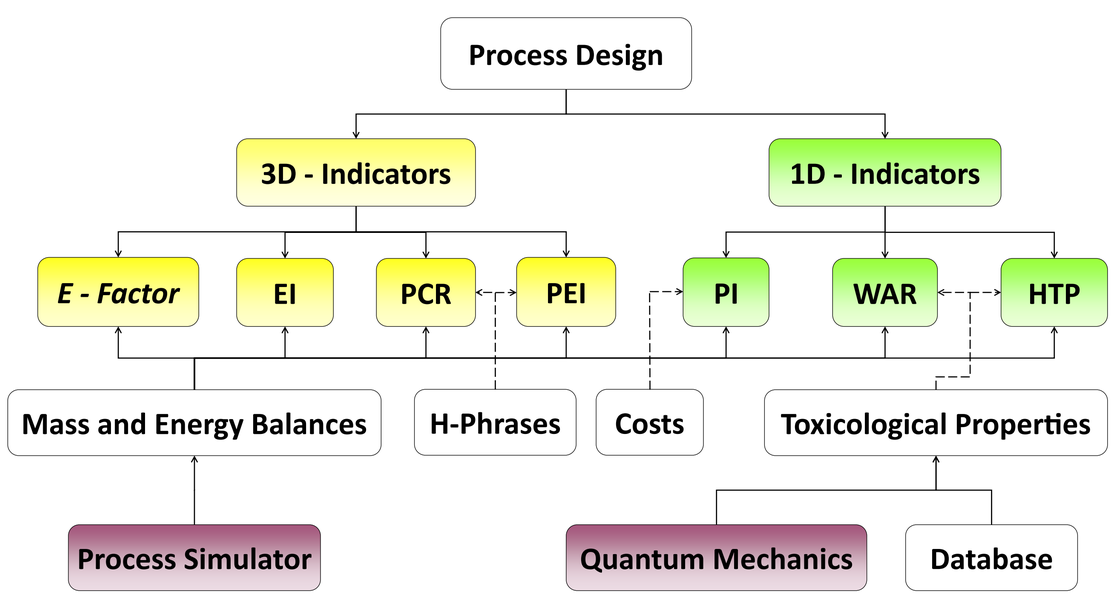
This work extends a general framework for the prediction of industrial sustainability, *i.e.* Process Sustainability Prediction (PSP) Framework proposed by Fermeglia et al. [1] for continuous design processes, implementing features for sustainability evaluation of batch pharmaceutical and biotech industrial processes. The procedure proposed allows a proper selection among different industrial batch plants alternatives employing a broad methodology that comprehend each aspect of sustainability, *i.e.* economy, environment and society. Two categories of sustainability indicators are adopted: three dimensional indicators (3D-indicators), to obtain a global estimation of sustainability performance of process designs, and one dimensional indicators (1D-indicators) to provide a deeper evaluation of each contribution to sustainability. The resulting procedure allows performing a sustainability evaluation on different industrial batch plants alternatives using representative indicators and metrics to identify the most sustainable design.

Sustainability Evaluation Methodology

The methodology proposed by Martins et al. [2], containing 3D-indicators, has been updated, modified and extended including the concept of time, related to discontinuous processes as pharmaceutical ones. The methodology takes into account E-factor (proposed by Sheldon [3]), Energy Intensity (EI), Potential Chemical Risk (PCR) and Potential Environmental Impact (PEI) modified by considering the cycle time of batch reactors and H-Phrases.

The 3D-indicators are calculated using the results obtained from process simulation coupled with a toxicological database, containing data from EPA, other sources, and an in-house procedure for the estimation of toxicological properties based on molecular modelling.

One dimensional indicators are focused on single contribution to sustainability, *e.g.* Waste Reduction Algorithm (WAR) [4] focused on environmental issues, Profit Intensity, an index based on Materials Intensity [2] and modified to inspect economic aspects, and HTP (Hazard Toxicity Potential) developed to define the hazard risks for employers inside the chemical plant.



3D - Indicators

Three dimensional evaluation provides an overview of sustainability performance of process design under study, taking into account all contribution to sustainability at once.

E-Factor

E-factor evaluates the yield of the process in terms of raw materials consumption.

$$E = \frac{mass\ of\ raw\ materials - mass\ of\ desired\ product}{mass\ of\ desired\ product}$$

Energy Intensity (EI)

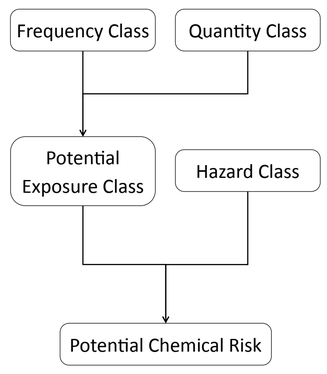
Energy Intensity takes into account the performance from an energetical point of view focusing on non-renewable sources consumption.

$$EI = \frac{mass\ fuels_{nonrenewable}\ equivalent}{output}$$

$$output = \frac{mass\ of\ product + mass\ of\ saleable\ coproducts}{mass\ of\ product}$$

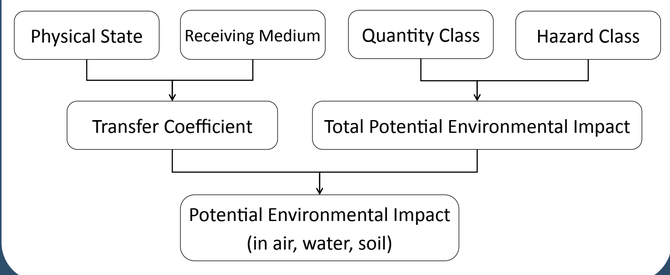
Potential Chemical Risk (PCR)

Potential Chemical Risk (Vincent et al. [5]) analizes the human health risk related to hazardous chemicals inside the industrial plant. Each chemical is assigned to a series of classes, depending on frequency of usage, quantity adopted and hazard related to each chemical. The final value is the result of the sum of PCR specifical for each substance.



Potential Environmental Impact (PEI)

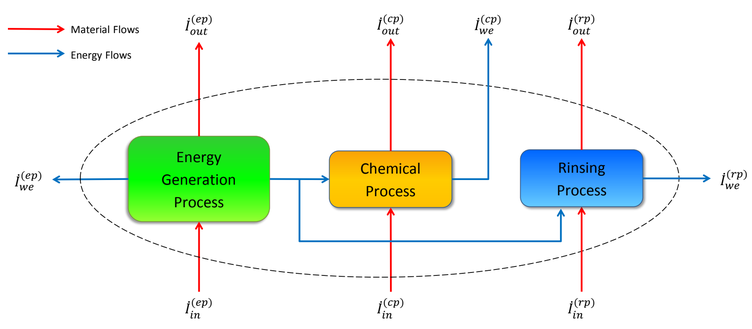
Potential Environmental Impact [5] inspects the environmental issues due to polluting chemicals. The procedure to calculate the final score is the same as the one adopted for PCR evaluation, following a series of assignments to classes for each chemical within the process. Physical state of substances has to be defined to address the impact on different medium.



1D - Indicators

Waste Reduction (WAR) Algorithm

The Waste Reduction Algorithm (Young and Cabezas, [4]) calculation starts from mass and energy balances and toxicological properties of chemicals involved. The methodology has been modified in order to include the time of charge, reaction and discharge of chemicals from reactor and the introduction of new substances for rinsing, which is a more common operation in discontinuous processes than in continuous ones.

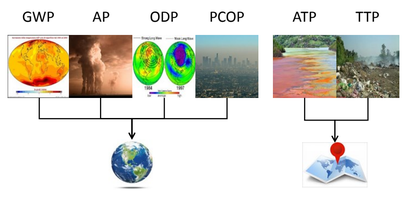


$$i_{out}^{(t)} = i_{out}^{(cp)} + i_{out}^{(ep)} + i_{out}^{(rp)} + i_{we}^{(cp)} + i_{we}^{(ep)} + i_{we}^{(rp)}$$

$$\dot{i}_{out}^{(t)} = \frac{i_{out}^{(cp)} + i_{out}^{(ep)} + i_{out}^{(rp)} + i_{we}^{(cp)} + i_{we}^{(ep)} + i_{we}^{(rp)}}{\sum_p \dot{P}_p}$$

$$i_{gen}^{(t)} = i_{out}^{(cp)} - i_{in}^{(cp)} + i_{out}^{(ep)} - i_{in}^{(ep)} + i_{out}^{(rp)} - i_{in}^{(rp)} + i_{we}^{(cp)} + i_{we}^{(ep)} + i_{we}^{(rp)}$$

$$\dot{i}_{gen}^{(t)} = \frac{i_{out}^{(cp)} - i_{in}^{(cp)} + i_{out}^{(ep)} - i_{in}^{(ep)} + i_{out}^{(rp)} - i_{in}^{(rp)} + i_{we}^{(cp)} + i_{we}^{(ep)} + i_{we}^{(rp)}}{\sum_p \dot{P}_p}$$



Hazard Toxicity Potential (HTP)

Hazard Toxicity Potential evaluates the social contribution to sustainability using a one dimensional perspective. It is focused on hazards related to adoption of chemicals within the chemical plant. Scores come from OSHA TWA values, LD50 or other Threshold limit values sources.

$$HTP = \sum_k mass_k * (Score_k^{HTPI} + Score_k^{HTPE})$$

Profit Intensity (PI)

Profit Intensity provides an estimation on economic aspects of sustainability in order to get a hint about the profit related to process alternatives. The mass of each chemical involved in inlet and outlet streams and the price of the relative substance is compulsory for the calculation.

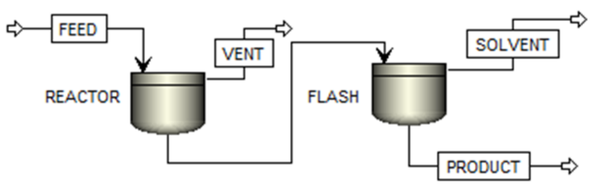
$$PI = \frac{\sum_i (m_i^{in} * price_i) - \sum_i (m_i^{out} * price_i)}{output}$$

$$output = \frac{\sum_i (m_i^{out} * price_i)}{mass\ of\ desired\ product * price}$$

Case study

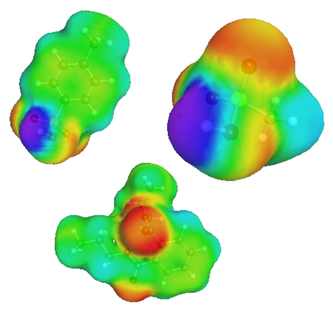
The methodology proposed has been validated performing the sustainability evaluation on two different batch process designs for the esterification of phthalic acid with propanol. The reactants are mixed in a batch reactor with a different catalysts for each alternative: methanesulfonic acid (Design A) and p-toluenesulfonic acid (Design B) keeping constant the molar ratio between phthalic acid and catalyst. The chemical plant of two unit operations consists in a batch reactor in which esterification occurs for 24 hours, followed by a flash for the separation of the mixture. During esterification a vent stream removes water in excess, moving the equilibrium reaction towards products.

The process has been simulated in AspenPlus environment in order to obtain mass and energy balances. The energy consumption is equal for both alternatives and has been calculated as 465 kW/hr.



		Design A				Design B			
Chemical	*Units*	*Feed*	*Vent*	*Solvent*	*Products*	*Feed*	*Vent*	*Solvent*	*Products*
phthalic acid	kg/hr	1000	0	0	0.19	1000	0	0	0.57
n-propanol	kg/hr	3000	1770.8	480.32	27.09	3000	1775.1	480.09	24.52
methanesulfonic acid	kg/hr	115.7	0.02	0.03	115.65	0	0	0	0
p-toluenesulfonic acid	kg/hr	0	0	0	0	207.3	5.58	32.34	169.39
water	kg/hr	0	205.42	10.86	0.08	0	204.33	11.53	0.06
dipropyl phthalate	kg/hr	0	0.39	0.19	1499.17	0	0.38	0.19	1493.61

The estimation of logKow using COSMO-RS has been performed to retrieve missing data.



Chemical	*logKow*
phthalic acid	0.950
1-propanol	0.547
methanesulfonic acid	-0.666
p-toluenesulfonic acid	1.885
dipropyl phthalate	2.564

Results and Conclusions

3D - Analysis

	E-Factor	*EI*	*PCR*	*PEI*
Design A	1.7453	334.4525	430303	4935
Design B	1.8169	335.6975	460003	5285
Variation AB	+4.10%	+0.37%	+6.90%	+7.09%

Design A arises as the most sustainable alternative as it scores a lower value for each index among 3-D indicators. This is due to the lower molecular weight of methane-sulfonic acid, therefore a lower amount of catalyst is needed to keep the same molar ratio reactant/catalyst.

1D - Analysis

	Design A	*Design B*	*Variation AB*
$i_{out}^{(t)}$	49898.26	50078.54	+0.36%
$\dot{i}_{out}^{(t)}$	33.2710	33.5157	+0.74%
$i_{gen}^{(t)}$	46586.92	46582.87	-0.01%
$\dot{i}_{gen}^{(t)}$	31.0631	31.1762	+0.36%

The alternatives show a comparable contribution in terms of environmental impact, a little higher for Design B. This is due to the similar behavior of the two catalyst in terms of environmental issues.

	Design A	*Design B*	*Variation AB*
HTP	1024.8424	1003.1082	-2.12%
PI	-4,509,794	-4,461,821	+1.06%

HTP for Design A is higher than HTP for Design B due to the lower LD_{50} value for methanesulfonic acid. A chemical with a higher LD_{50} represents a substance with lower toxicity thus HTP indicator points out that Design B is more social sustainable than Design A. Design A is the most profitable due to a higher yield of reaction therefore Design A scores a lower value on index PI.

References

[1] Fermeglia M., Toma L. (2009). Computer Aided Design for Sustainable Industrial Processes: Specific Tools and Applications. IFAC Proceedings Volumes (IFAC-PapersOnline), 7(PART 1), 405–410.

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[3] Sheldon, R. A. (1992). Organic synthesis - past, present, and future. Chem. and Ind.-London, 903–906.

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