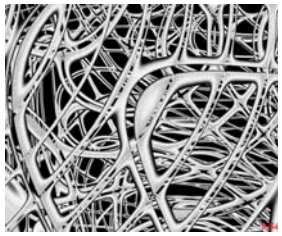
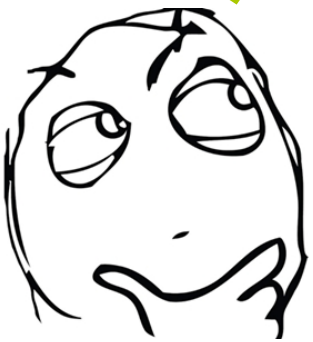
Les modèles thermodynamiques prédictifs face au défi des bioprocédés

Rafael Lugo, Jean-Charles de Hemptinne





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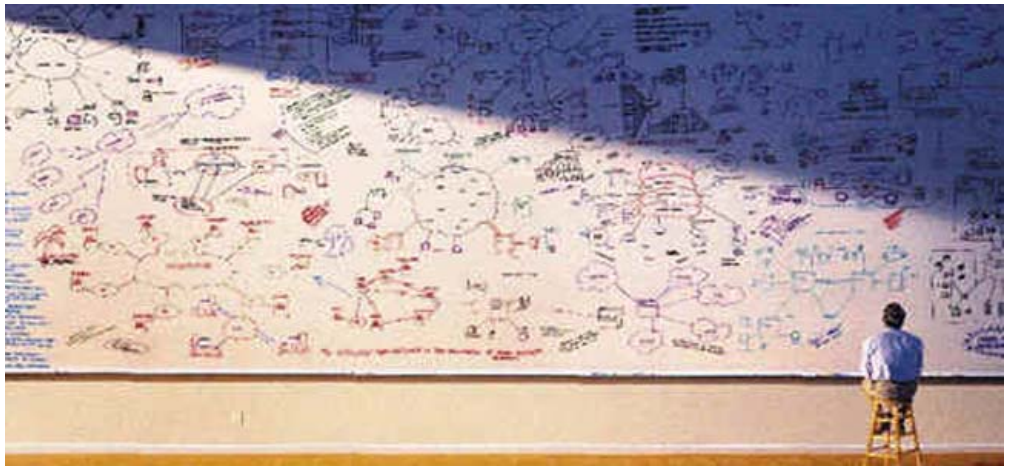
Avant propos

Rigorous application of thermodynamics to bioprocesses may clearly be seen as a daunting task in view of the astronomical complexity of the reaction mixtures, giant biological molecules, intramolecular forces, multiple driving forces and the multitude of phases and biological, chemical and physical processes, which have to be dealt with. However, rational, efficient and rapid process development and equipment design can only be achieved on the basis of a sound scientific foundation, as it is available nowadays, e.g. for the petrochemical industries. The more extensive

Von Stockar & van der Wielen, 1997

The generality and versatility of thermodynamics allow application to all materials, no matter how complex. Those who seek new applications of thermodynamics need not exclude biomacromolecules; they too are subject to the laws of thermodynamics.

Dey & Prausnitz, 2011



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Ordre du jour

- A quoi sert un modèle prédictif ?
- L'exemple du génie chimique / génie pétrolier
  - Des états correspondants aux équations d'état cubiques avec règles de mélange complexes … et au-delà
- Les « nouvelles » approches thermodynamiques
  - Les équations SAFT et l'exemple de GC-PPC-SAFT
  - Les approches COSMO
  - Le modèle NRTL-SAC
- Quelques exemples d'application dans le domaine biotechnologies / bioprocédés
- Perspectives

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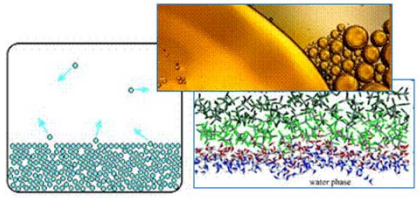
A quoi sert un modèle prédictif ?

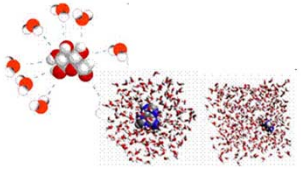
Qu'est-ce qu'un <u>modèle thermodynamique prédictif</u> ?

- Modèles prédictifs
  - Modèle théorique sans ajustement ou ajusté sur un minimum de données et utilisable (en *P*, *T* , *x* ou sur un large spectre de molécules) au-delà de la base d'ajustement (extrapolation)
  - Un modèle empirique ajusté sur les données disponibles aura une applicabilité fortement limitée.
  - Pour extrapoler, pour faire du criblage, pour faire une estimation … on préférera des approches prédictives
  - Si besoin de précision, on ajustera …
- Les modèles 100% prédictifs n'existent pas
  - Plus bases théoriques sont fortes, moins on a besoin d'ajustement

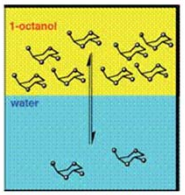


Phase equilibria (VLE, LLE, …SLE)

Solubility



Solvation, hydration



Partition coefficients

De quels <u>modèles</u> dispose-t-on pour <u>prédire</u> le comportement thermodynamique ?

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L'exemple du génie chimique : les états correspondants

5. The complete expansion of Eq. (3.50) shows all the molecular parameters which may be needed for a reduced equation of state for fluids deviating from the simple corresponding-states principle. This equation is represented by:

$T_r = T/T_c$

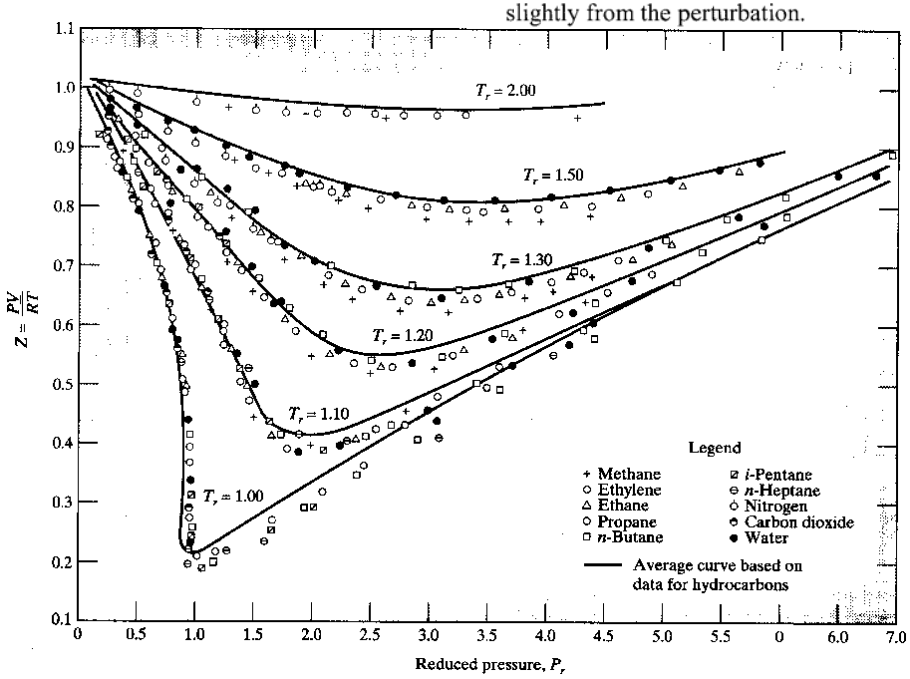
$P_r = P/P_c$

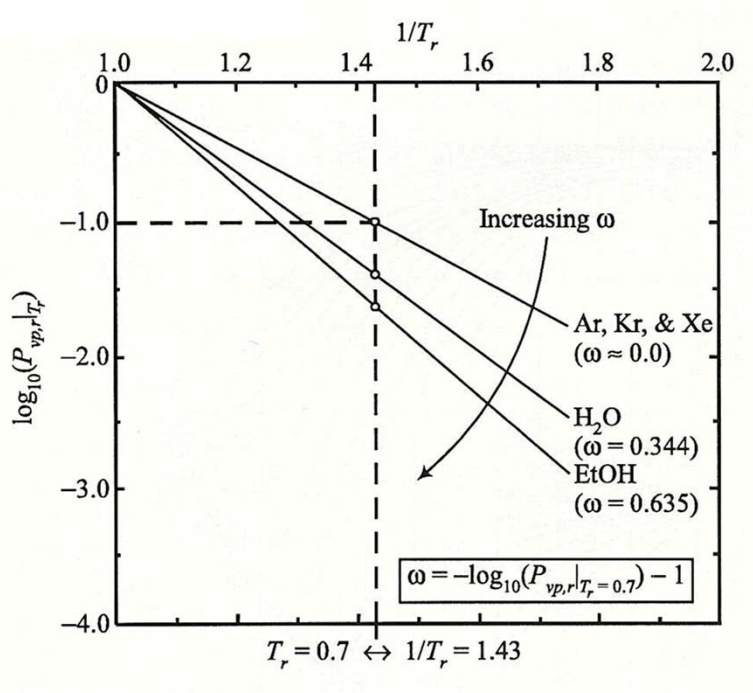
$$Z = f\left(\frac{\varepsilon_0}{kT}, \frac{Nr_0^3}{V}, \frac{\mu^2}{\varepsilon_0 r_0^3}, \frac{\theta^2}{\varepsilon_0 r_0^5}, \kappa\frac{\bar{\alpha}}{r_0^3}, \frac{\mu^2\bar{\alpha}}{\varepsilon_0 r_0^6}, \frac{\mu^2\theta^2}{\varepsilon_0 r_0^8} \cdots\right). \qquad (3.54)$$

P_c

T_c

The $\bar{\alpha}/\sigma_0^3$ term enters from an Axilrod-Teller (1943) nonadditivity correction to three-body interactions, and not directly from the perturbation treatment. The reduced $\mu^2\bar{\alpha}$ term arises chiefly from the three-body second term, and only slightly from the perturbation.





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L'exemple du génie chimique : les équations d'état cubiques

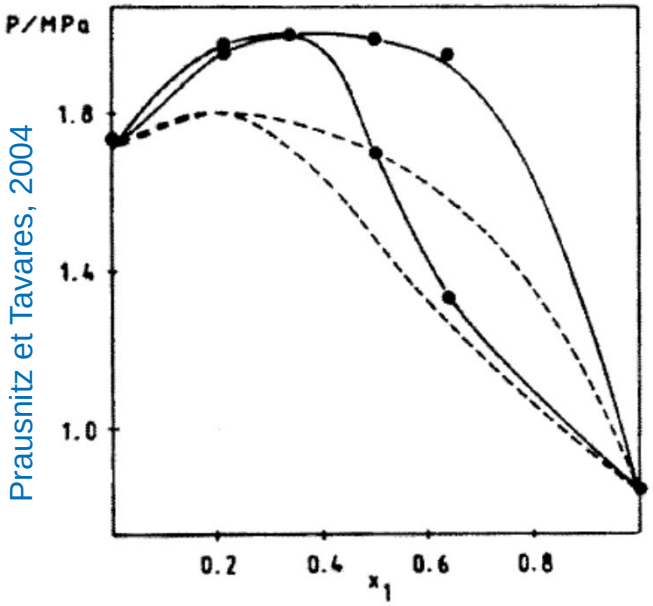
$$P = \frac{RT}{v-b} - \frac{a(T)}{v(v+b)}$$ Peng-Robinson

$$P = \frac{RT}{v-b} - \frac{a(T)}{v(v+b)+b(v-b)}$$ Soave-Redlich-Kwong

$$a = f(T_c, P_c, \omega) \qquad b = f(T_c, P_c)$$

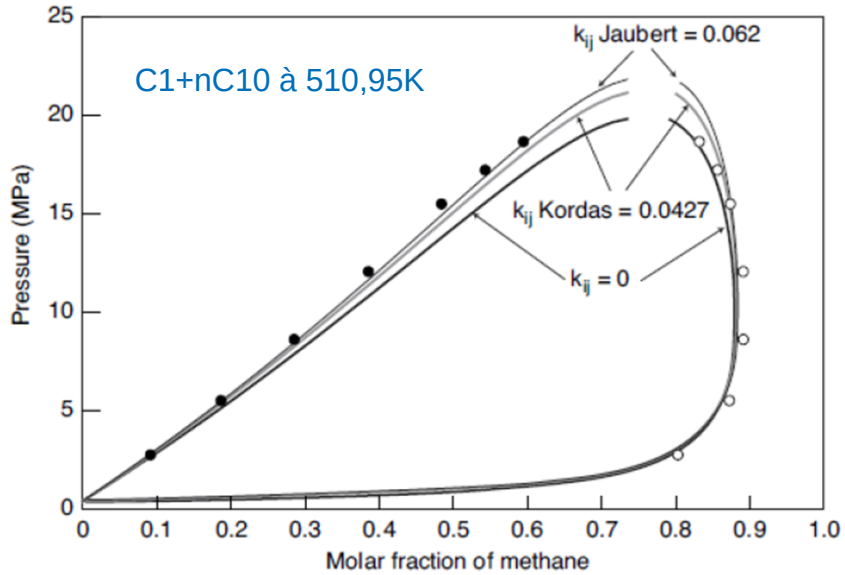
$$a = \sum_i \sum_j x_i x_j \sqrt{a_i a_j}\left(1-k_{ij}\right)$$

$$b = \sum_i x_i b_i$$



Prausnitz et Tavares, 2004

Figure 18. Calculated and experimental VLE for sulfur dioxide (1)-propane (2) at 50 °C.



http://books.ifpenergiesnouvelles.fr/ebooks/thermodynamics/04/exo_04_04.html

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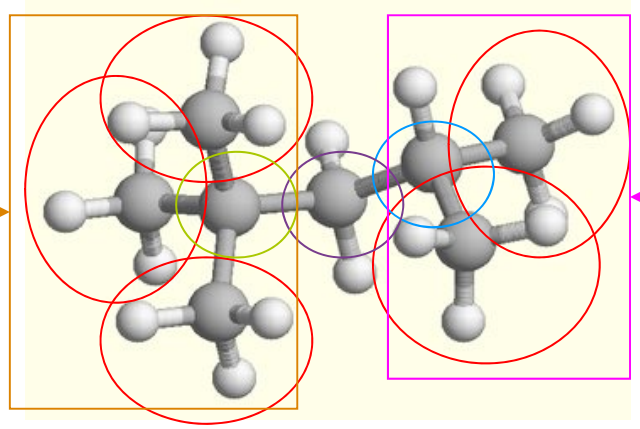
L'exemple du génie chimique : d'où viennent les Tc, Pc et ω?

Si les molécules ne sont pas renseignées dans les BdD, on utiliser les **méthodes de contribution de groupes**

$$f(X) = \sum_i N_i C_i + w \sum_i M_i D_i + z \sum_i O_i E_i$$

1er ordre 2nd ordre 3ème ordre

Les méthodes de Marrero-Gani (2001) sont parmi les plus utilisées pour estimer les Tc, PC et ω des molécules (hydrocarbures, oxygénées, soufrées, azotées).



1er ordre

1x C	-0,0671
1x CH	0,2925
1x CH_2	0,7141
5x CH_3	0,8491
	5,185

2nd ordre

$(CH_3)_2CH$-	-0,0035
$(CH_3)_3C$-	0,0072

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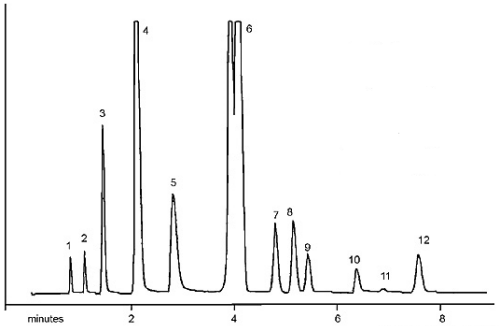
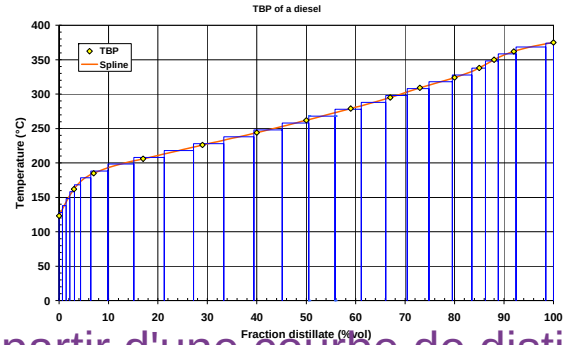
L'exemple du génie chimique : quid des charges complexes ?



On identifie les constituants majoritaires par des techniques analytiques GC, GC2D, a...)



A partir d'une courbe de distillation, on identifie des pseudo-constituants par classe de volatilité

→Le génie chimique pétrolier dispose ainsi d'une palette d'outils ayant atteint une grande maturité et permettant de traiter un spectre large de fluides pétroliers …

→La raison du succès tient à ce que cette thermodynamique est focalisée sur la description et la restitution de la **volatilité**

→C'est aussi l'une de ses limites puisque les **non idéalités de la phase liquide** sont fortement sous estimées !

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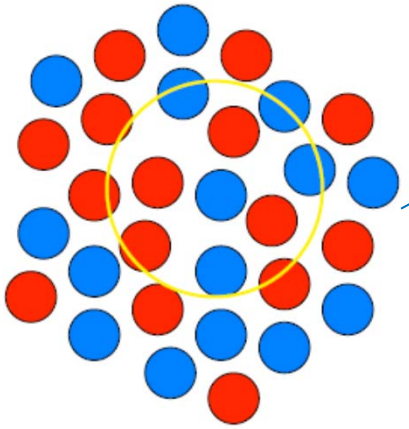
L'exemple du génie chimique : les non idéalités de la phase liquide



Composition locale différente de la composition globale en raison des interactions spécifiques (e.g. polarité, liaisons hydrogène, …)

Wilson

$$\ln\gamma_1 = -\ln(x_1 + \Lambda_{12}x_2) + x_2\left[\frac{\Lambda_{12}}{x_1 + \Lambda_{12}x_2} - \frac{\Lambda_{21}}{\Lambda_{21}x_1 + x_2}\right]$$

$$\ln\gamma_2 = -\ln(x_2 + \Lambda_{21}x_1) - x_1\left[\frac{\Lambda_{12}}{x_1 + \Lambda_{12}x_2} - \frac{\Lambda_{21}}{\Lambda_{21}x_1 + x_2}\right]$$

$$\ln\gamma_1 = \ln\frac{\Phi_1^*}{x_1} + \frac{z}{2}q_1\ln\frac{\theta_1}{\Phi_1^*} + \Phi_2^*\left(l_1 - \frac{r_1}{r_2}l_2\right) - q'_1\ln(\theta'_1 + \theta'_2\tau_{21}) + \theta'_2 q'_1\left(\frac{\tau_{21}}{\theta'_1 + \theta'_2\tau_{21}} - \frac{\tau_{12}}{\theta'_2 + \theta'_1\tau_{12}}\right)$$

$$\ln\gamma_2 = \ln\frac{\Phi_2^*}{x_2} + \frac{z}{2}q_2\ln\frac{\theta_2}{\Phi_2^*} + \Phi_2^*\left(l_2 - \frac{r_2}{r_1}l_1\right) - q'_2\ln(\theta'_2 + \theta'_2\tau_{12}) + \theta'_1 q'_2\left(\frac{\tau_{12}}{\theta'_2 + \theta'_1\tau_{12}} - \frac{\tau_{21}}{\theta'_1 + \theta'_2\tau_{21}}\right)$$

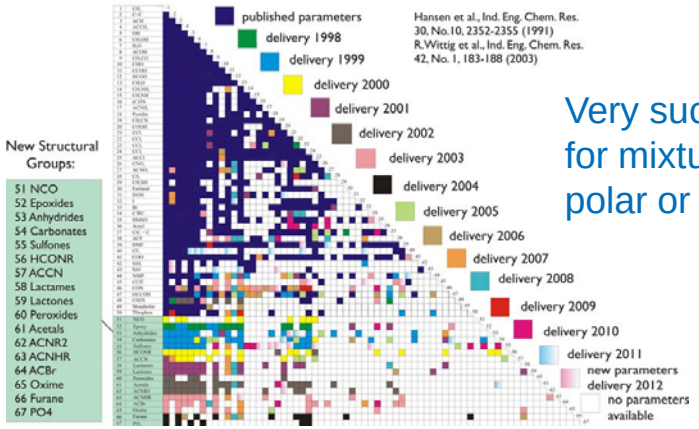
NRTL

$$\ln\gamma_1 = x_2^2\left[\tau_{21}\left(\frac{G_{21}}{x_1 + x_2G_{21}}\right)^2 + \frac{\tau_{12}G_{12}}{(x_2 + x_1G_{12})^2}\right]$$

$$\ln\gamma_2 = x_1^2\left[\tau_{12}\left(\frac{G_{12}}{x_2 + x_1G_{12}}\right)^2 + \frac{\tau_{21}G_{21}}{(x_1 + x_2G_{21})^2}\right]$$

UNIQUAC

UNIFAC : group contribution model



Very succesful predictive model for mixtures containing polar or associating molecules

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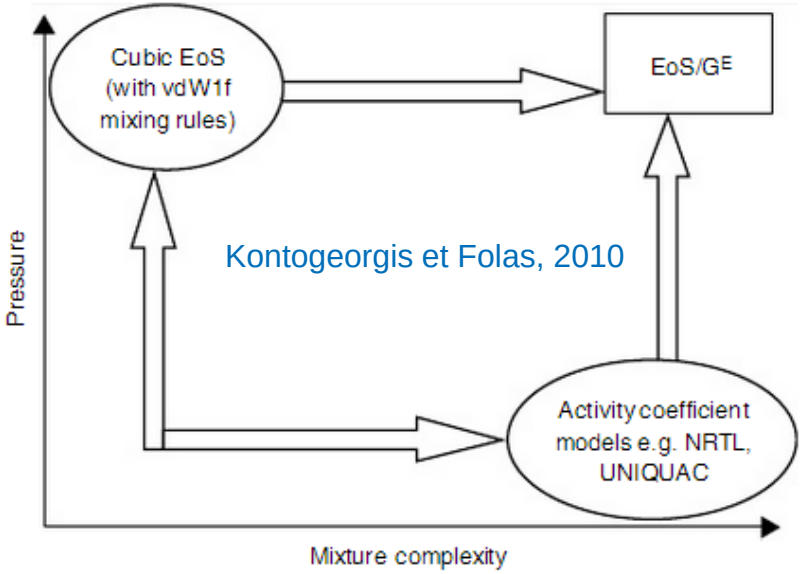
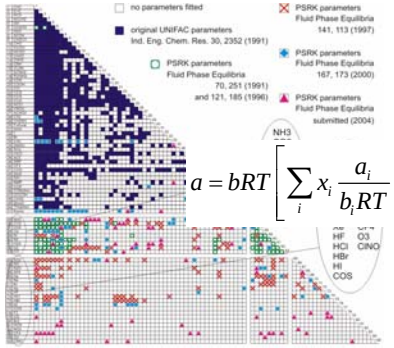
L'exemple du génie chimique : les équations d'état prédictives



Règles de mélange d'Huron-Vidal, Wong-Sandler, MHV1, MHV2, …



PSRK

$$a = bRT\left[\sum_i x_i \frac{a_i}{b_i RT} + \frac{1}{A_0}\left(\frac{G^E}{RT} + \sum_i x_i \ln\left(\frac{b}{b_i}\right)\right)\right]$$

$$P = \frac{R \cdot T}{v + c - b} - \frac{\alpha \cdot a(T)}{(v + c) \cdot (v + c + b) + b \cdot (v + c - b)}$$

VTPR $\quad g^E_{res} = R \cdot T \cdot \sum x_i \cdot \ln \gamma_{res,i}$

PPR78

$$k_{ij}(T) = \frac{-\frac{1}{2}\sum_{k=1}^{N_g}\sum_{\ell=1}^{N_g}(\alpha_{ik} - \alpha_{jk}) \cdot (\alpha_{i\ell} - \alpha_{j\ell}) A_{k\ell}\left(\frac{298{,}15}{T/K}\right)^{\left(\frac{B_{k\ell}}{A_{k\ell}} - 1\right)} - \left(\frac{\sqrt{a_i}}{b_i} - \frac{\sqrt{a_j}}{b_j}\right)^2}{2\frac{\sqrt{a_i \cdot a_j}}{b_i \cdot b_j}}$$

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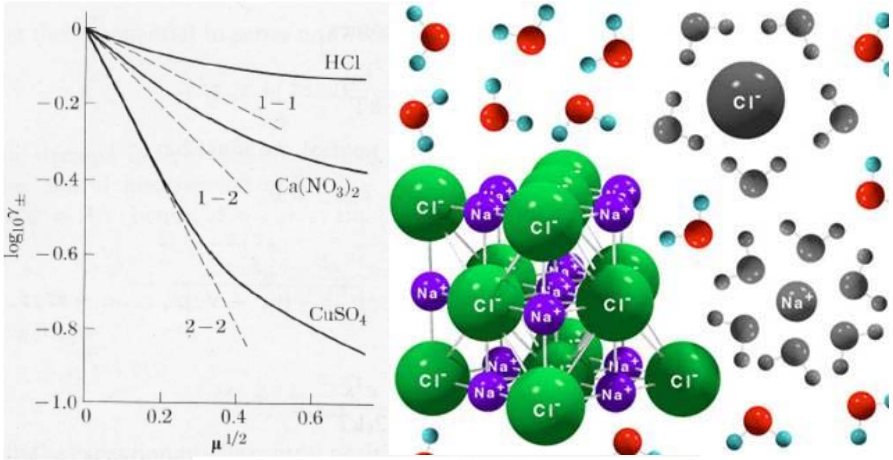
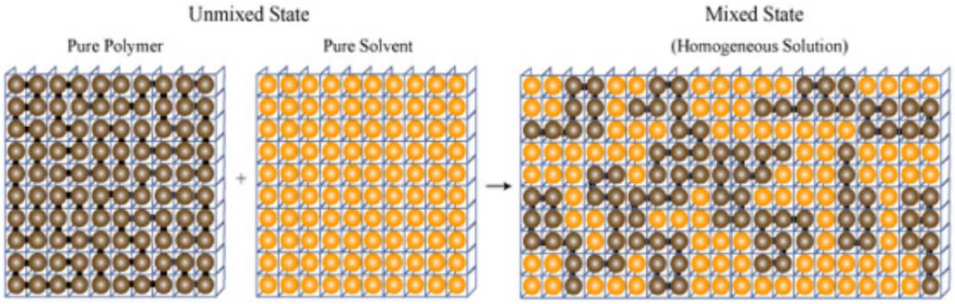
L'exemple du génie chimique : autres systèmes complexes



$$\ln \gamma_{\pm} = 2.303 \log \gamma_{\pm} = A' \sqrt{I} z_{+} z_{-}.$$

Electrolytes

Loi de Debye-Hückel



Polymères

Théorie de Flory-Huggins

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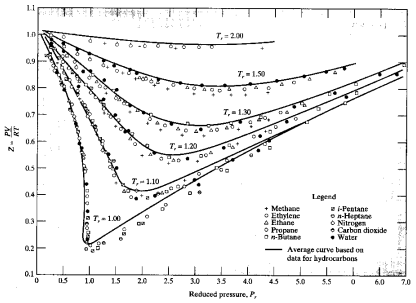
Nouvelles approches thermodynamiques : introduction

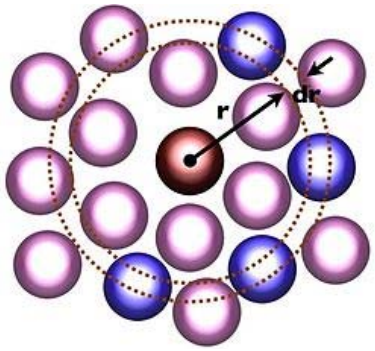
e.g. Etats correspondants

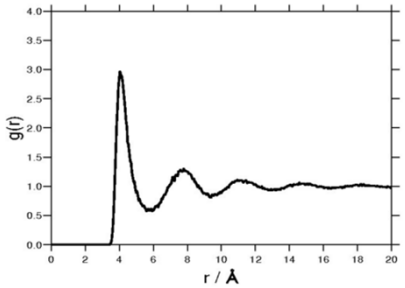
Conformal solution theory



Théorie des phases fluides

Perturbation theory





L'énergie libre de Helmholtz est obtenue en « corrigeant » le comportement d'un fluide de référence avec des perturbations qui dépendent de g(r)

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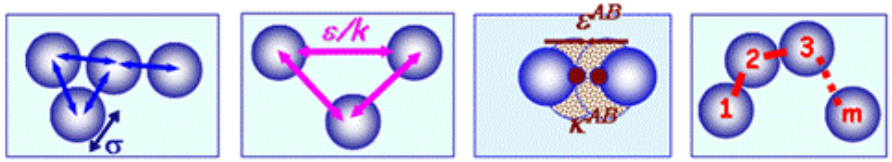
Nouvelles approches thermodynamiques : la famille des équations SAFT

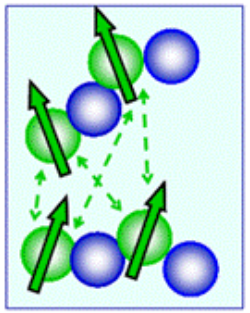
- Les équipes du LSPM et d'IFPEN développent depuis plusieurs années une version polaire de SAFT

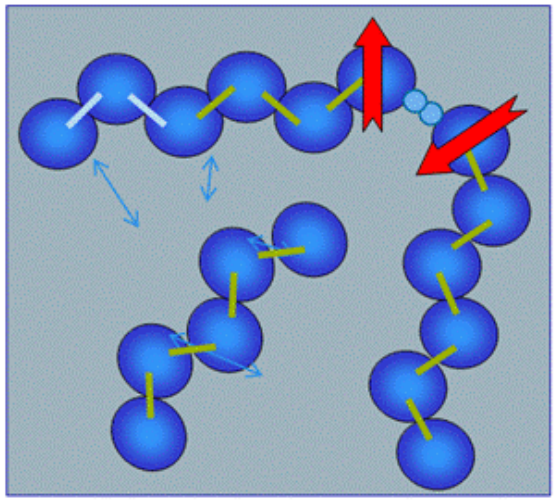
SAFT – Statistical Associating Fluid Theory

$$\frac{A - A^{\circ}}{NkT} = m\left(a^{hs} + a^{disp}\right) + a^{assoc} + a^{chain} + a^{polaire/polarisable}$$



répulsion attraction association terme de chaîne





PC-SAFT – Perturbed Chain (Gross & Sadowski, 2001)
GC-SAFT – Group Contribution (Tamouza, 2004)
PPC-SAFT – Polar Perturbed Chain (Nguyen-Huynh, 2009)
ePPC-SAFT – electrolytes version (Rozmus, 2012)

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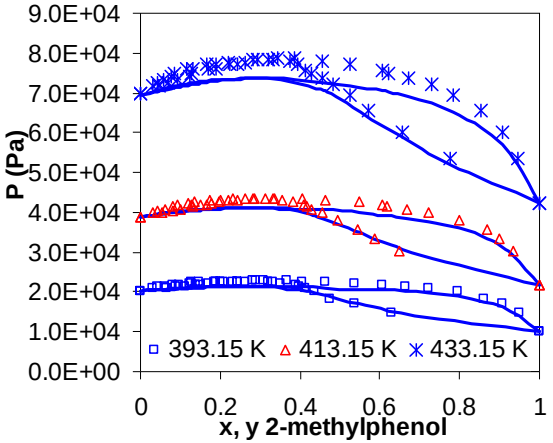
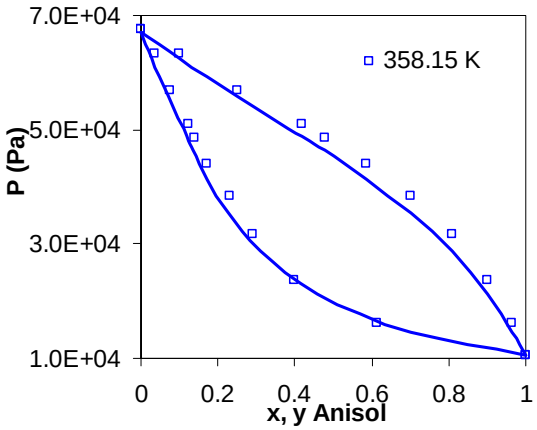
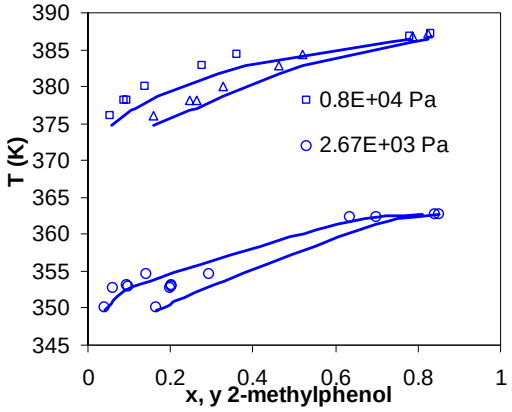
Nouvelles approches thermodynamiques : quelques exemples avec GC-PPC-SAFT



2-méthylphénol + décane

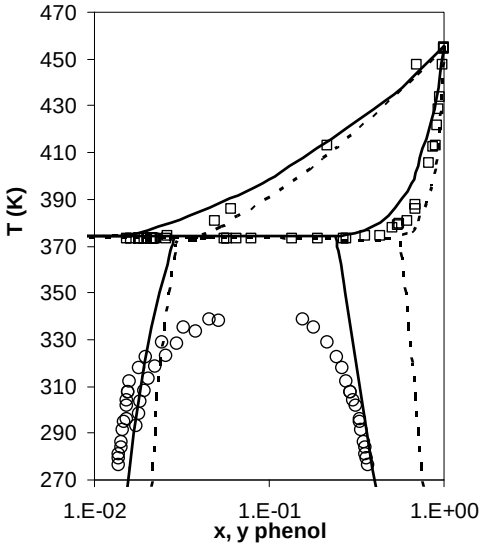


Anisole + heptane



2-méthylphénol + benzaldehyde

Phénol + eau (Pa)



Les limites de la contribution de groupes

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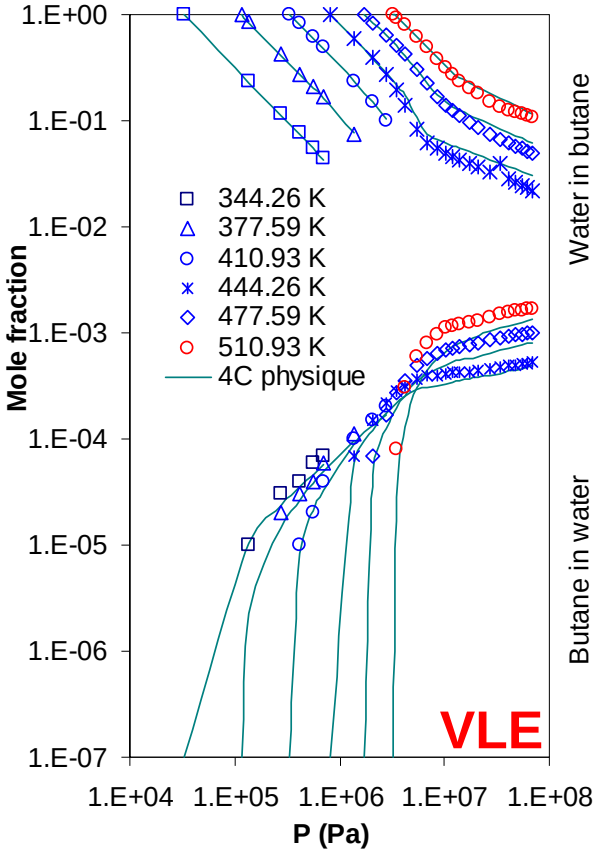
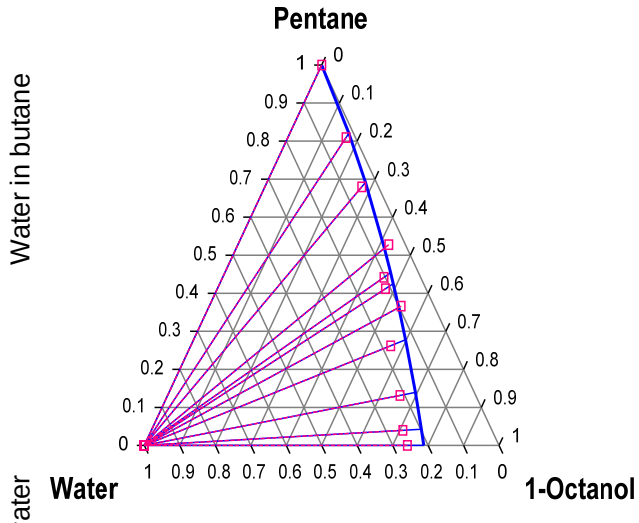
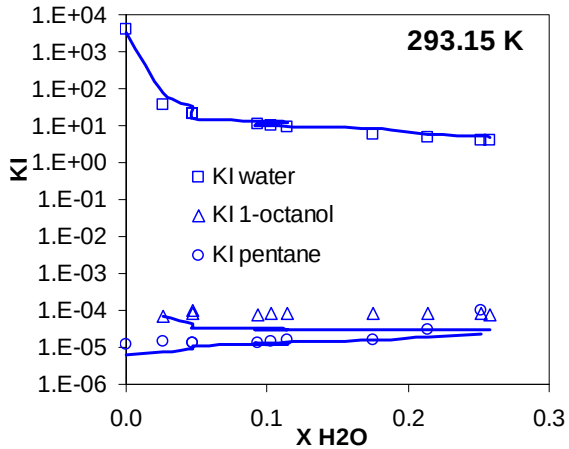
Nouvelles approches thermodynamiques : quelques exemples avec GC-PPC-SAFT

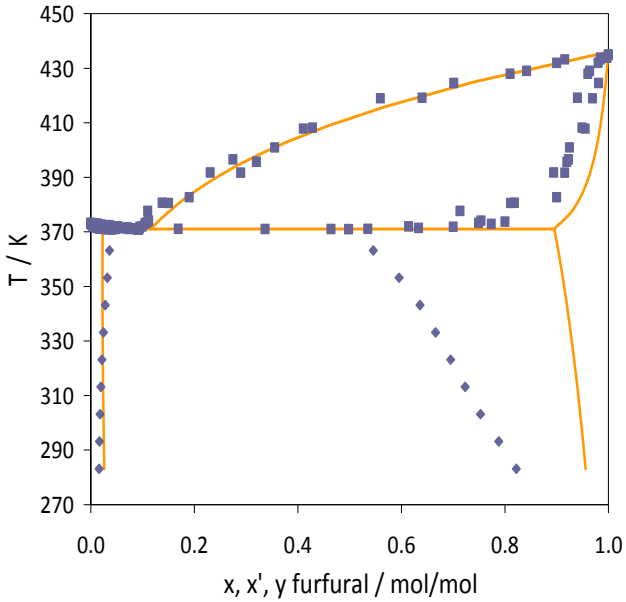
Nguyen-Huynh *et al.*, 2011







Grandjean *et al.*, 2012



Mélange furfural-eau

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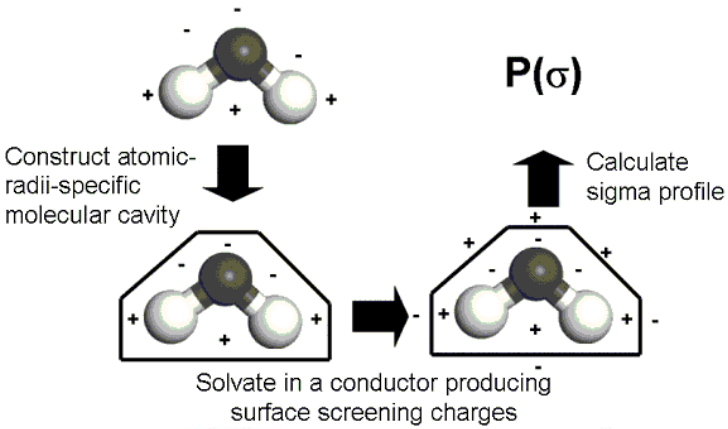
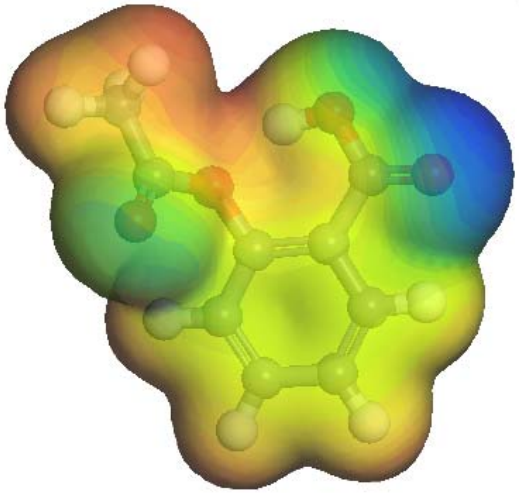
Nouvelles approches thermodynamiques : les approches COSMO

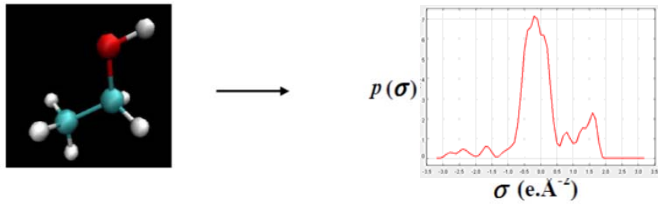
- COSMO-RS (société COSMOLogic), COSMO-SAC (code Open Source)



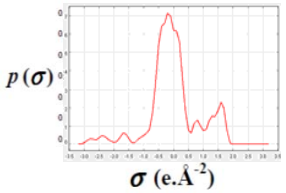


calculs ab initio

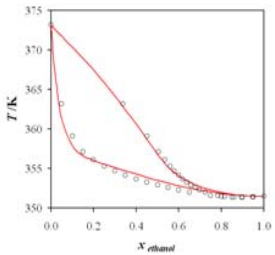
σ-profile $p_i(\sigma)$ des corps purs i + volume + surface



Base de données de profile σ



Modèle mathématique cosmo-RS



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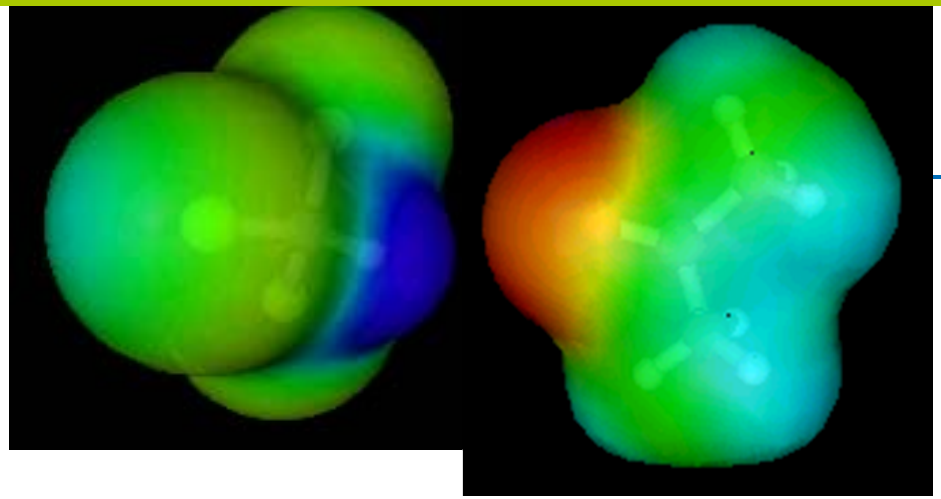
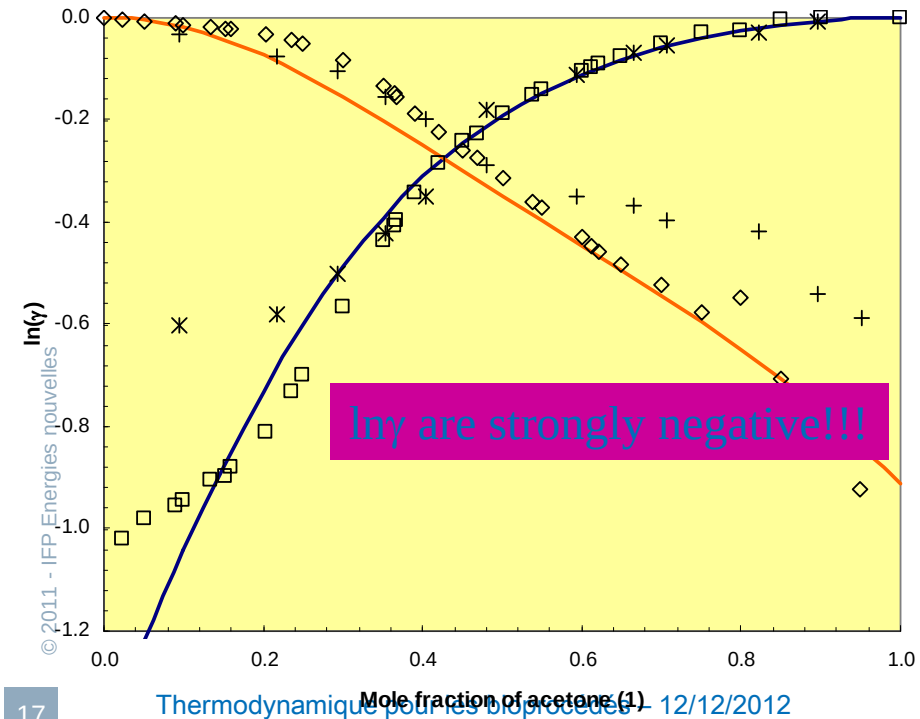
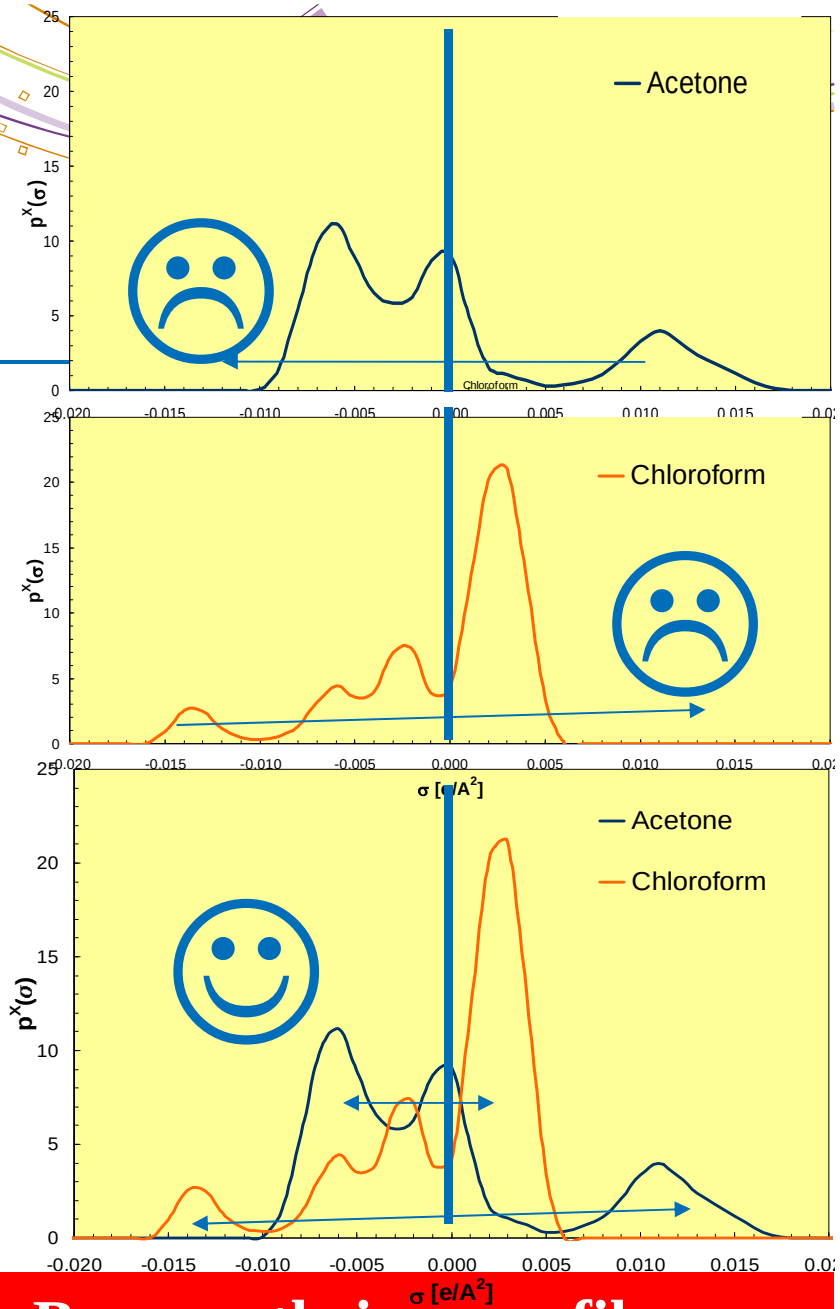
Why do acetone and chloroform like each other so much?







Because their σ-profiles are almost complementary!

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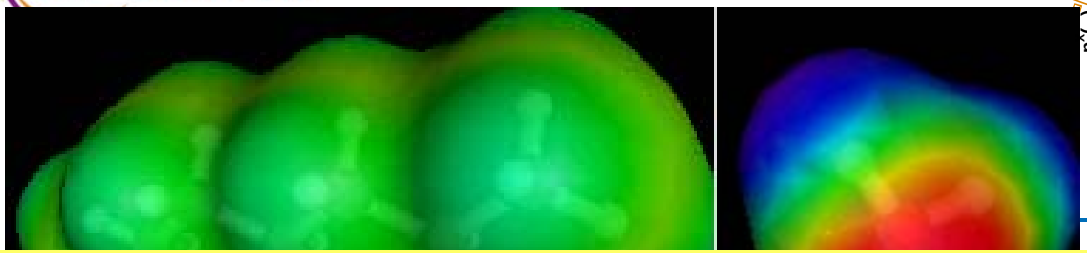
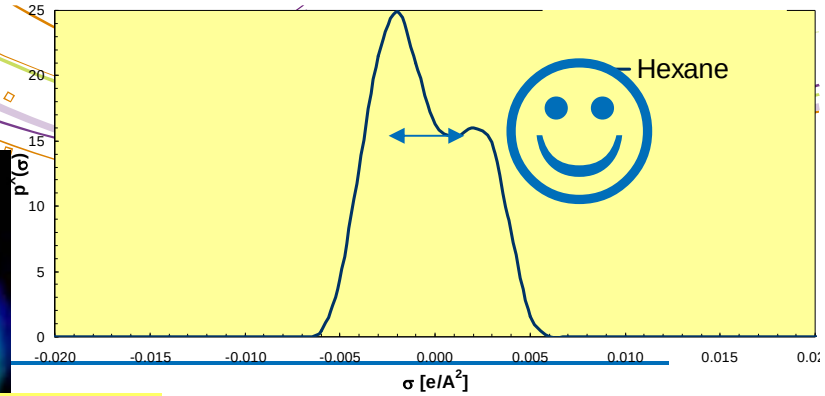
Hydrophobicity: hexane-water



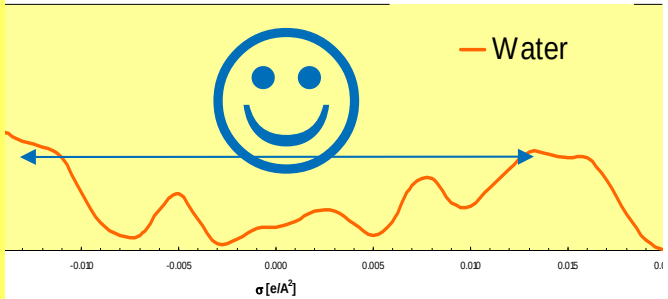


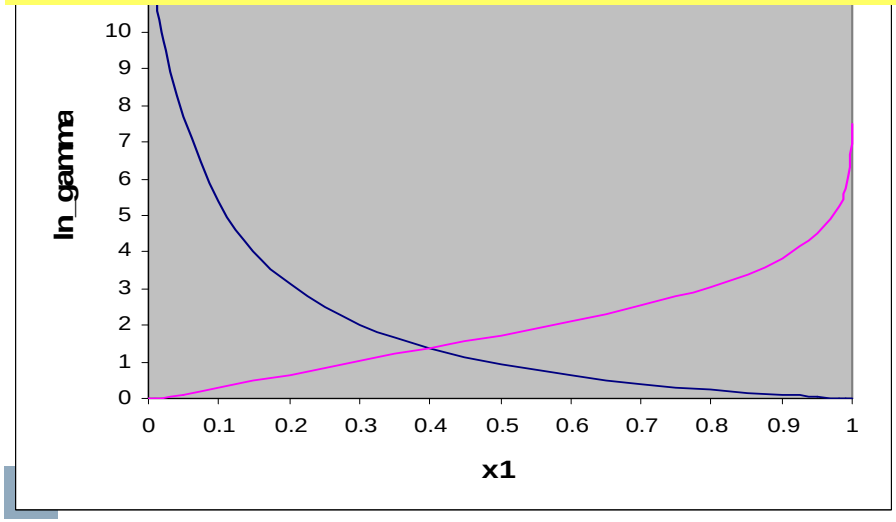
$\ln\gamma^\infty$ values are 13 for hexane in water and 8 for water in hexane!!! Hexane and water are only marginably soluble in each other!

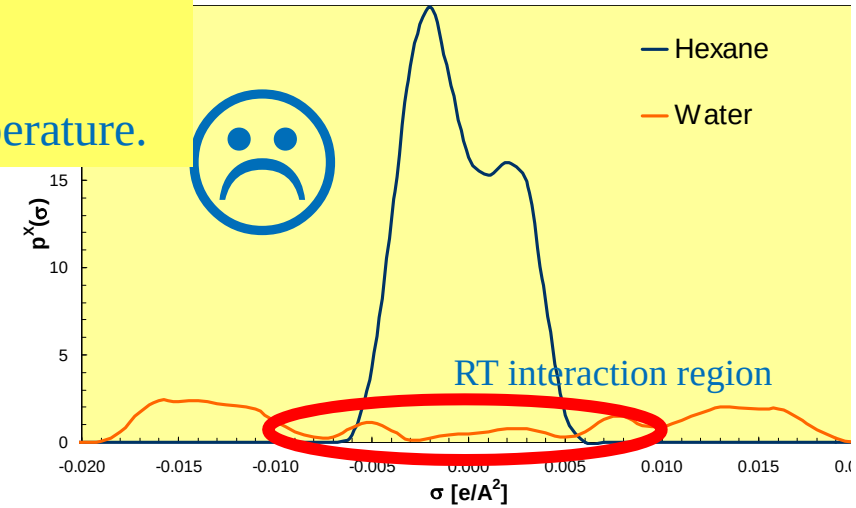
Hexane in water selects the few less polar surface segments of the water. This causes an almost negligiable H^{ex} but goes along with a large loss of entropy.

➔The hydrophobic effect is of entropic nature!

➔Water has a solubility minimum at about room temperature.







Hexane and water hate each other!

Nouvelles approches thermodynamiques : NRTL-SAC

Cheng & Song, 2004

$$\ln \gamma_I = \ln \gamma_I^C + \ln \gamma_I^R$$

$$\ln \gamma_I^R = \ln \gamma_I^{lc} = \sum_i r_{i,I}[\ln \Gamma_i^{lc} - \ln \Gamma_{i,I}^{lc}]$$

$$\ln \gamma_i^C = \ln \frac{\Phi_I}{x_I} + 1 - r_I \sum_J \frac{\Phi_J}{r_J}$$

$$r_I = \sum_i r_{i,I}$$

$$\Phi_I = \frac{r_I x_I}{\sum_J r_J x_J}$$

$$\ln \Gamma_i^{lc} = \frac{\sum_j x_j G_{ji} \tau_{ji}}{\sum_k x_k G_{ki}} + \sum_l \frac{x_l G_{il}}{\sum_k x_k G_{kl}} \left(\tau_{il} - \frac{\sum_j x_j G_{jl} \tau_{jl}}{\sum_k x_k G_{kl}} \right)$$

$$\ln \Gamma_{i,I}^{lc} = \frac{\sum_j x_{j,I} G_{ji} \tau_{ji}}{\sum_k x_{k,I} G_{ki}} + \sum_l \frac{x_{l,I} G_{il}}{\sum_k x_{k,I} G_{kl}} \left(\tau_{il} - \frac{\sum_j x_{j,I} G_{jl} \tau_{jl}}{\sum_k x_{k,I} G_{kl}} \right)$$

Chaque molécule est représentée par un quadruplet pondérant les quatre types de comportement

X : hydrophobe
Y- : polaire attractif
Y+: polaire répulsif
Z : hydrophile

TABLE I.3: Paramètres d'interaction binaire pour le modèle NRTL-SAC.

Type du segment 1	X	X	Y^-	Y^+	Z
Type du segment 2	Y^-	Z	Z	Z	Y^+
τ_{12}	1,643	6,547	-2,000	2,000	1,643
τ_{21}	1,834	10,949	1,787	1,787	1,834
α	0,2	0,2	0,3	0,3	0,2

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Applications dans le domaine des bioprocédés

Table 1
Potential role of thermodynamics in biotechnology

Prediction of biomolecular properties
Prediction of phase equilibria for downstream processing
Structural and functional stability of proteins and other biomolecules
Biocatalysis: Effect of T, pH, P, solvents and solutes on activity and selectivity
Correct driving forces and equilibrium position for general bioprocess design
Thermodynamic effects in cellular growth, including heat generation
Efficiency of cellular metabolism: Optimal biomass and product yields
Efficiency of bioprocesses

Von Stockar & van der Wielen, 1997

Table 20.3 *Major challenges and applications of thermodynamics in biotechnology*

Application	References	Thermodynamics needed	Comments/status
Controlled drug release – drug delivery via polymeric devices	Prausnitz[29]	Solubility of pharmaceuticals in polymers (SLE)	Michaels *et al.*[58] model (FH + diffusion) with limited success for a few pharmaceuticals
Solvent screening for pharmaceuticals (separation and recovery of amino acids and antibiotics)	Franck *et al.*[23] Kolar *et al.*[26] Abildskov *and* O'Connell[19–21] Stockar *et al.*[34] Prausnitz *et al.*[57]	SLE (drug solubility in liquids)	QSAR of various types[59,60] Classical models (HSP, UNIFAC) – capabilities but also limitations Hybrid models: NRTL–SAC from ASPEN Quantum chemistry: COSMO–RS New theoretically oriented EoS, e.g. PC–SAFT
Novel separations for pharmaceuticals and other biomolecules – SCFE	Larson and King[22] Prausnitz *et al.*[57]	Solubility of biomolecules in CO_2–co-solvent (SGE)	Limited modeling success for complex molecules and co-solvents
Novel separations for proteins – reverse micelles	Prausnitz[32]		
Understanding of protein–protein interactions in solutions	Prausnitz *et al.*[57] Gupta and Olson[16] Sandler[38]	Osmotic second virial coefficient – as a function of solubility and link to intermolecular potential	Obtained via osmometry or LALS
Understanding of the mechanisms of certain diseases (cataract, Alzheimer's, sickle-cell anemia)	Prausnitz[33] Galkin *et al.*[61] Pande *et al.*[62]	Protein aggregation and complexing (SLE, LLE)	Thermodynamics and colloid theory (DLVO)
Polyelectrolyte hydrogels for controlled release devices, contact lenses, etc.	Prausnitz[32]	Swelling	
'Classical' separation methods for proteins, e.g. protein precipitation from aqueous solutions using salts and selective separation	Prausnitz[2,29] Sandler[38] Chen and Mathias[14]	SLE, LLE of water–protein–salt as a function of numerous parameters (temperature, salt–protein concentration, ionic strength, pH, etc.)	Various models available of unknown predictive value
ATPS for protein separation	Prausnitz[32] Prausnitz and Tavares[7]	LLE of water–protein–salt (s)–polymer (s), e.g. PEG or Dextran	

Kontogeorgis & Folas, 2010

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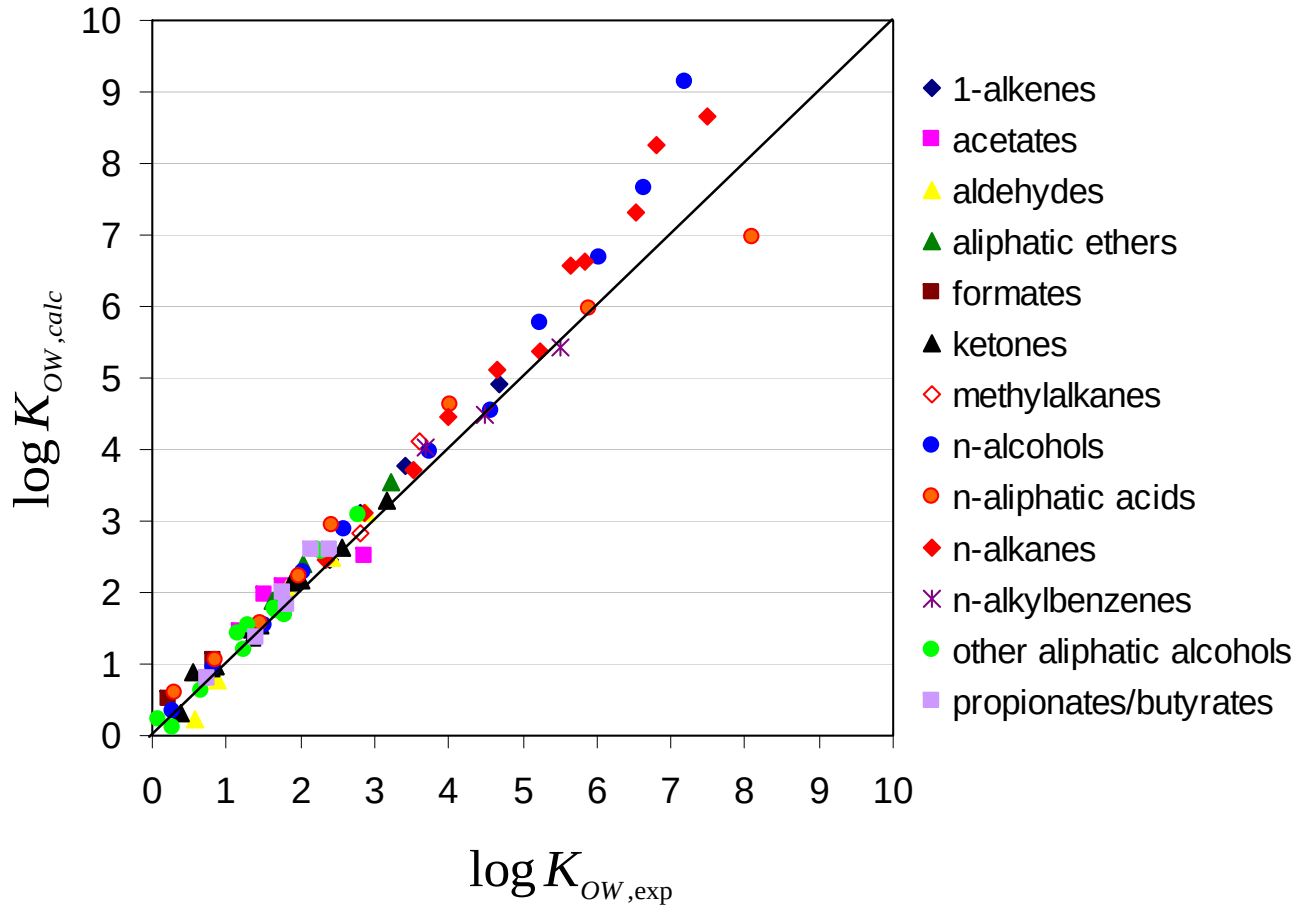
Applications dans le domaine des bioprocédés : calcul de Kow par GC-PPC-SAFT



Travail de thèse en cours non publié (merci à TB Nguyen)

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Nouvelles approches thermodynamiques : quelques résultats issus de MEMOBIOL

Table 2. Octanol–Water Partition Coefficients (Log P) for Some Biofuel-Related Compounds at 298.15 K

system	CAS number	experimental (or estimated) values of log P[51−53]	COSMO-RS	COSMO-SAC		mCOSMO-SAC		UNIFAC
			BP-TZVP	VT-2005	new geometry[a]	VT-2005	new geometry[a]	
fumaric acid	110-17-8	0.46	0.4078	0.0718	0.4788	−0.0551	0.3847	−0.5220
itaconic acid	97-65-4	−0.34 (EST)[b]	0.0623	0.1785	−0.1276	0.0671	−0.2342	−0.1153
levulinic acid	123-76-2	−0.49	−0.3795	−0.1547	−0.3300	−0.1693	−0.3511	−0.5477
glycerol	56-81-5	−1.76	−1.1474	−1.4731	−1.6434	−1.4233	−1.6024	−1.5473
sorbitol	50-70-4	−2.20	−0.6512	−1.7864	−2.2037	−1.7053	−1.9763	−3.2105
furfural	98-01-1	0.41	0.2059	−0.1232	0.2928	−0.1777	0.2611	0.7132
anisole	100-66-3	2.11	2.2183	1.6020	1.8245	1.4998	1.7135	2.1970
m-cresol	108-39-4	1.96	1.9731	1.5838	1.7948	1.4431	1.6454	2.7259
vanillin	121-33-5	1.21	1.1670	1.0430	1.2017	0.9486	1.0914	1.1247
quinone	106-51-4	0.20	0.3072	0.0561	0.0733	0.0439	0.0622	
AAD[c]			0.3202	0.3671	0.1214	0.4207	0.1818	0.4143
R^d			0.9525	0.9753	0.9961	0.9744	0.9983	0.9587

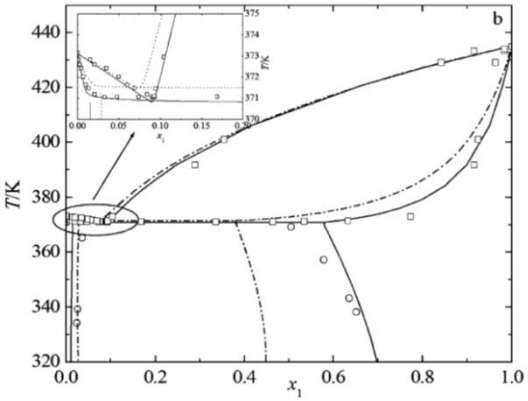

Figure 6. VLE and LLE of the furfural (1) + water (2) mixture at pressure P = 101.3 kPa predicted with (— and - · -) COSMO-based models compared to (□ and ○) experimental data:[60] (a) curves predicted with (—) COSMO-SAC and (- · -) mCOSMO-SAC predictions and (b) curves predicted with COSMO-RS + (—) BP-TZVP and (- · -) BP-SVP databases. (□, VLE data; ○, LLE data).

Li et Paricaud, 2012

Les approches COSMO-SAC ou COSMO-RS donnent des résultats comparables et légèrement meilleurs que ceux d'UNIFAC

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Applications bioprocédés : coefficient d'activité / solubilité d'acides aminés

Pinho *et al.*, 1997

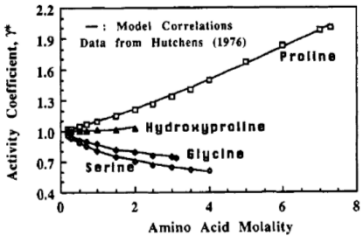


Figure 3. Experimental and calculated values for activity coefficients of amino acids in water at 298.15 K.

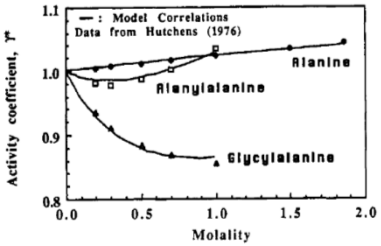


Figure 4. Experimental and calculated values for activity coefficients of alanine and some peptides in water at 298.15 K.

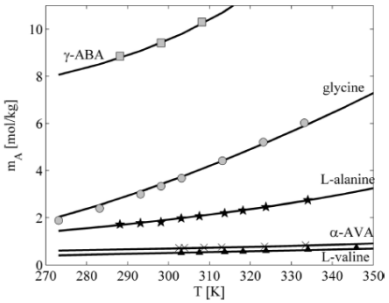
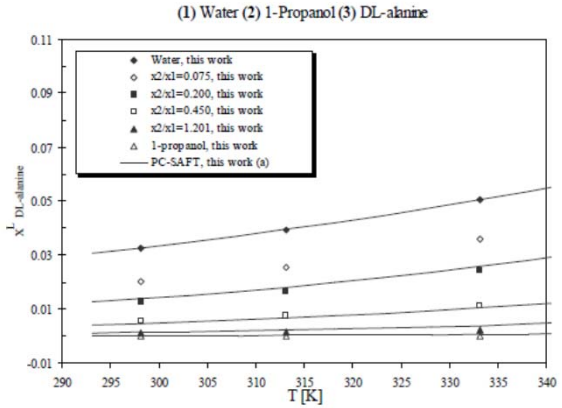


Figure 4. Amino-acid solubilities in water. Symbols represent experimental data: (squares) γ-ABA, (circles) glycine, (stars) L-alanine, (crosses) DL-α-AVA, (triangles) L-valine; lines are calculations with PC-SAFT.

Held *et al.*, 2011



Fonseca Ferreira, 2011

Utilisation de PC-SAFT (paramètres des acides aminés purs ajustés sur les binaires eau-acide, seul un kij est requis pour

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R + \ln \gamma_i^{D-H} \qquad (15)$$

UNIFAC modifié (terme de Debye-Huckel)

Table 6.4 Binary interaction PC-SAFT parameters of amino acid/water systems.

	Glycine	DL-alanine	L-serine	L-threonine	L-isoleucine
Water	-0.10	-0.10	-0.12	-0.10	-0.03

Table 6.5 Hypothetical fusion properties for amino acids.

Amino acid	Enthalpy of melting ΔH_o [kJ.mol^{-1}]	SD	Melting temperature T_o [K]	SD	Difference in the heat capacity ΔC_p [kJ.mol^{-1}.K^{-1}]	SD	Solubility data source	ARD* (%)
Glycine	21.97	1.8E-1	489.78	2.4E0	neglected		(a, g)	1.68
DL-alanine	15.98	3.2E-2	581.72	1.0E0	neglected		(a, b, g)	0.33
L-serine	24.54	9.8E-1	375.28	3.7E0	neglected		(c, d, e, g)	8.19
L-threonine	17.72	1.6E-1	637.12	5.8E0	neglected		(f, g)	1.45
L-isoleucine	11.27	8.9E-1	621.28	3.7E+1	0.073	6.1E-3	(g, h)	1.08

(a) Dalton and Schmidt (1933); (b) Dunn et al. (1933); (c) Hutchens (1976); (d) Jin and Chao (1992); (e) Luk and Rousseau (2006); (f) Profir and Matsuoka (2000); (g) This work; (h) Zumstein and Rousseau (1989).

Estimation des propriétés de fusion des acides aminés

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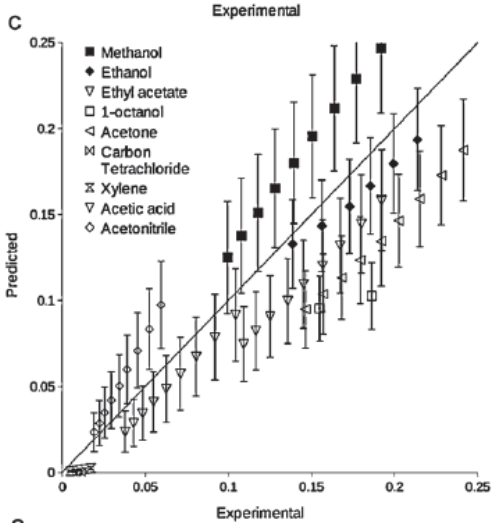
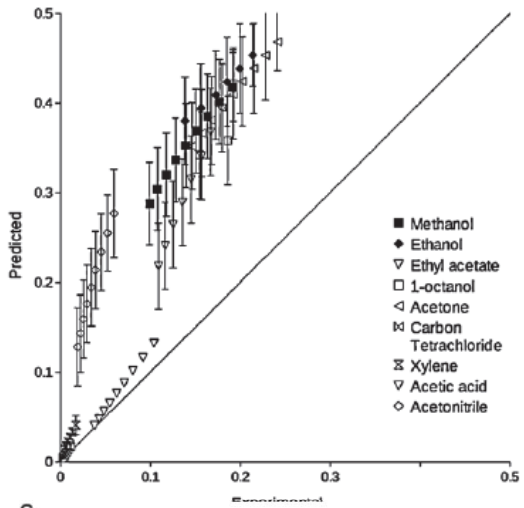
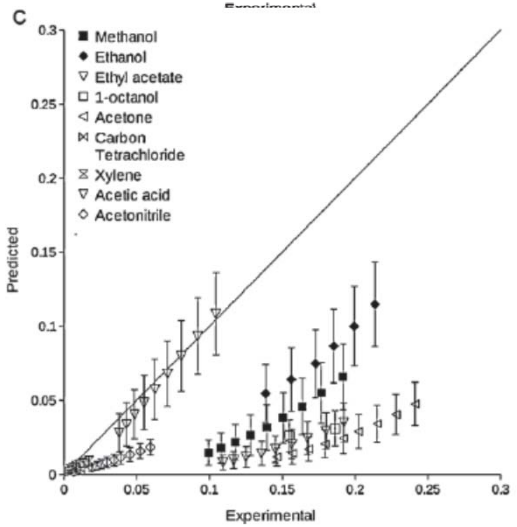
Applications bioprocédés : prédiction avec UNIFAC, COSMO-SAC et NRTL-SAC







Bouillot *et al.*, 2011

Solubilité de l'acide salycilique dans différents solvants

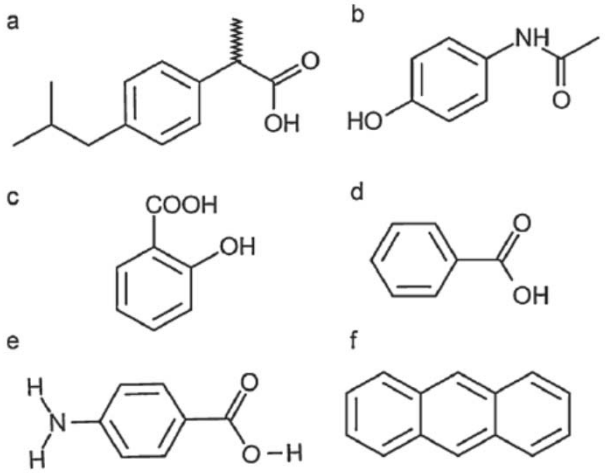


Fig. 1. (a) Ibuprofen, (b) paracetamol, (c) salicylic acid, (d) benzoic acid, (e) 4-aminobenzoic acid and (f) anthracene.

Aucun modèle ne parvient à prédire convenablement les solubilités ou leur comportement en fonction de la température

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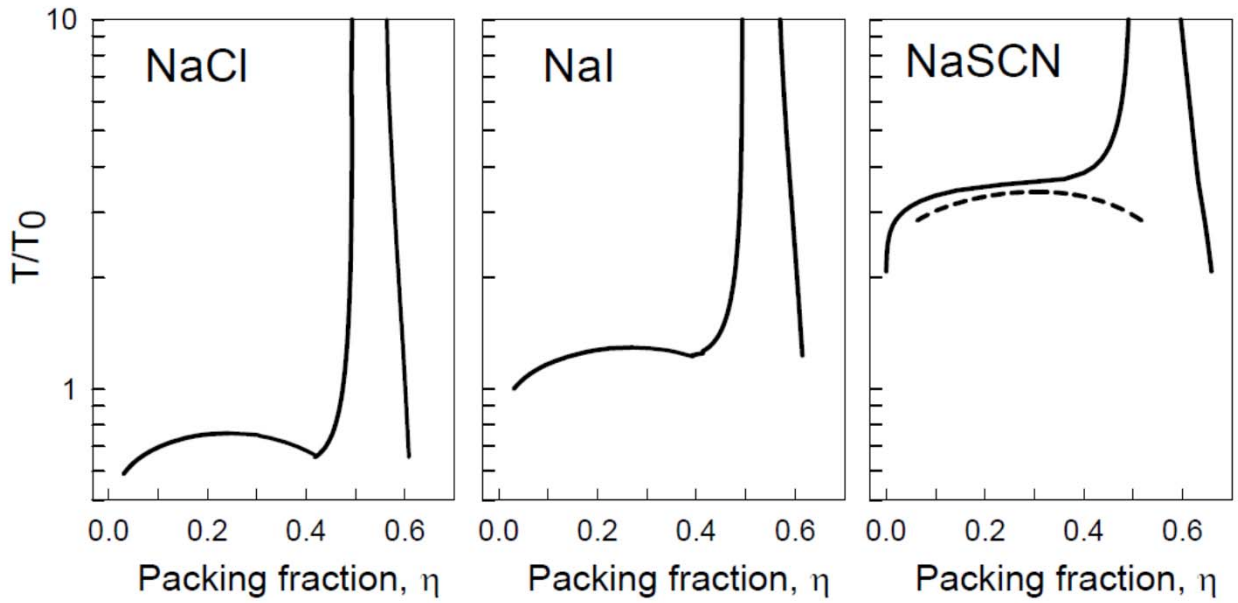
Applications bioprocédés : diagrammes de phase des protéines



Bostrom et al, 2006

$$\frac{A}{Nk_BT} = \frac{A^{HS}}{Nk_BT} + \frac{A^{P}}{Nk_BT}$$

Utilisation de la théorie de la perturbation (appliquée via un potentiel de force moyenne ajusté sur des simulations Monte Carlo) pour restituer le comportement solide-fluide de la lysozime dans des solutions d'électrolytes

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Applications bioprocédés : remarques finales (Kontogeorgis et Folas, 2010)

- Pour les produits pharmaceutiques, les modèles disponibles sont les extensions de NRTL ou d'UNIFAC (éventuellement des versions « locales »), les approches COSMO ou bien les approches plus empiriques basées sur les paramètres de solubilité
- Des approches de type UNIFAC (étendu) ou plus récemment PC-SAFT sont disponibles pour traiter les systèmes en présence d'acides aminés (et parfois les peptides)
- Des approches pur modéliser le comportement thermodynamique des protéines (travaux de Prausnitz) ou bien sur les processus d'adsorption des protéines (Kontogeorgis et Folas, 2010) sont disponibles

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Axes de travail futurs

- Développement d'approches prédictives
  - Travaux théoriques sur les équations pour tenir compte de la complexité (e.g. interactions intermoléculaires, ramifications, coopérativité, …)
  - Travaux sur les méthodes de paramétrage (e.g. contributions de groupes, utilisation de descripteurs moléculaires, indices
- Etablir les liens avec les données expérimentales et analytiques disponibles
  - Faute de pouvoir utiliser la volatilité, quelles propriétés globales peuvent permettre de développer des approches prédictives
- Renforcer également les liens avec la simulation moléculaire et le calcul quantique
  - Peut aider à comprendre le comportement et à paramétrer les équations dans certains cas

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Applications bioprocédés : prédiction avec UNIFAC, COSMO-SAC et NRTL-SAC

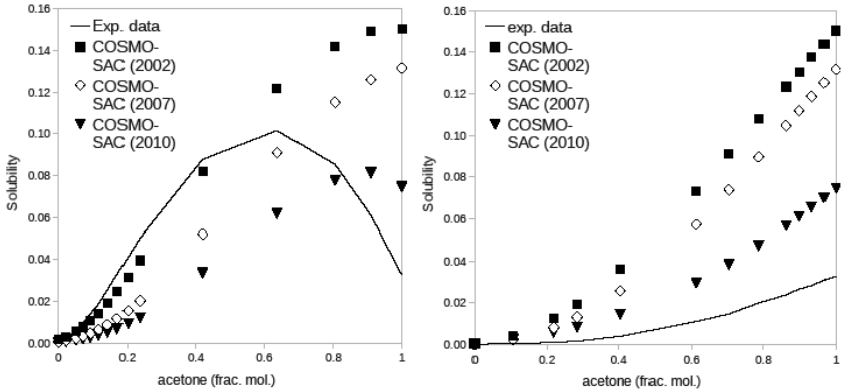
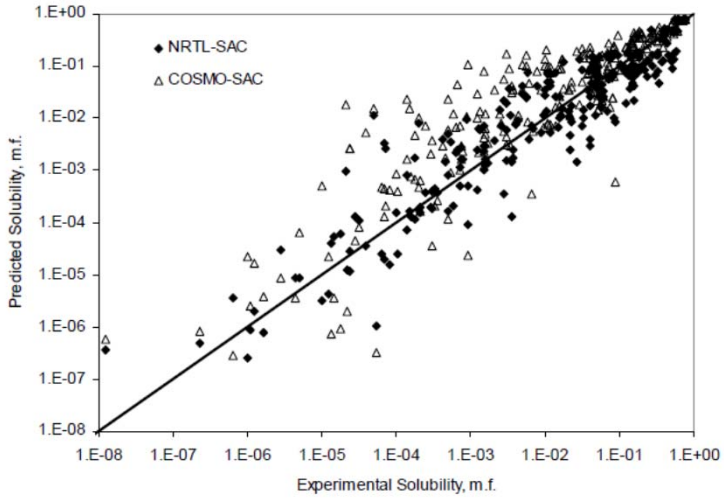


Figure 1:. Solubility prediction of paracetamol at 20 °C in mixtures of water/acetone and toluene/acetone as a function of the acetone molar fraction using COSMO-SAC 2002, 2007 and 2010.

Bouillot et al, 2011



Mullins, 2007

Figure 5.19: NRTL-SAC and COSMO-SAC predicted solubilities for 17 solutes and 258 experimental solubility points at 298.15 K, except acetaminophen solubility at 303.15 K, on a logarithmic base 10 scale.[27]

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Quelques applications bioprocédés : diagrammes de phase avec protéines

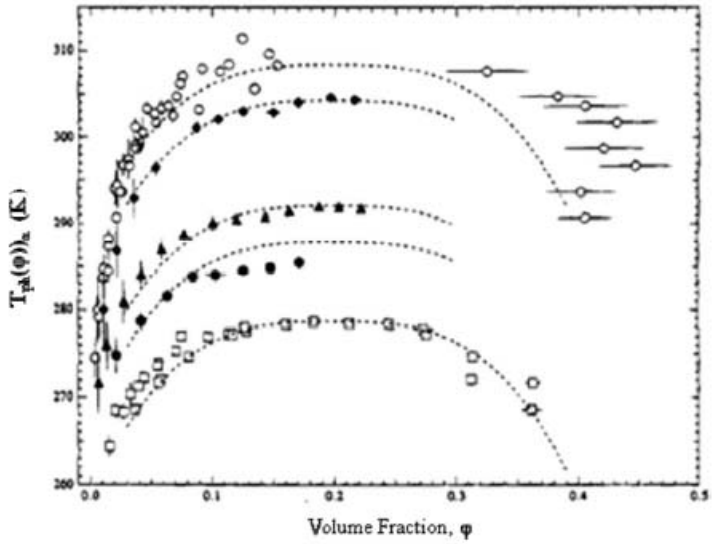

Figure 4-3. Sections of the coexistence surface for aqueous two-protein solutions of γ_{IIIa} and γ_{IIIb} Crystallin at different fixed compositions, α, defined as the ratio of the number of γ_{IIIa} Crystallin molecules to the total number of protein molecules. Experimentally determined points correspond to α = 0.0 (□), α = 0.18 (●), α = 0.28 (▲), α = 0.64 (♦), and α = 1.0 (○). The dotted curves represent theoretical predictions. Adapted from ref 19.

$$\frac{G}{V} = \frac{G_o}{V} + \frac{k_B T}{\Omega_P}\left[\varphi \ln \varphi - \frac{\varphi - 6\varphi^2 + 4\varphi^3}{(1-\varphi)^2}\right] - \frac{k_B T}{\Omega_P} U \varphi^2$$

Lattice model (mean field approximation)

Carnahan-Starling equation for tne entropy of mixing of hard spheres

Prausnitz, 2003

Dey & Prausnitz, 2011

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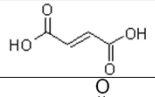
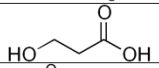
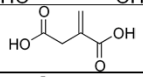
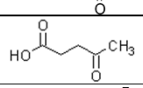
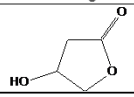
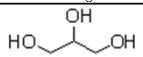
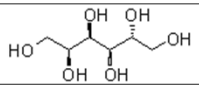
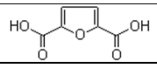
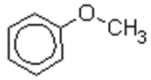
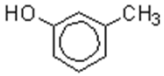
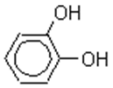
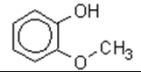
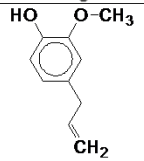
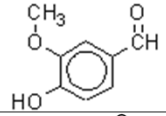
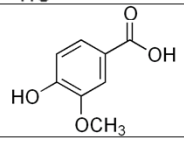
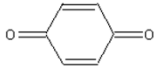
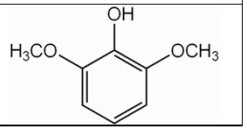
What molecules ?

Nom	Formule
Acide fumarique	
Acide 3-hydroxypropionique	
Acide Itaconique	
Acide Levulinique	
3-hydroxybutyrolactone	
Glycerol	
Sorbitol	
Furfural	
2,5 furane acide dicarboxylique	

Nom	Formule
Anisole	
m-Cresol	
Catechol	
Guaiacol	
Eugenol	
Vanillin	
Acide vanilic	
Quinone	
Syringol	

- **Pure**

- In binary / ternary solutions with **Solvents** (water, toluene, hexane, octanol …)

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What predictive models ? (2)

- Molecular Simulation methods
  - Use of Gibbs Ensemble Monte Carlo for phase equilibria (Panagiotopoulos , Mol. Phys., 1987) with AUA and UA force fields
  - Use of either Monte Carlo or molecular dynamics (LAMMPS) for phase properties (density, energy, derivative properties)
  - Description of molecules using the Anisotropic United Atom (AUA), TraPPE-UA and PCFF force fields
    - Extended coverage, large applicability
    - Good compromise between accuracy and computing time

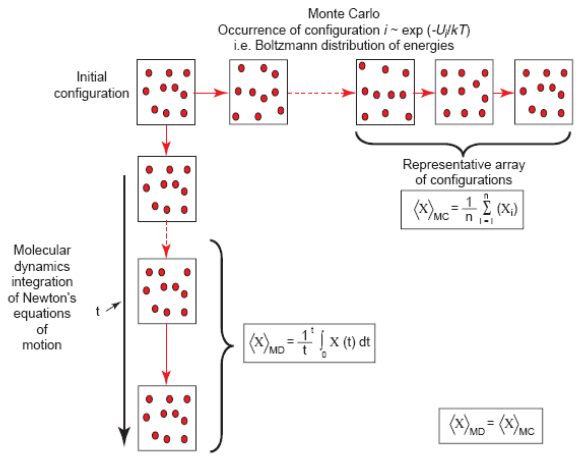
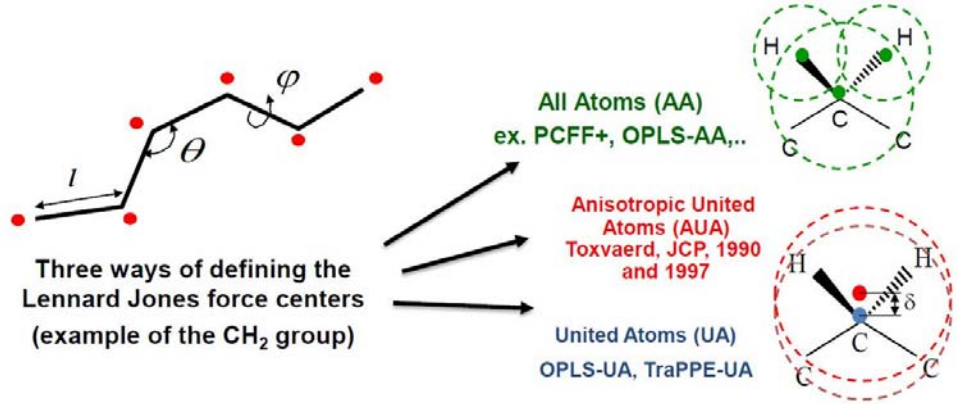


Figure 2

The two ways of building a statistical ensemble: Molecular dynamics (MD) and Monte Carlo (MC) simulation. Average properties can be determined from time averages in MD and from ensemble averages in MC. Both averages are equivalent, as a consequence of the



$$U = \underbrace{\sum_{i,j} U^{LJ}{}_{ij} + \sum_{i,j} U^{el}{}_{ij}}_{\text{Lennard-Jones and Electrostatic energy (inter- and intra-molecular)}} + \underbrace{\sum_{k} U^{stretch}(l_k) + \sum_{m} U^{bend}(\theta_m) + \sum_{n} U^{tors}(\varphi_n)}_{\text{Intramolecular energy associated with stretching, bending and torsion}}$$

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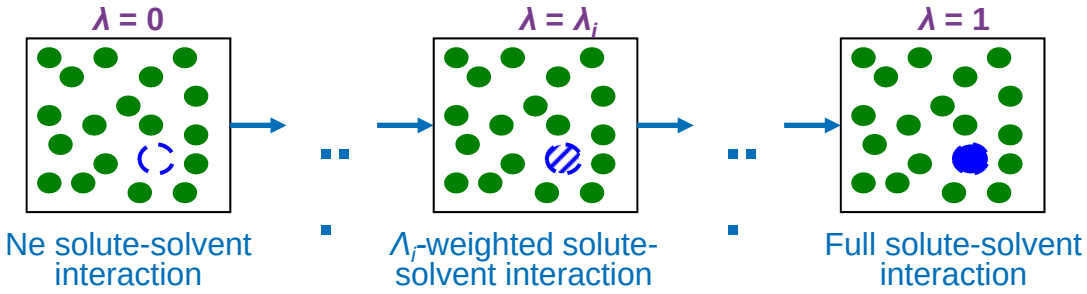
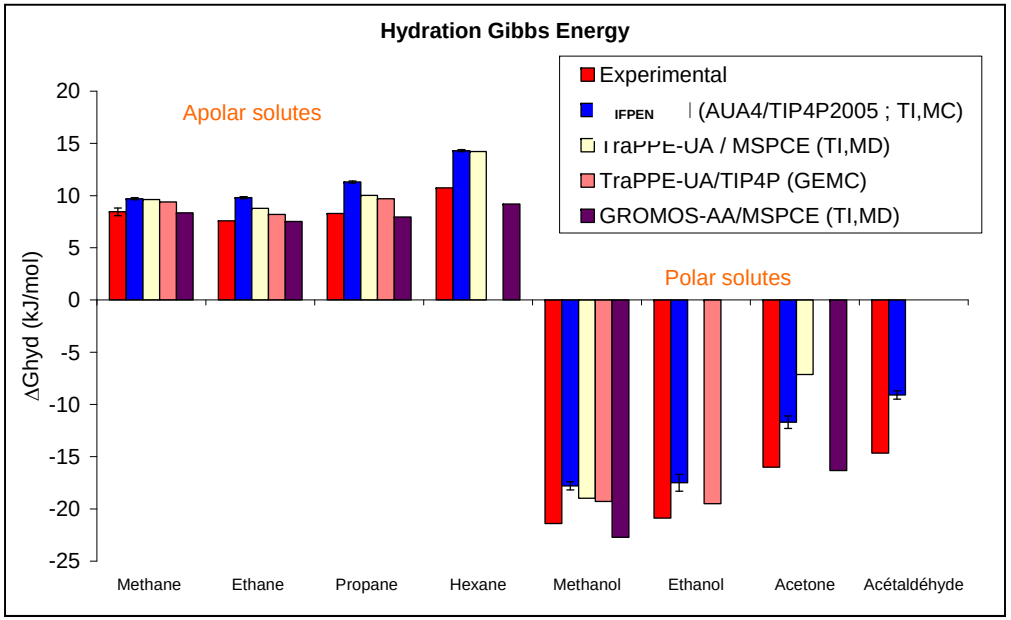
WP2 – Implementaion of the Thermodynamic Integration algorithm in the MC Gibbs code and evaluation

- **Thermodynamic integration is used:**
  - To predict solvation / hydration energies
  - To predict solubilities and inifinite dilution states
  - To predict partition coefficients
  - Can be used to predict K_{OW}





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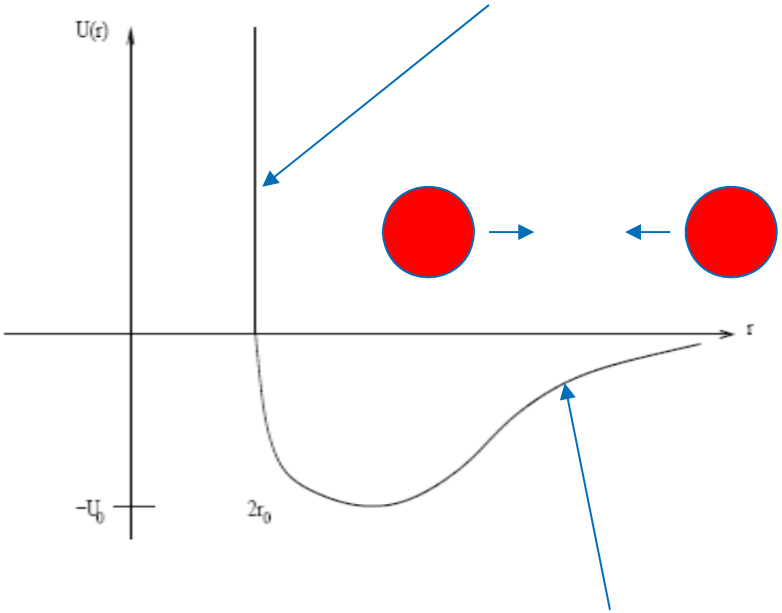
L'exemple du génie chimique

Forces répulsives prépondérantes



Forces attractives prépondérantes

2 paramètres :

U_0 (ou ε)

r_0 (ou σ/2)

On peut se rapporter à des grandeurs macroscopiques mesurables :

Symbol	Meaning	Definition
r^*	dimensionless distance	r/σ
E^*	dimensionless energy	E/ϵ
T^*	dimensionless temperature	kT/ϵ
U^*	dimensionless internal energy	U/ϵ
t^*	dimensionless time	$t/[\sigma(m/\epsilon)^{0.5}]$
v^*	dimensionless velocity	$v/(\epsilon/m)^{0.5}$
F^*	dimensionless force	$F\sigma/\epsilon$
P^*	dimensionless pressure	$P\sigma^3/\epsilon$
D^*	dimensionless self diffusion coefficient	$D/[\sigma(\epsilon/m)^{0.5}]$

Utiliser une température et une pression caractéristiques : Tc et Pc

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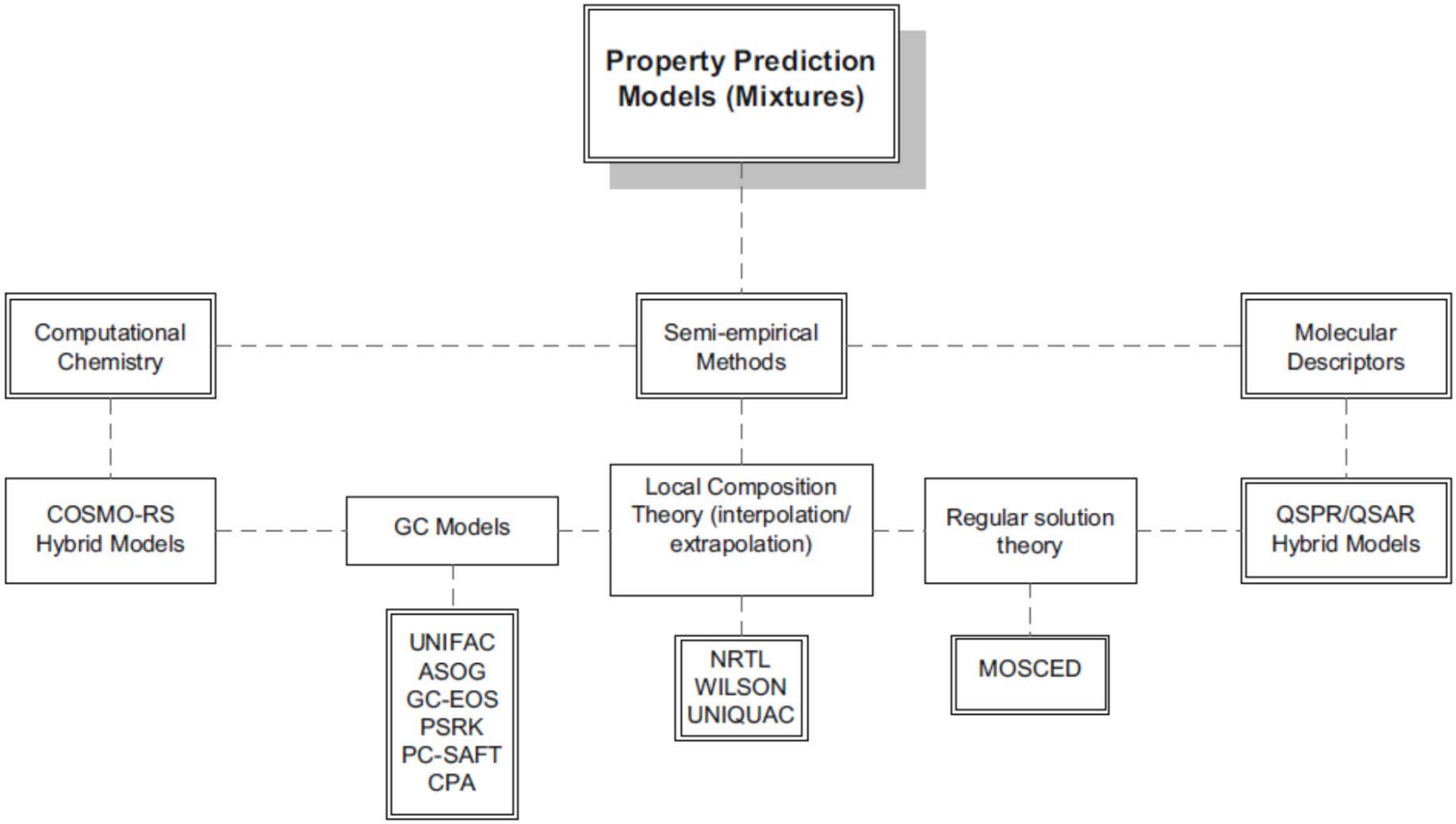

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Table 2
ESF course on thermodynamics for biochemical engineers

Course structure

	Lecturers	Potential applications
Fundamentals		General insight into phase equilibria
Phase equilibrium thermodynamics of non-electrolytes. Homogeneous mixtures, excess properties, VLE, LLE, SLE in non-electrolyte systems, activity coefficient models.	J.M. Prausnitz (UC Berkley)	
Assessment of thermodynamic properties. Direct methods and use of Gibbs–Duhem equation	C.A. Haynes (UC Vancouver)	
Large molecules and charged species		Solution behaviour of polymers and proteins, salting out, precipitations, extraction, chromatography, swelling of resins, phase splitting, etc.
Electrolytes	C.A. Haynes	
Polymers, polyelectrolytes, gels, demixing in polymersolutions, Donnan effect, swelling in hydrogels	J.M. Prausnitz	General relevance for DSP
Aqueous two-phase systems	C.A. Haynes	
Correlative approach for complex biomolecules. Hydrophobicity and polarity, log P approach	L.A.M. van der Wielen (TU Delft)	
Phase equilibria in protein solutions. Integral theory of solution, potentials of mean force	J.M. Prausnitz	
Proteins, and biocatalysis		Biocatalysis in general and in non-conventional media, biocatalyst engineering, protein engineering, DSP, inclusion body reprocessing
Conformational and structural stability of proteins. Enthalpic and entropic effects, salts, solvent, temperature, denaturation, renaturation	W. Norde (A.U. Wageningen)	
Phase and reaction equilibria in biocatalysis. Effects of co-solvents, pH and salts	L.A.M. van der Wielen, F.E.D. van Halselma (TU Delft)	
Irreversible thermodynamics		Insight, coupled fluxes in membrane processes, ion exchange, and living systems
Thermodynamics of open and irreversible systems	L.A.M. van der Wielen, U. von Stockar (ETH Lausanne)	
Mass transfer on the basis of IT. Multicomponent diffusion, multiple driving forces, flux coupling, membrane processes, ion exchange	L.A.M. van der Wielen	
Thermodynamics in living systems		Insight, heat removal, monitoring of bioprocesses, prediction of biomass and product yields, metabolic engineering
Energy dissipation in biotechnology. Heat generation, free energy dissipation and growth. Energy balances, biocalorimetry and monitoring of bioprocesses	U. von Stockar	
Description of microbial growth based on Gibbs energy yield and maintenance correlations	J.J. Heijnen (TU Delft)	
Optimal metabolic fluxes. Metabolic modelling and optimization	J.J. Heijnen	

Von Stockar & van der Wielen, 1997

- Précipitations, extraction, chromatographie, …
- Comportement en solution de polymères, d'espèces chargée, biocatalyse, protéines …
- Processus membranaires, systèmes vivants

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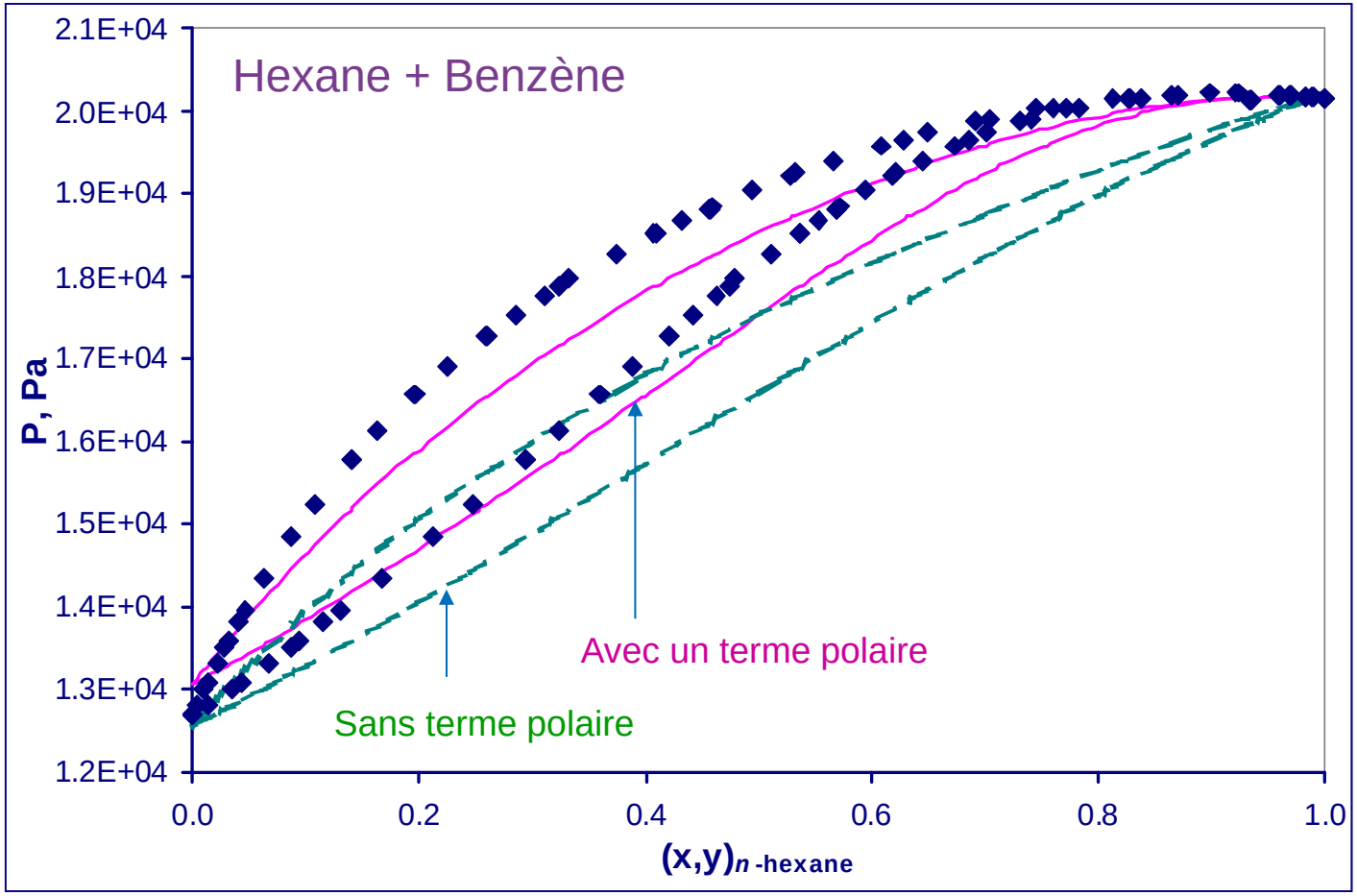
Nouvelles approches thermodynamiques : apport du terme polaire



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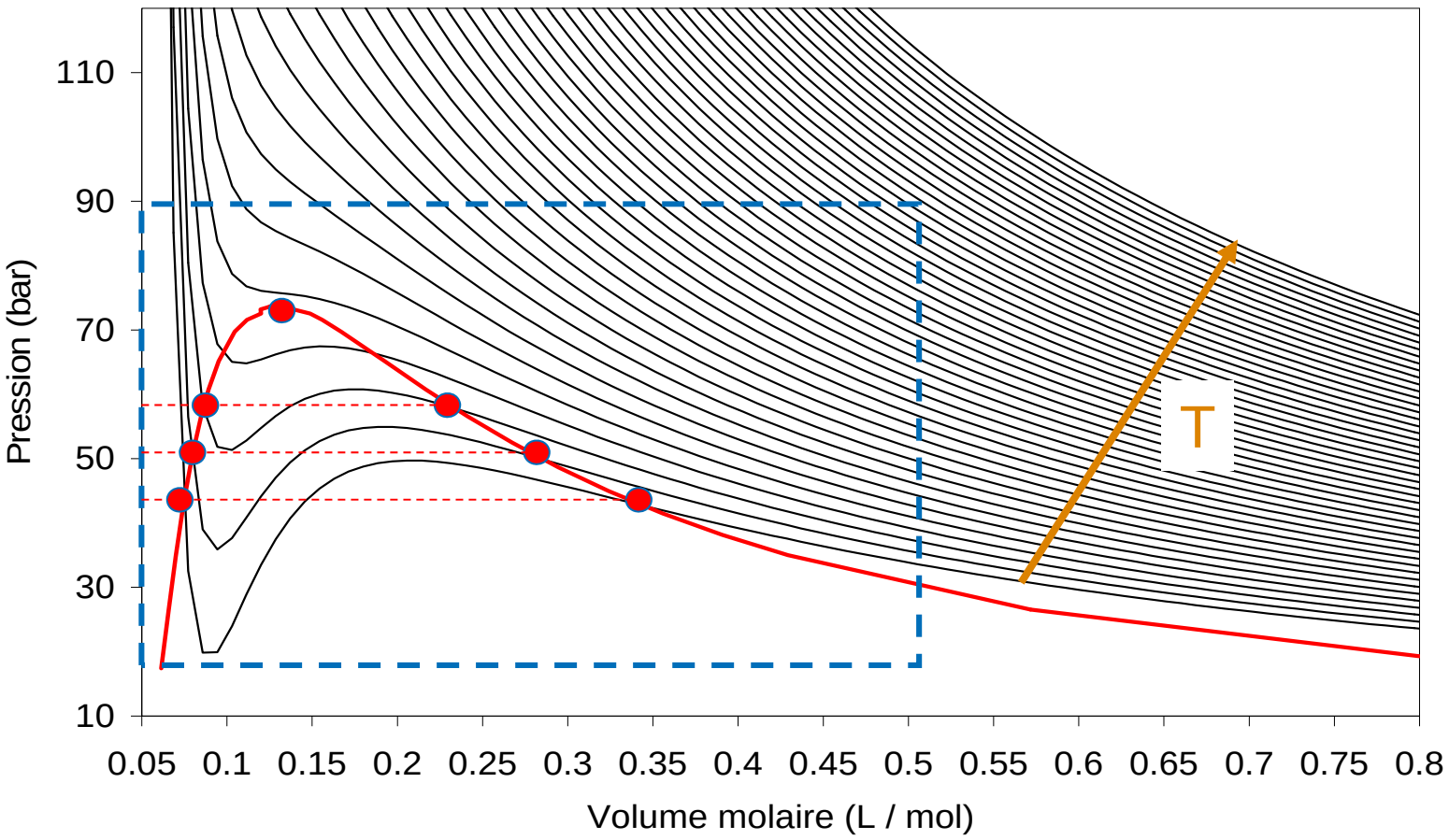
110
90
70
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30
10
Pression (bar)
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0.35
0.4
0.45
0.5
0.55
0.6
0.65
0.7
0.75
0.8
Volume molaire (L / mol)
T