

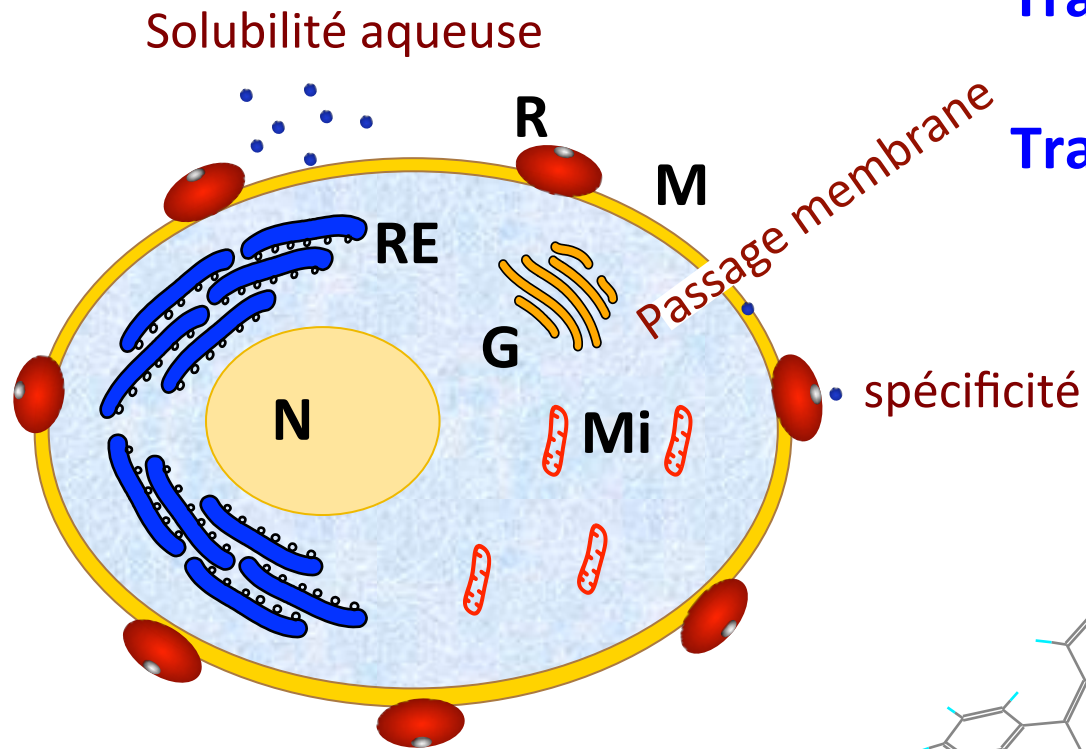
Phénomènes interfaciaux mis en jeu dans les interactions molécule-membrane

V. Rosilio

*Institut Galien Paris-Sud,
UMR CNRS 8612 - Université Paris-Sud 11*



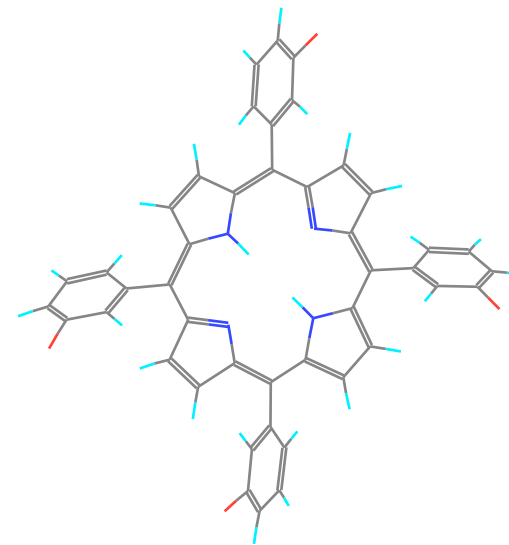
Challenges de la délivrance ciblée de substances aux cellules



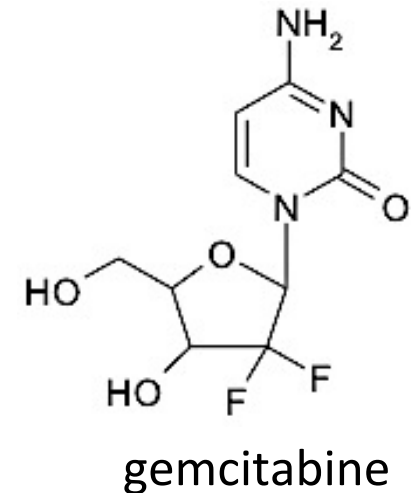
M: membrane plasmique
N: noyau
G: golgi
RE: reticulum endoplasmique
Mi: mitochondrie
R: récepteur membranaire

Transport passif (médié ou non)

Transport actif

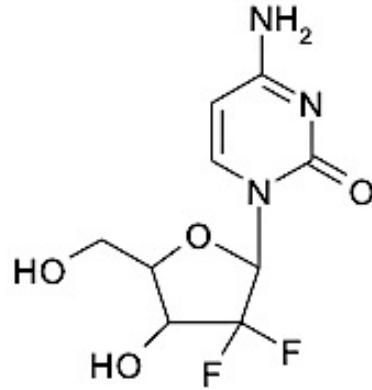


tetraphenylporphyrine (TPP)



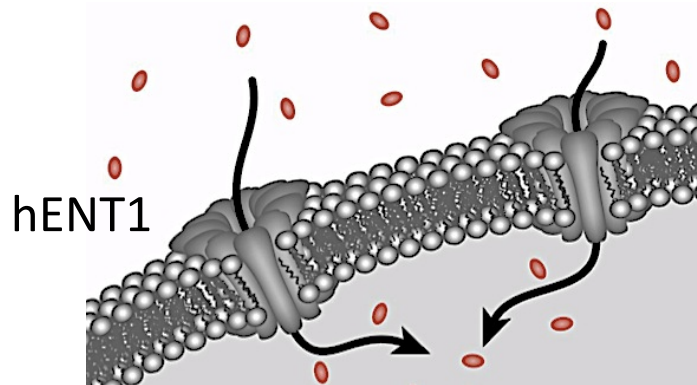
Interaction de la gemcitabine avec la cellule

Gemcitabine



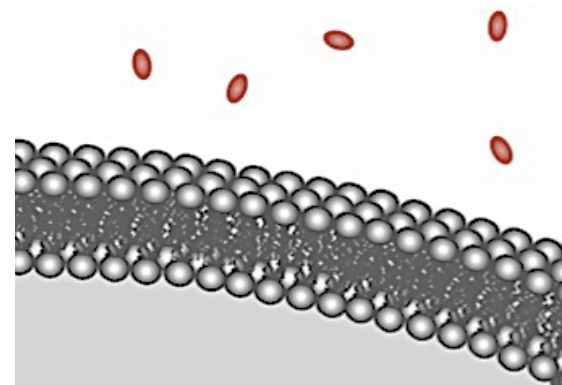
Hydrosoluble

Lignée cellulaire sensible



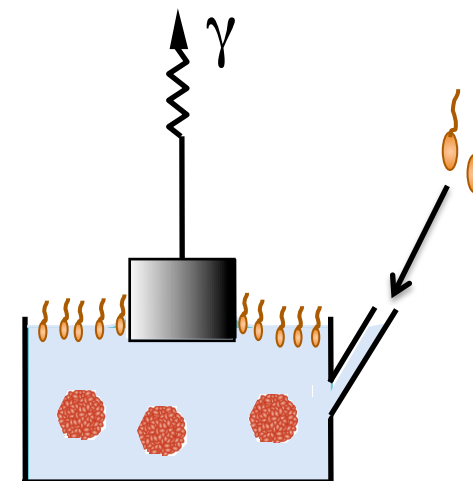
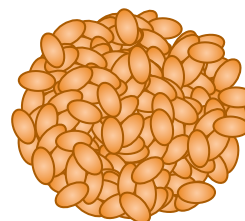
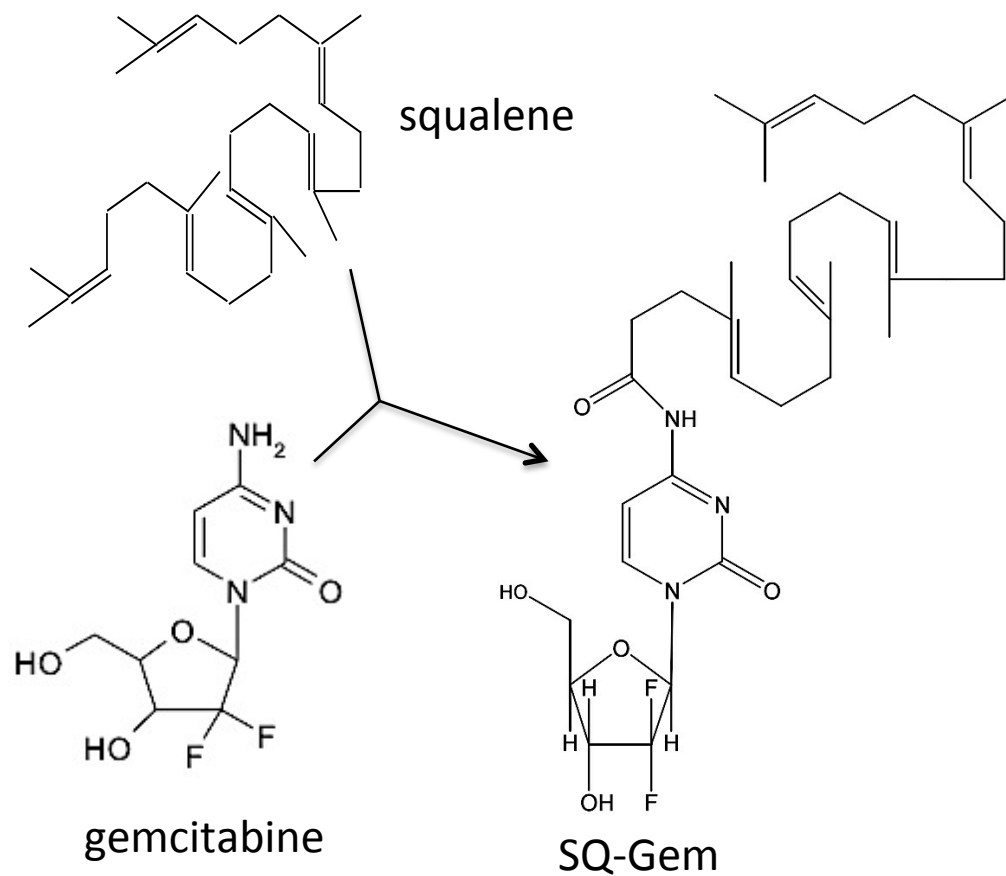
Transport actif

Lignée cellulaire résistante



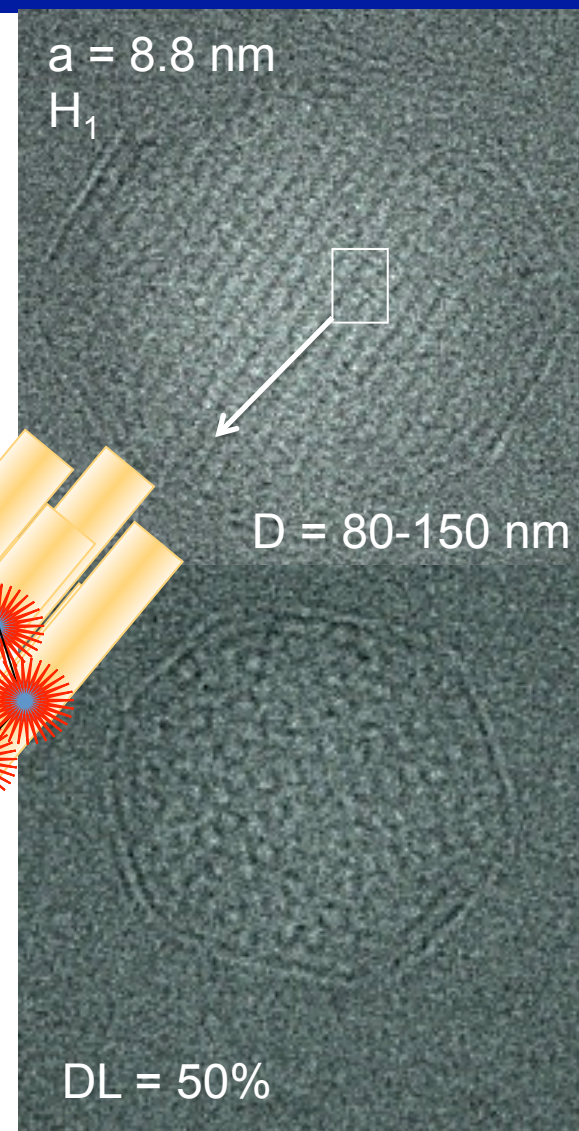
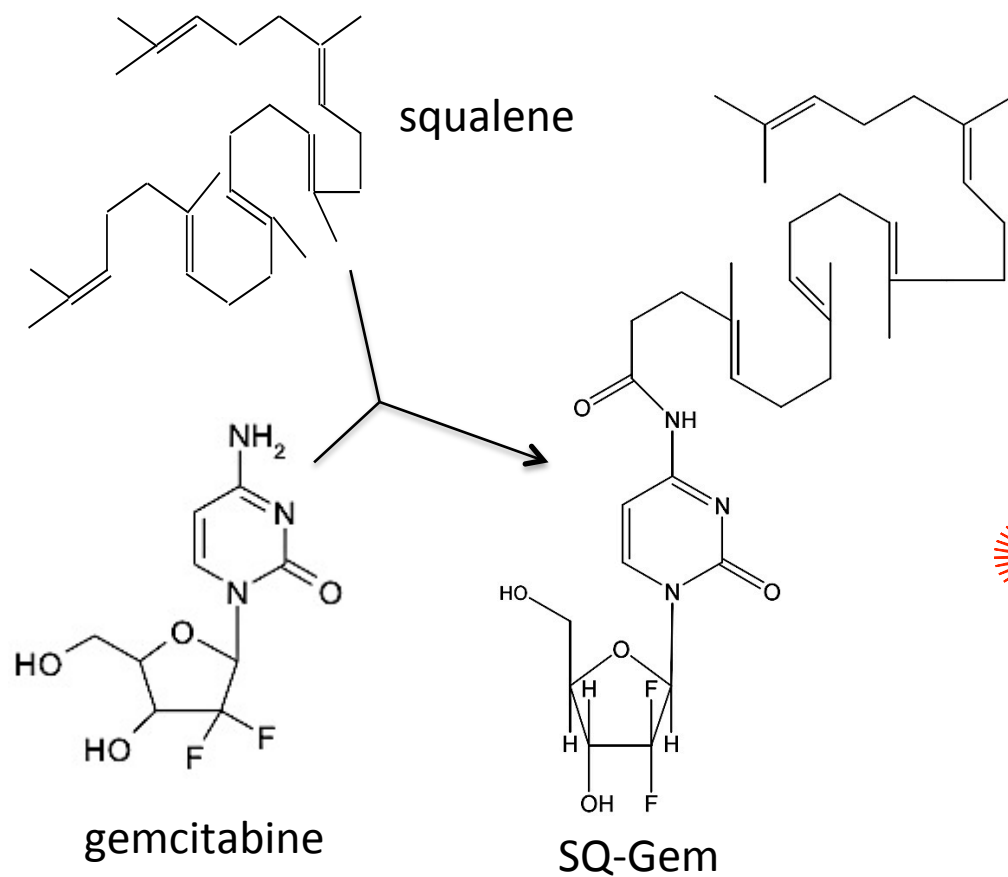
Pas de transport actif, ni passif

Le concept de la squalenoylation



Couvreur et al., *Nano Letters* 2006
Rosilio et al., *EP1761551 B1*, 2011
European Inventor Award finalists, 2013

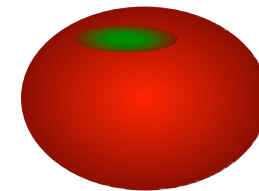
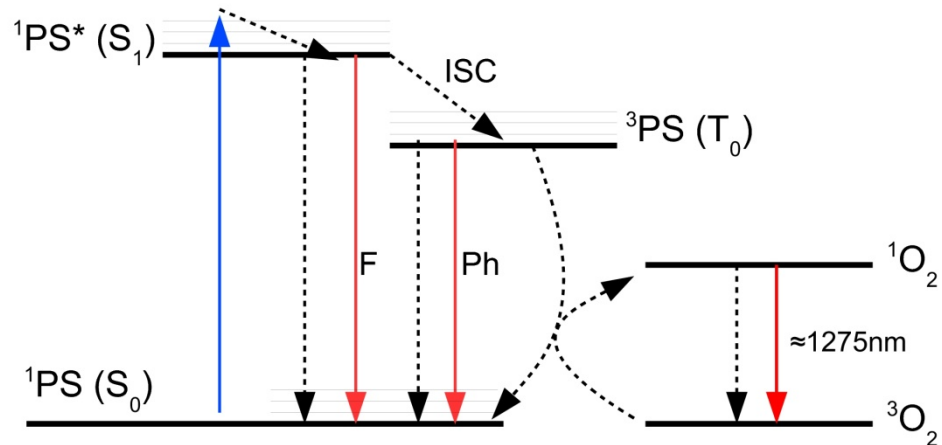
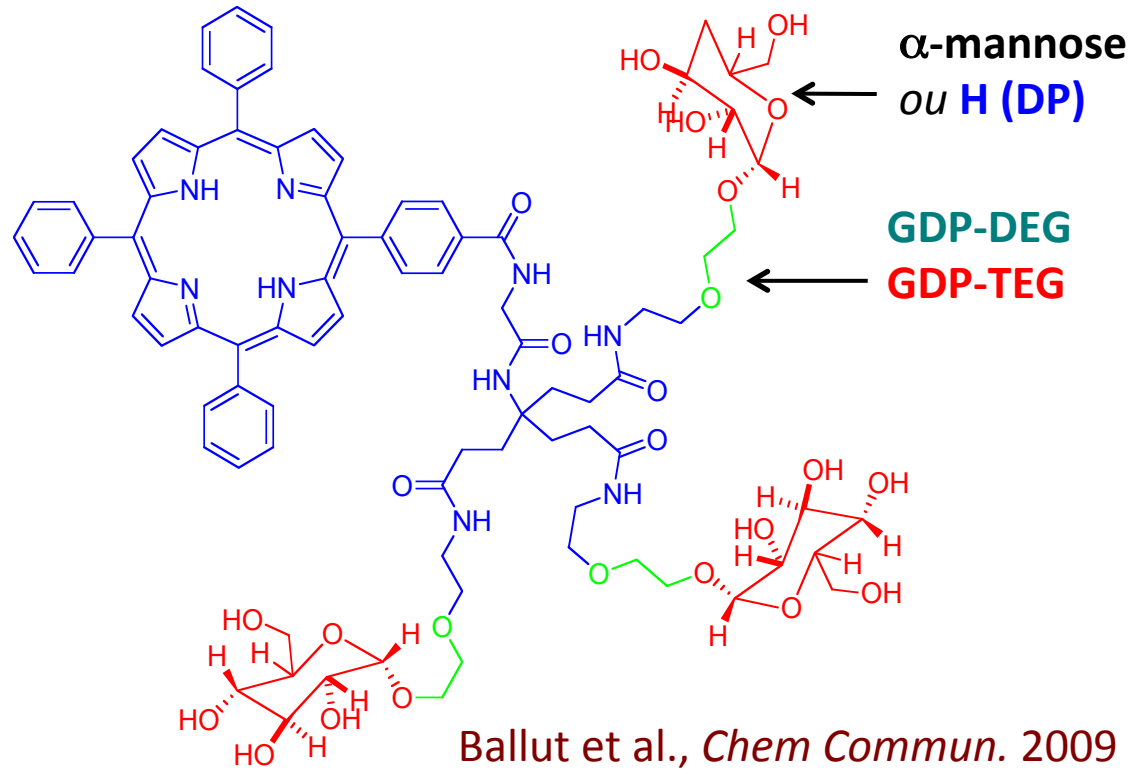
Le concept de la squalenoylation



Couvreur et al., *Nano Letters* 2006
Rosilio et al., *EP1761551 B1*, 2011
European Inventor Award finalists, 2013

Couvreur et al., *Small* 2008

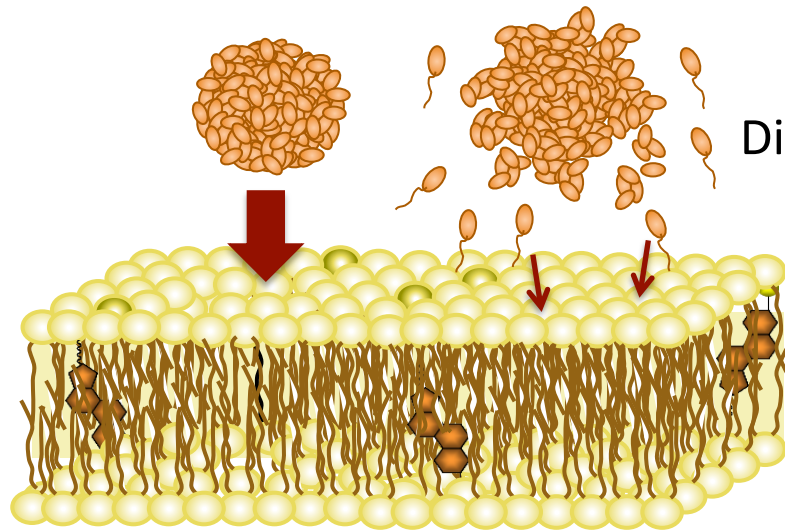
Porphyrines glycodendrimériques



récepteur lectinique
(Concanavalline A)

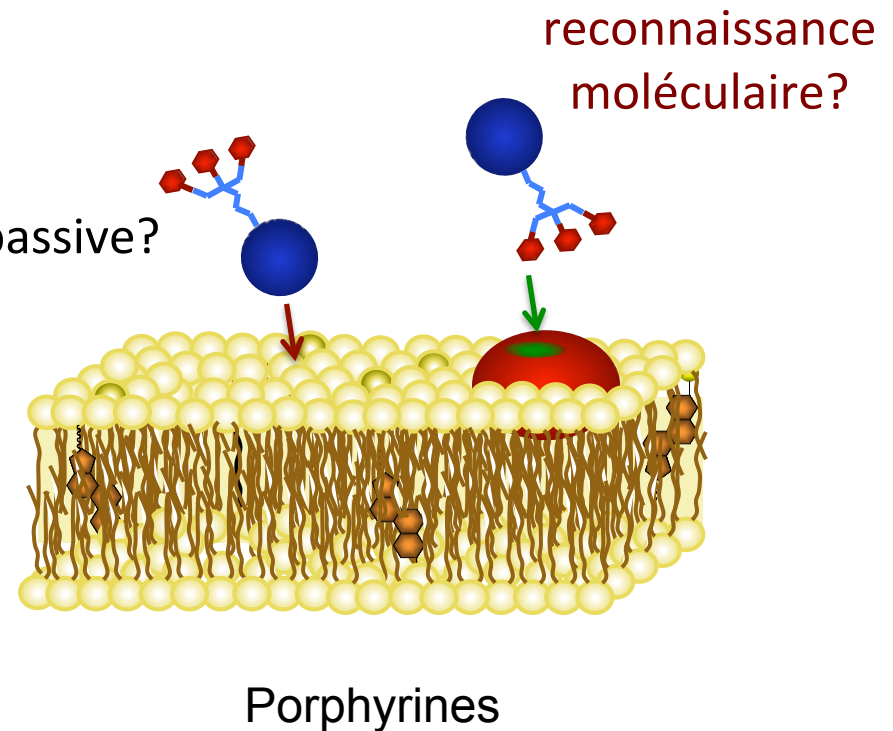
Mécanismes d'interaction avec la membrane?

endocytose?



SQ-Gem

Diffusion passive?

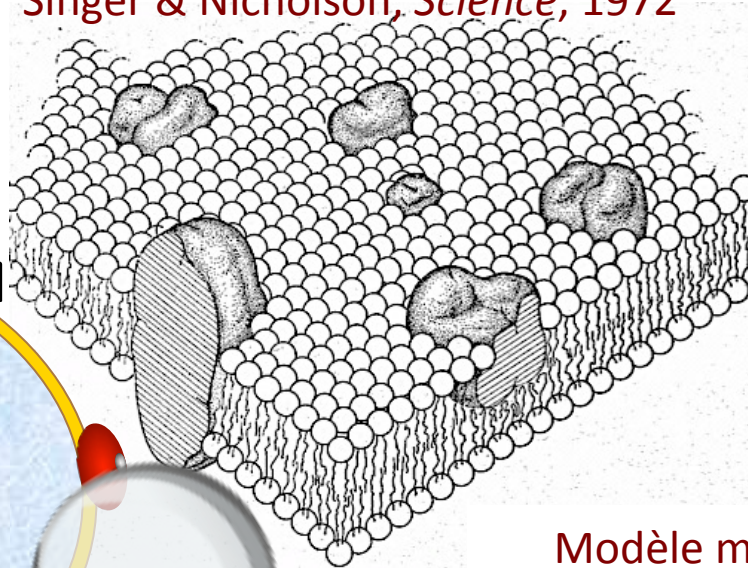


reconnaissance
moléculaire?

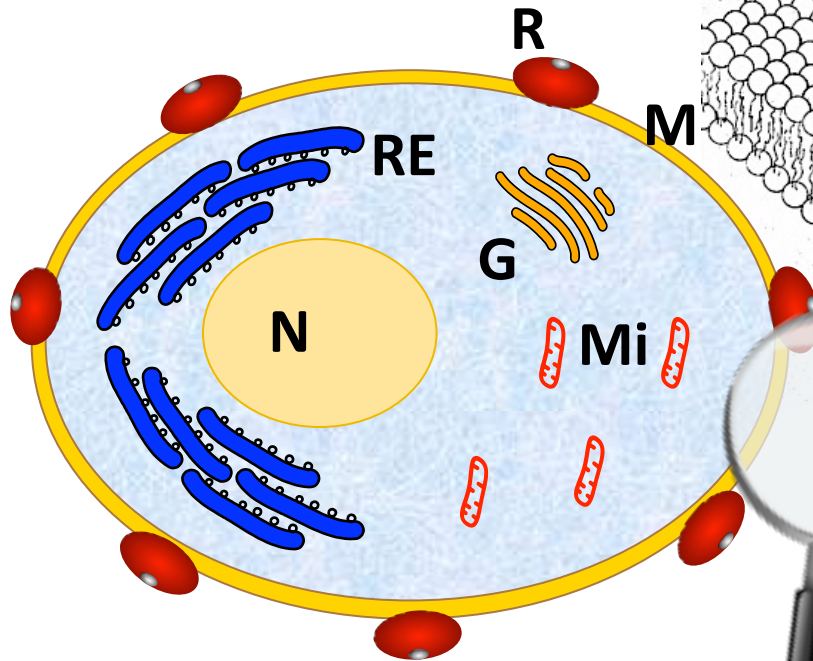
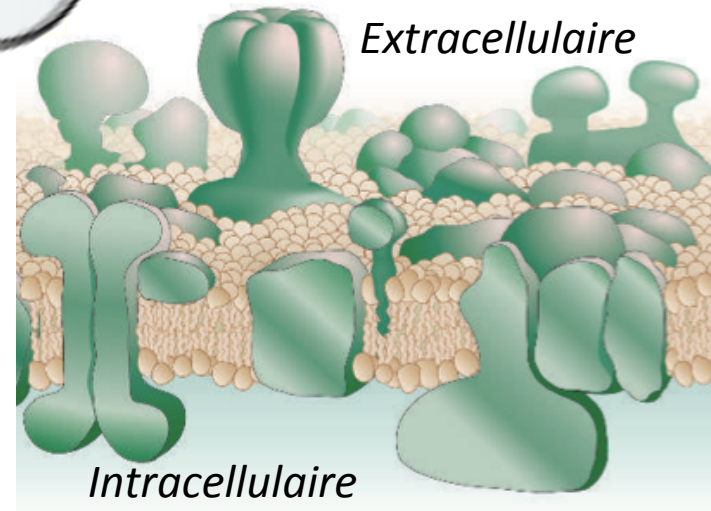
Porphyrines

Membranes cellulaires

Modèle mosaïque fluide,
Singer & Nicholson, *Science*, 1972



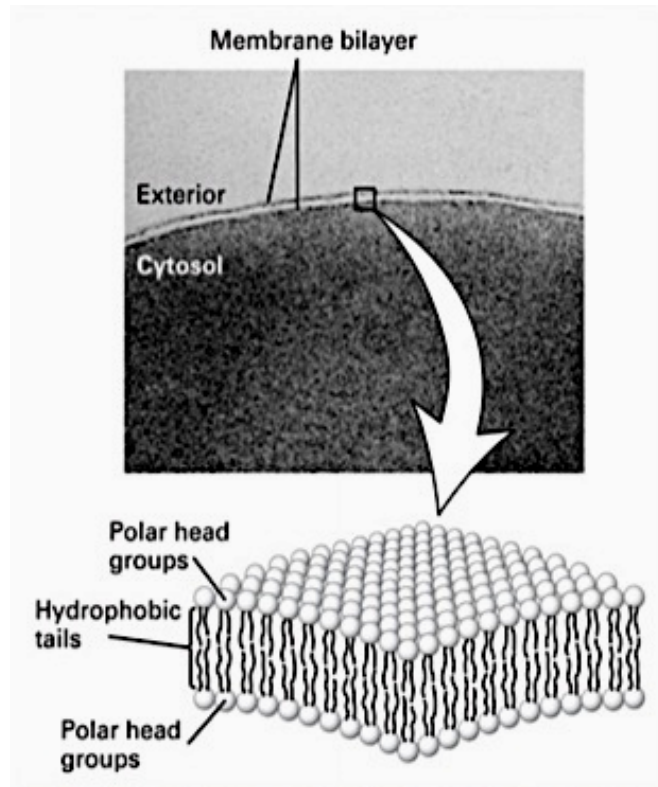
Modèle mosaïque,
Engelman, *Nature*, 2005



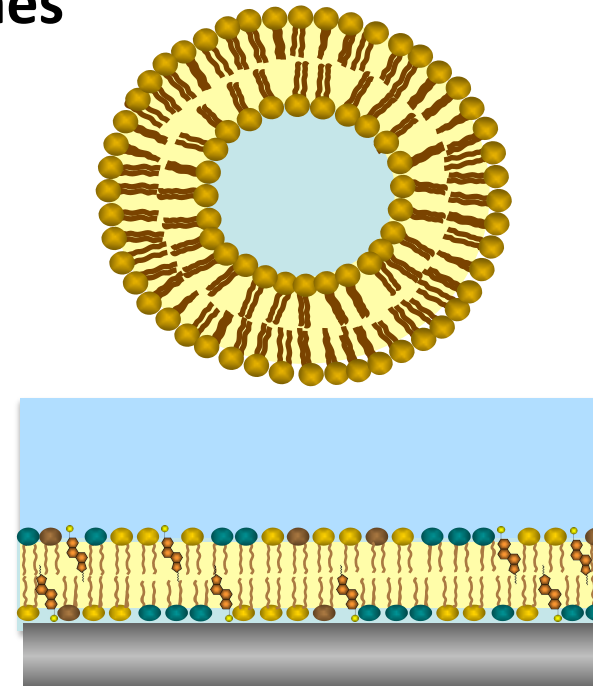
- M: membrane plasmique
- N: noyau
- G: golgi
- RE: reticulum endoplasmique
- Mi: mitochondrie
- R: récepteur membranaire

Modélisation de la membrane cellulaire

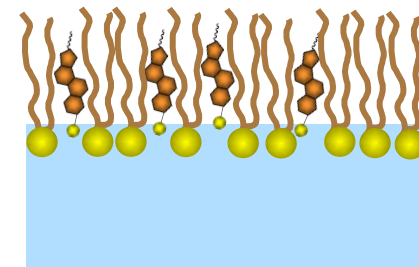
- Modèles bicouches et monocouches



bicouches



monocouches



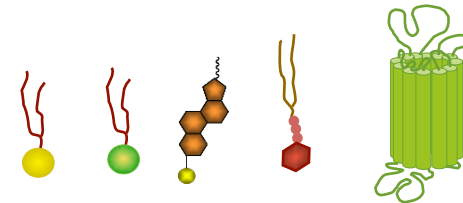
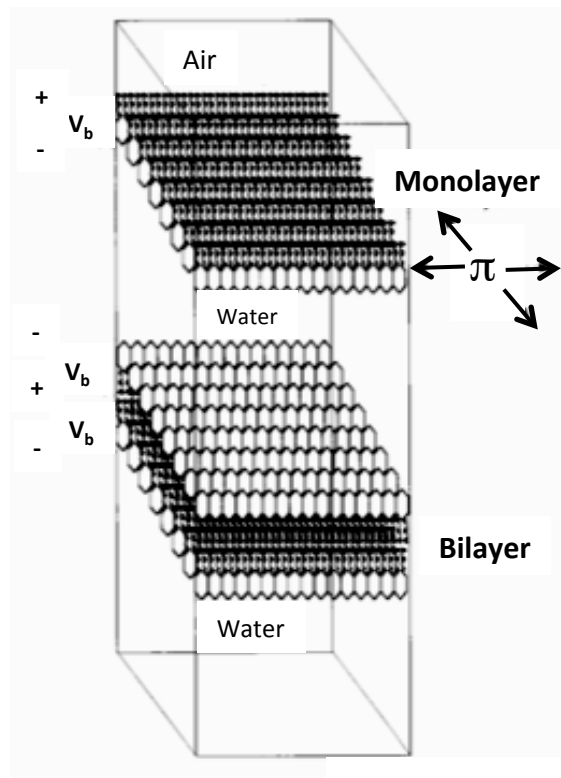
Alberts, Molecular Biology of the Cell 1985.

Modélisation de la membrane cellulaire

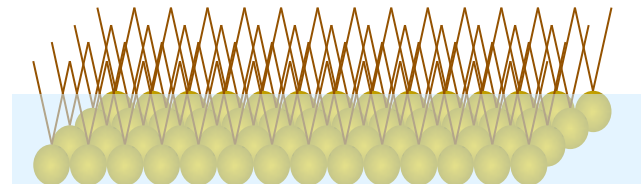
- Intérêt des monocouches dans l'approche biomimétique

Lipid monolayers: why use half a membrane to characterize protein-membrane interactions?

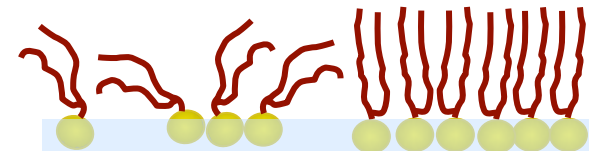
Howard Brockman *Curr. Opin. Struct. Biol.* 1999



contrôle de la composition



contrôle de la densité superficielle

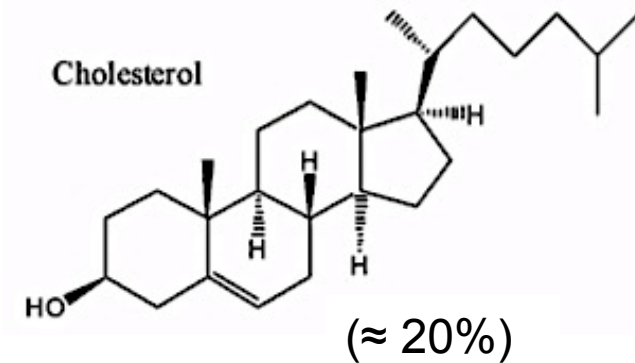
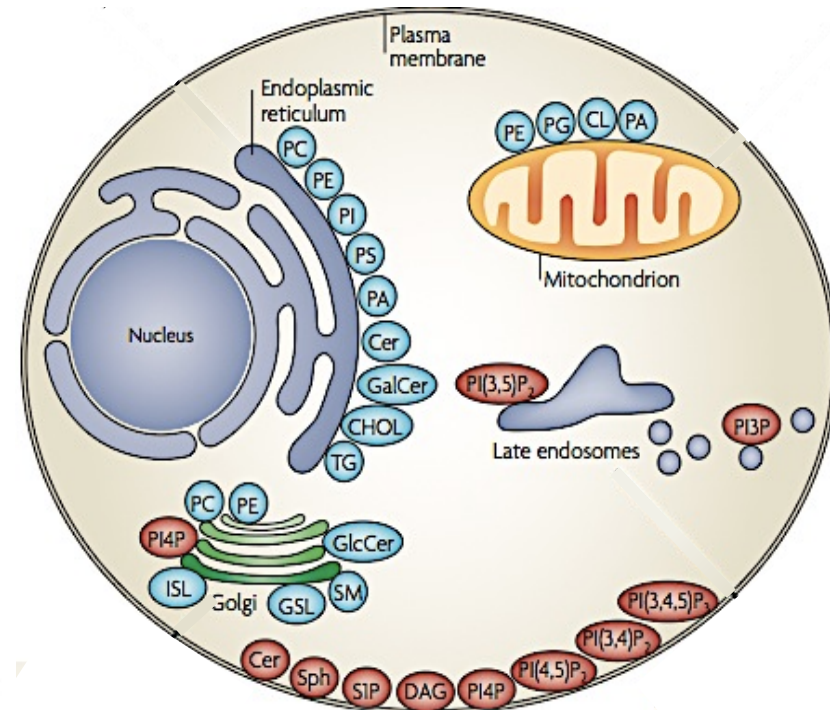
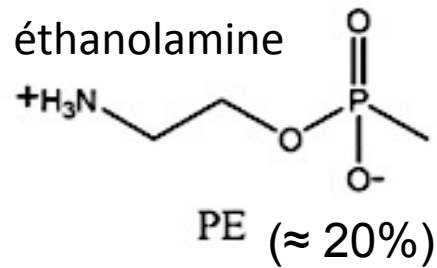
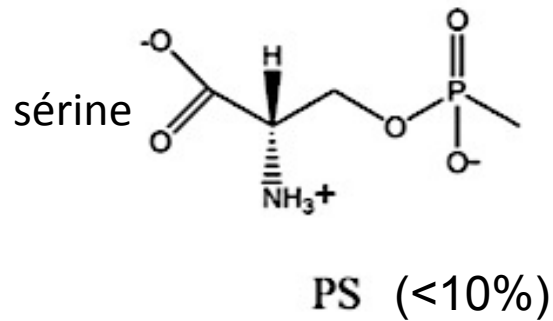
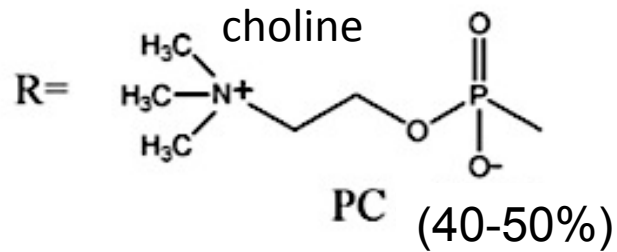


contrôle de la pression latérale

contrôle de la nature du milieu environnant

Lipides membranaires

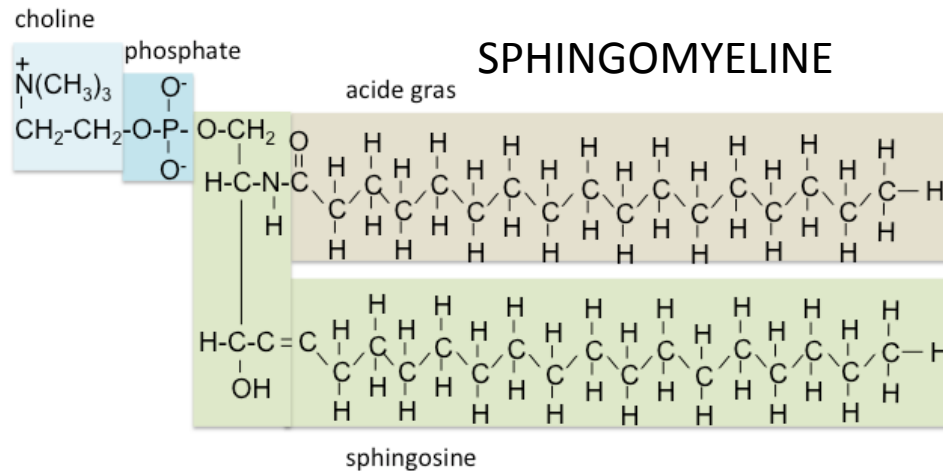
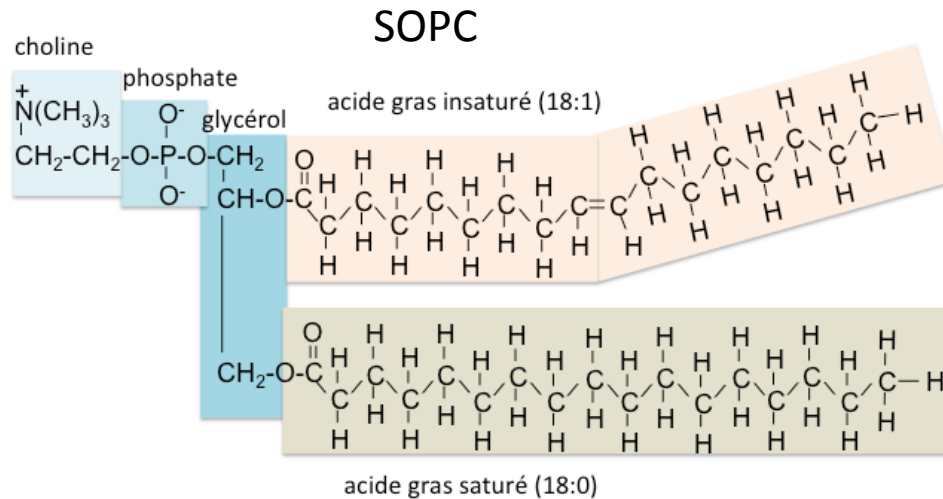
Composition lipidique des membranes,
van Meer, *Nat Rev Mol Cell Biol* 2008



R- glycérol-(chaîne d'acide gras)₂ : glycérophospholipide

ou R- sphingosine-acide gras : céramide

Propriétés des lipides membranaires



- **Propriétés des phospholipides**
- Géométrie globale (CPP)
- Température de transition de phase
- Nature des têtes polaires
- Conformation des chaînes acyl



Organisation latérale non aléatoire

Propriétés des lipides membranaires

- **Paramètre d'empilement** (*critical packing parameter*)

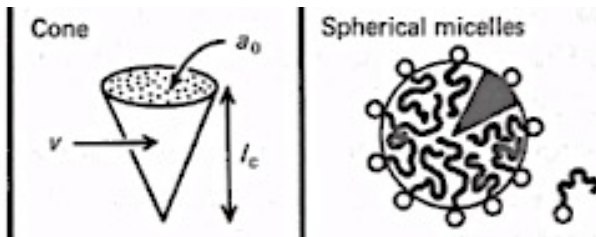
$$CPP = \frac{v_h}{a_p l_c}$$

a_p = aire moyenne par tête
 l_c = longueur de la chaîne
 v_h = volume chaîne hydrocarbonée

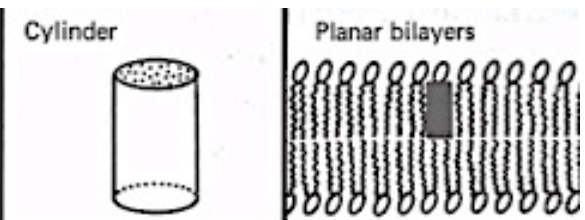
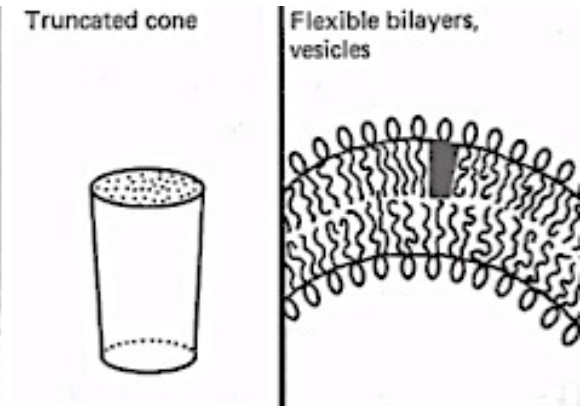
T, pH et I - dépendant

$$\frac{1}{2} < CPP < 1$$

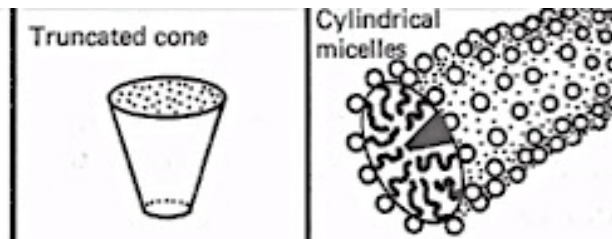
$$CPP < \frac{1}{3}$$



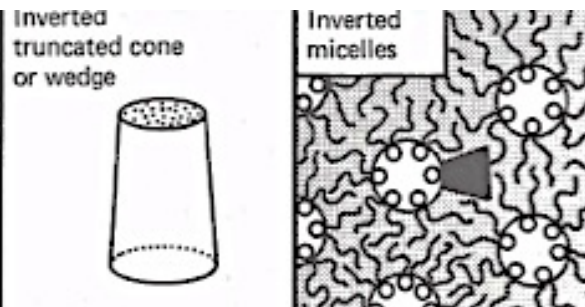
$$CPP \approx 1$$



$$\frac{1}{3} < CPP < \frac{1}{2}$$



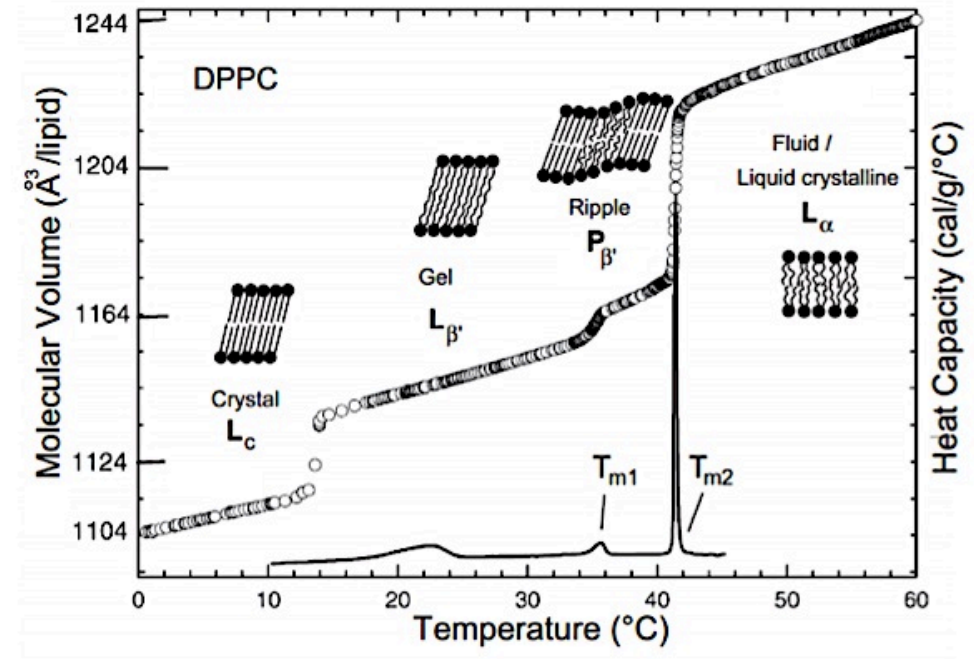
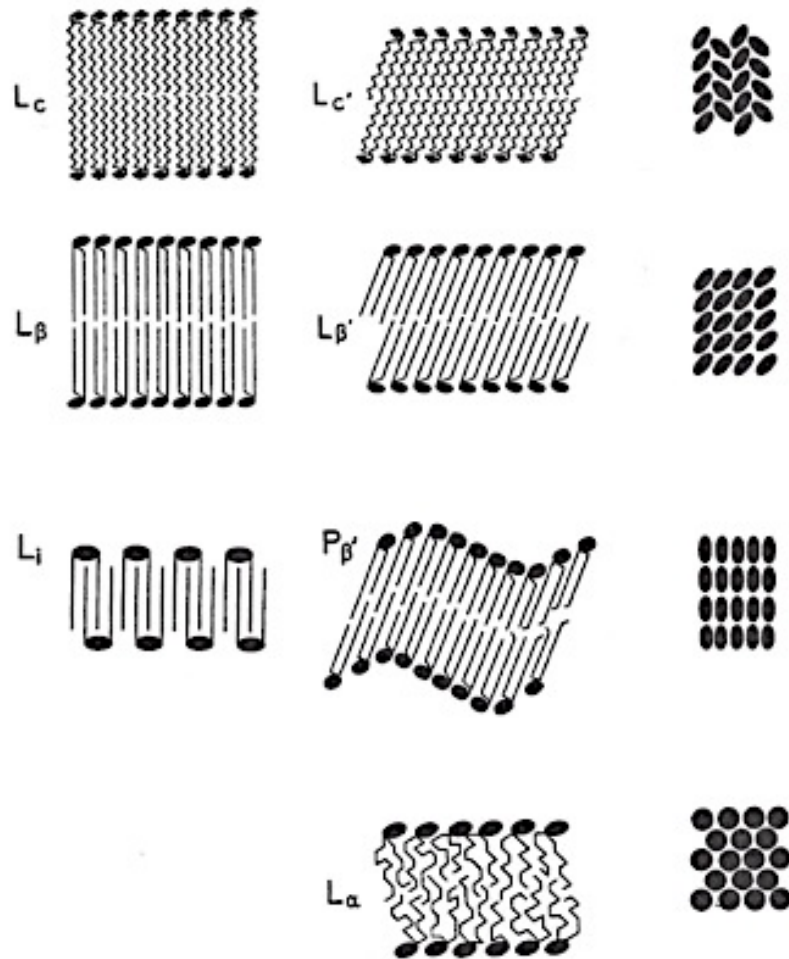
$$CPP > 1$$



Israelachvili, *Intermolecular Forces* 1992
 Nagarajan, *Langmuir* 2002

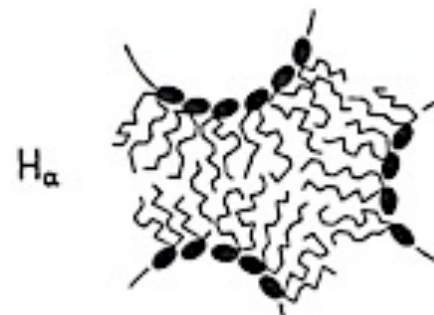
Propriétés des lipides membranaires

- Polymorphisme lyotrope et thermotrope



Wilkinson & Nagle, *BBA* 1982

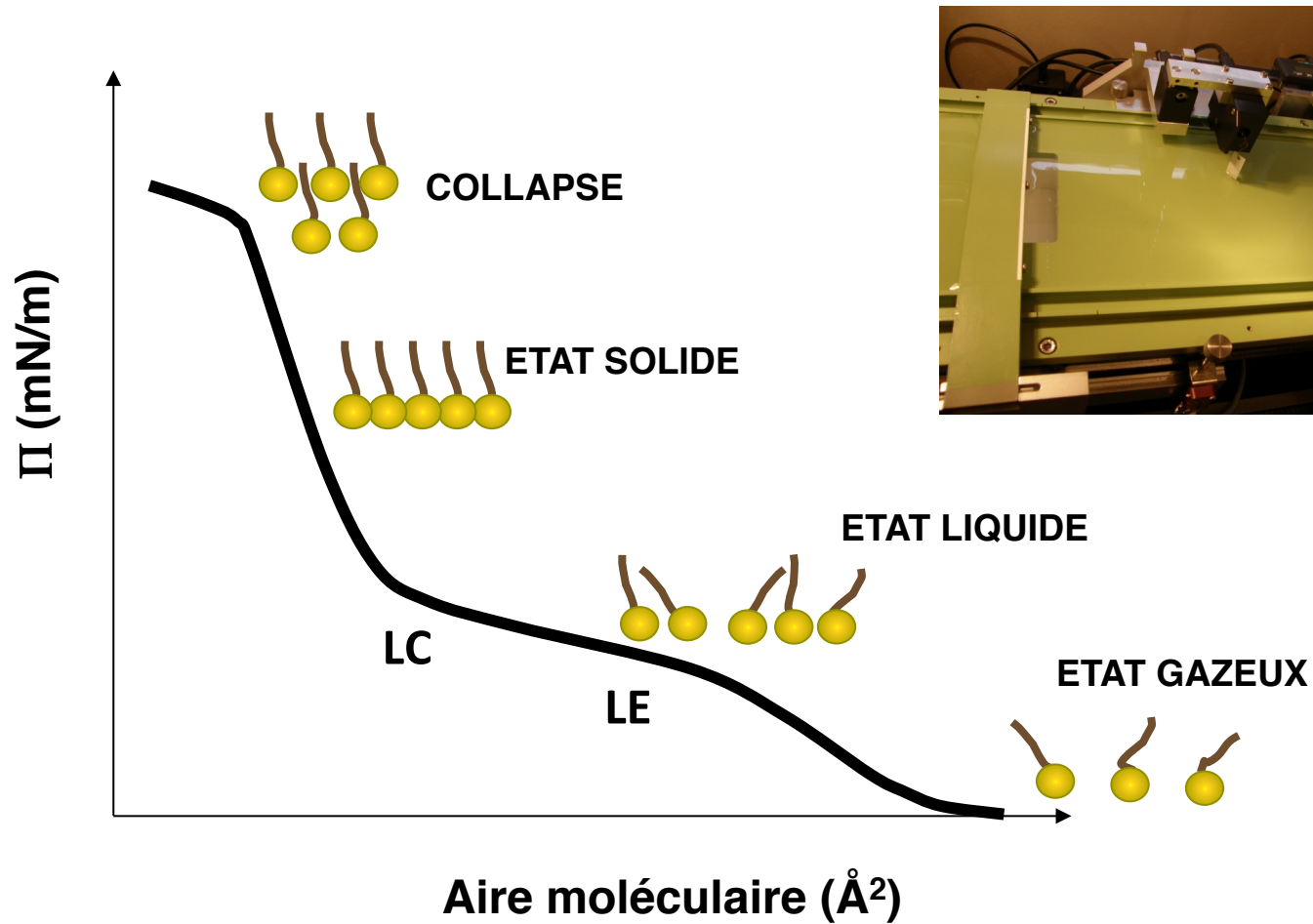
Barenholz & Cevc in *Physical Chemistry of Biological Interfaces* 2000



Propriétés interfaciales des lipides membranaires

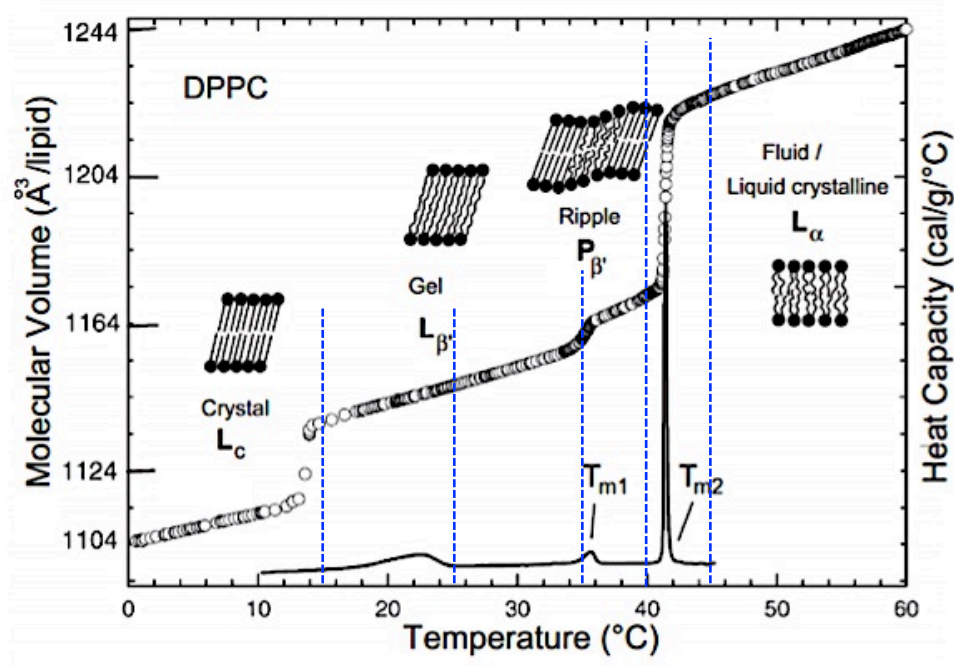
Isotherme π - A

- Changement d'état au sein d'une monocouche



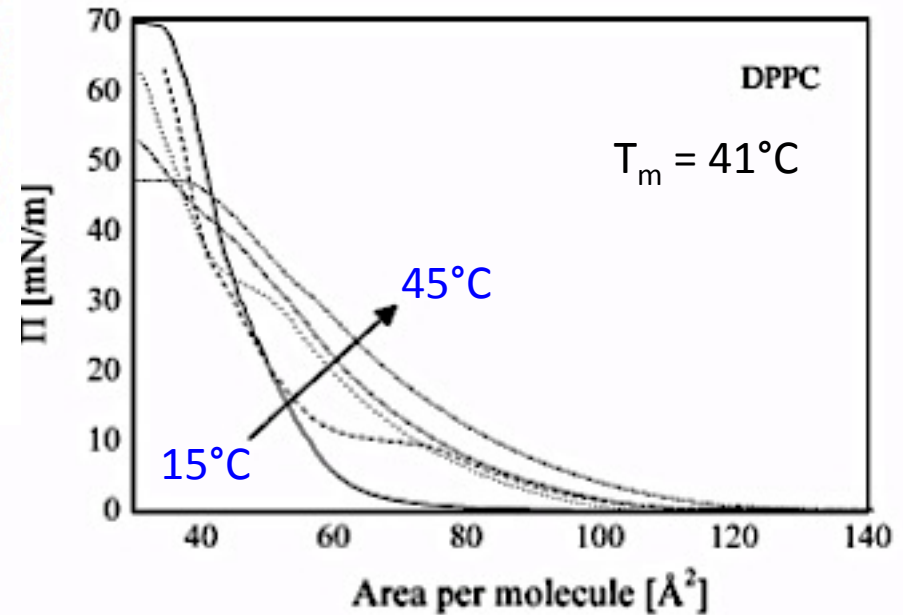
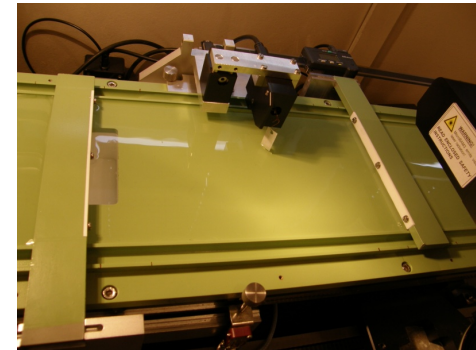
Propriétés des lipides membranaires

- Effet de la température sur le comportement interfacial de DPPC



Wilkinson & Nagle, *BBA* 1982

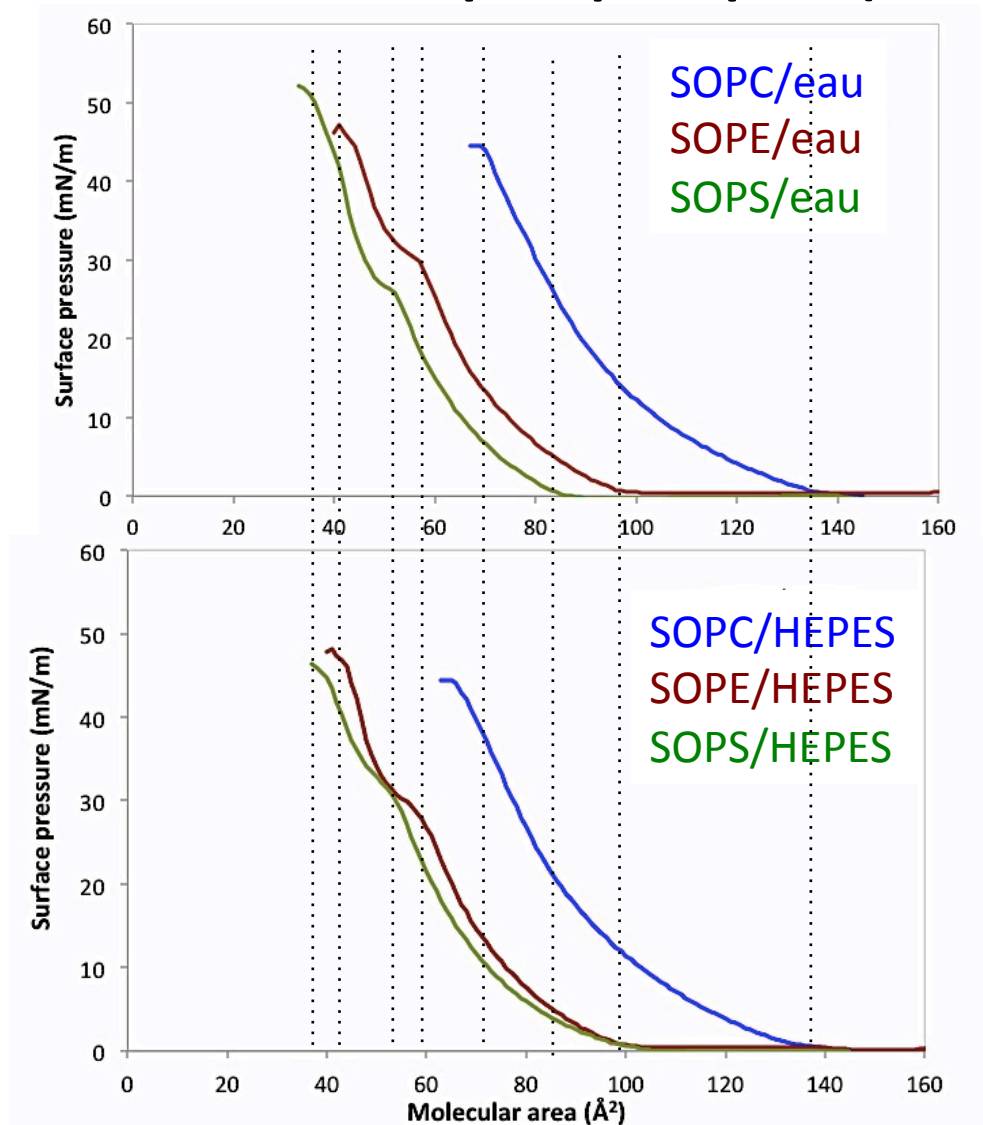
$$\pi = -\Delta\gamma$$



Bordi et al., *Colloids Surf B* 2008

Propriétés interfaciales des lipides membranaires

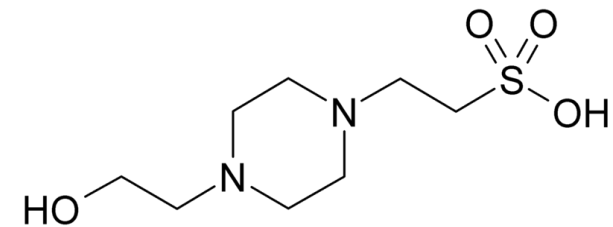
- Effet de la nature de la tête polaire sur le comportement interfacial du phospholipide (interface air/eau et air/tampon)



Température : $22 \pm 1^\circ\text{C}$

pH eau: 6.5

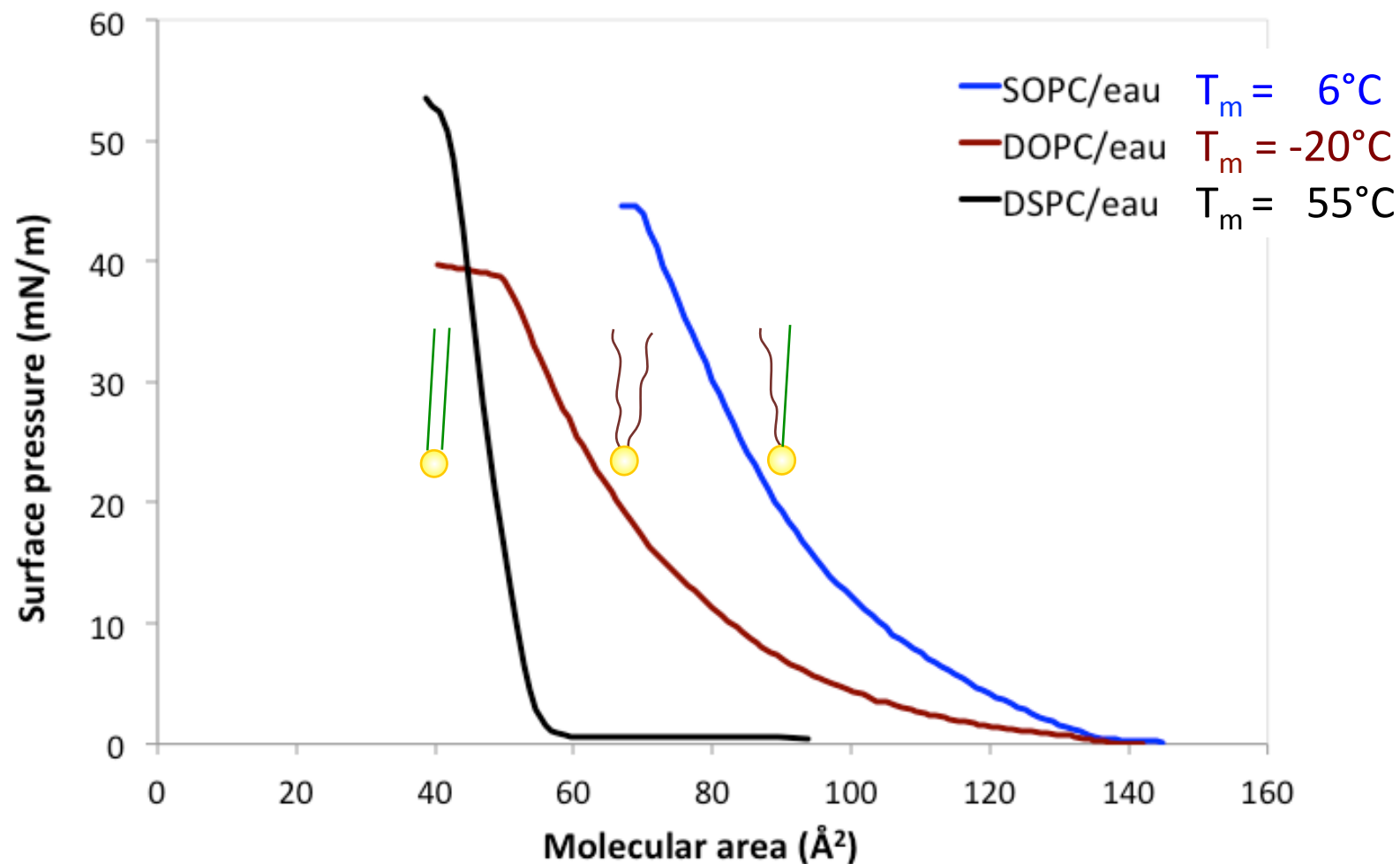
pH sol HEPES: 6.5



HEPES: 4-(2-hydroxyethyl)-1-piperazineethane sulfonic acid

Propriétés interfaciales des lipides membranaires

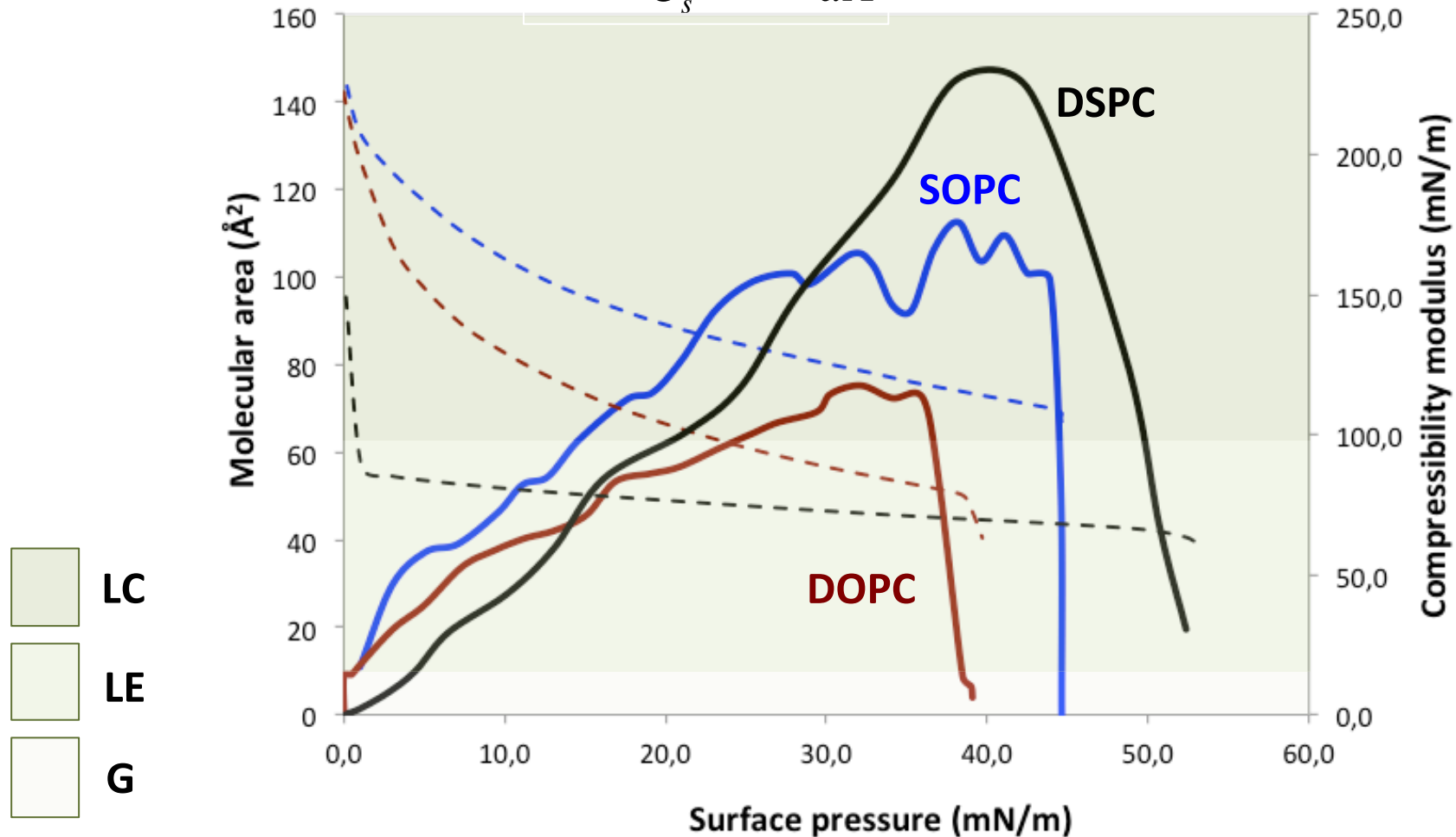
- Effet de la conformation des chaînes acyl sur le comportement des phospholipides
 - Comparaison de DSPC, DOPC et SOPC ($T = 22 \pm 1^\circ\text{C}$)



Propriétés interfaciales des lipides membranaires

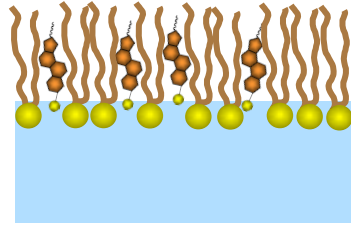
- Compressibilité latérale C_s des monocouches

$$C_s^{-1} = \frac{1}{C_s} = -A \frac{d\pi}{dA}$$



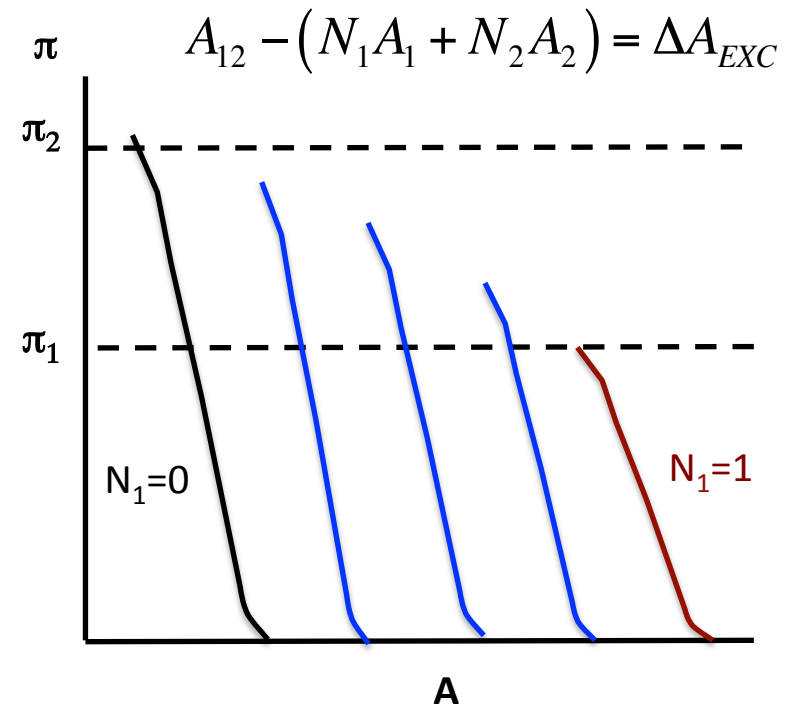
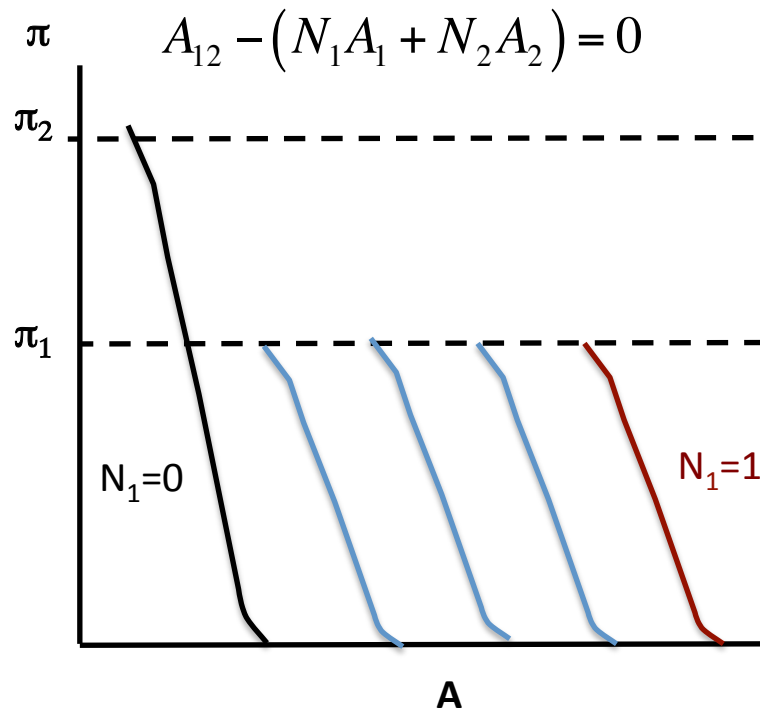
Propriétés interfaciales des lipides membranaires

- Mélanges de lipides:



— composants **immiscibles**

ou **miscibles**



$$\Delta G_m^\pi = \int_0^\pi (A_{12} - N_1 A_1 - N_2 A_2) d\pi + RT (N_1 \ln N_1 + N_2 \ln N_2)$$

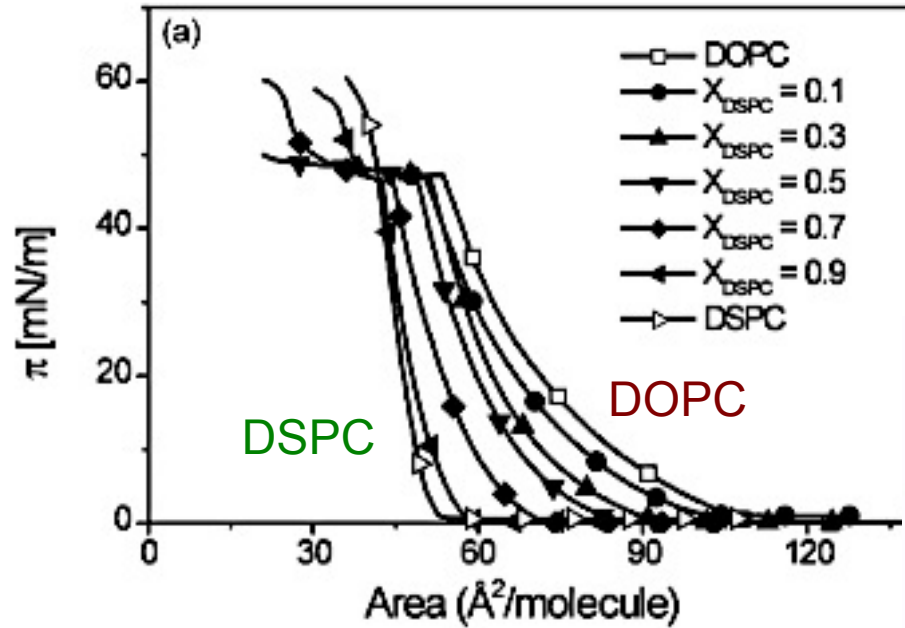
$\Delta G_{excès}^\pi$

+

$\Delta G_m^{Idéal}$

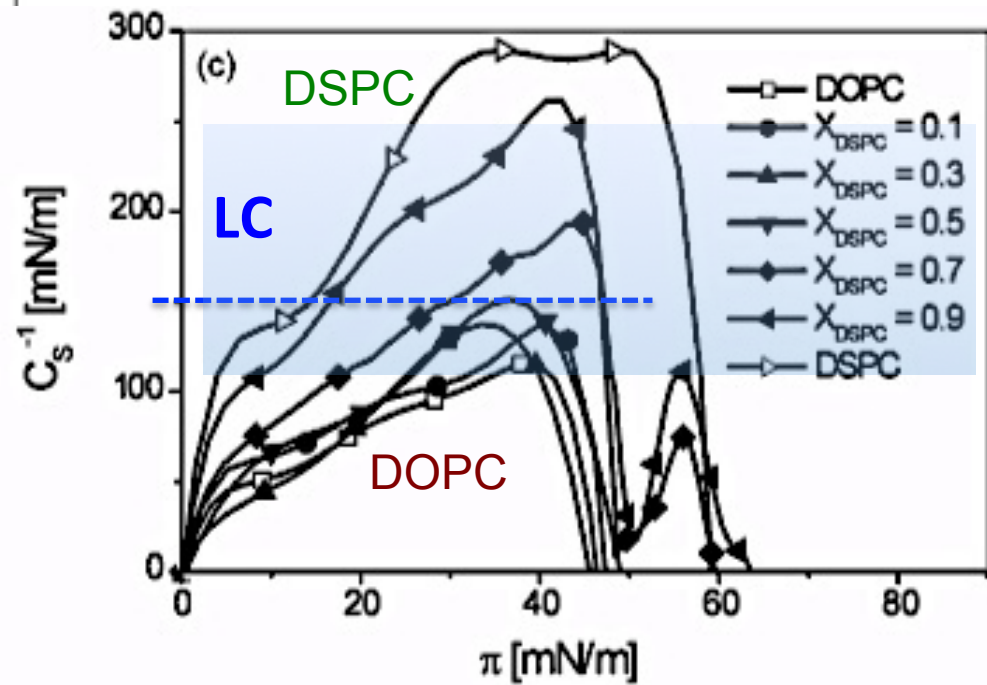
Propriétés interfaciales des lipides membranaires

- Mélanges DOPC-DSPC (1:1)



T_m (DOPC) = -20°C
 T_m (DSPC) = 55°C

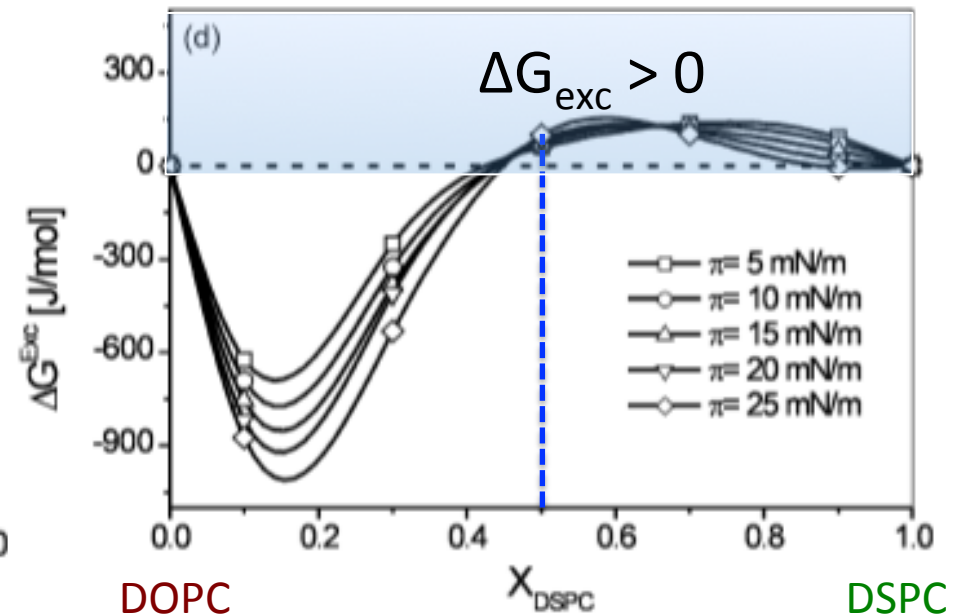
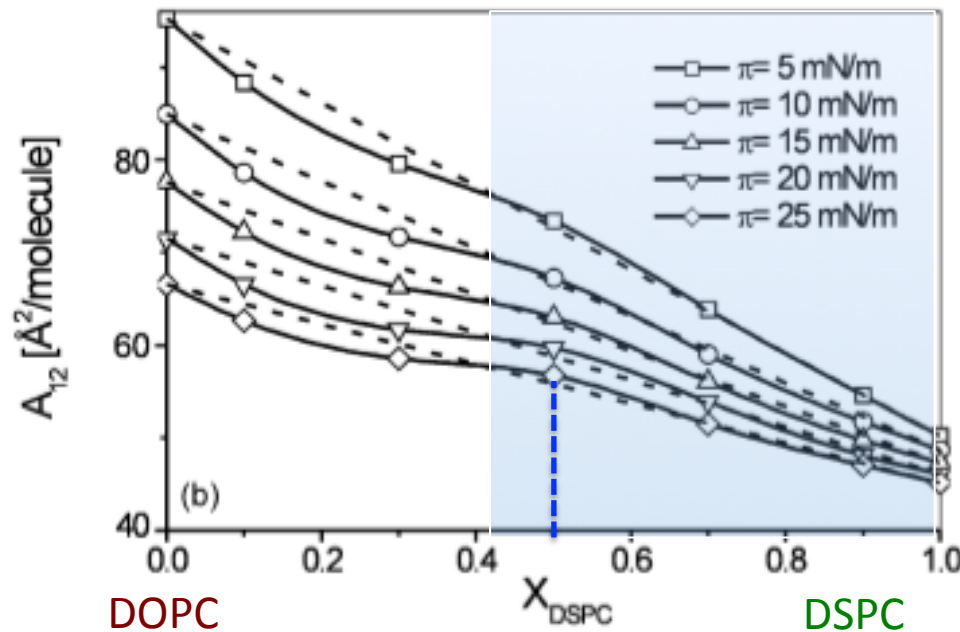
$$C_s^{-1} = -A \frac{d\pi}{dA}$$



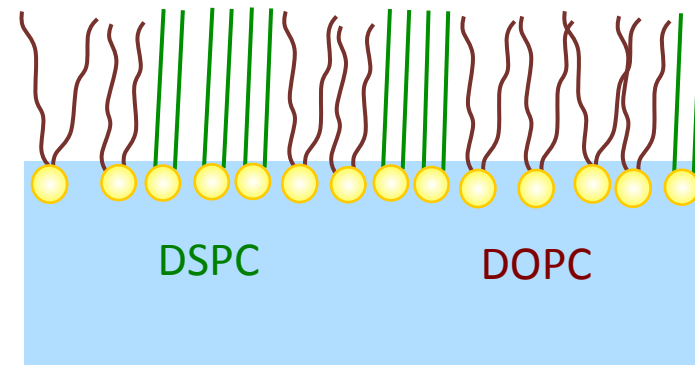
Propriétés interfaciales des lipides membranaires

- Mélanges DOPC-DSPC (1:1)

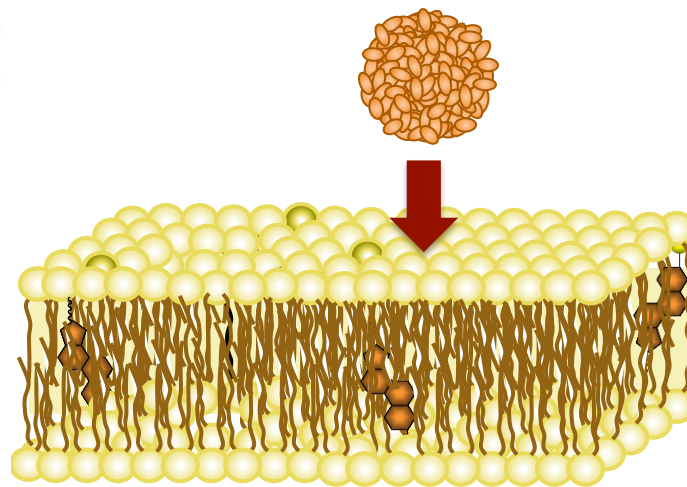
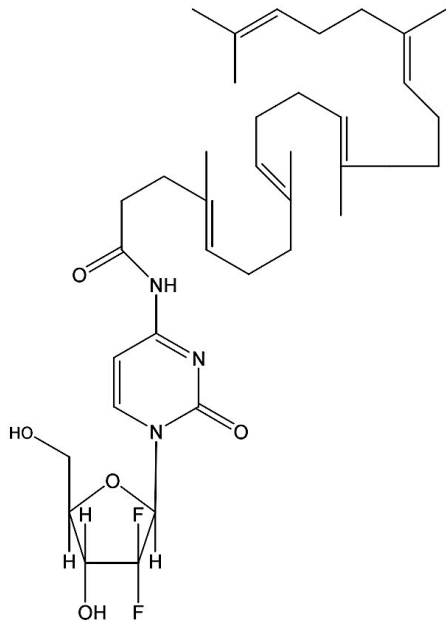
$$\Delta G_{excès}^{\pi} = \int_0^{\pi} (A_{12} - N_1 A_1 - N_2 A_2) d\pi$$



$$A_{12} - (N_1 A_1 + N_2 A_2) \approx 0$$

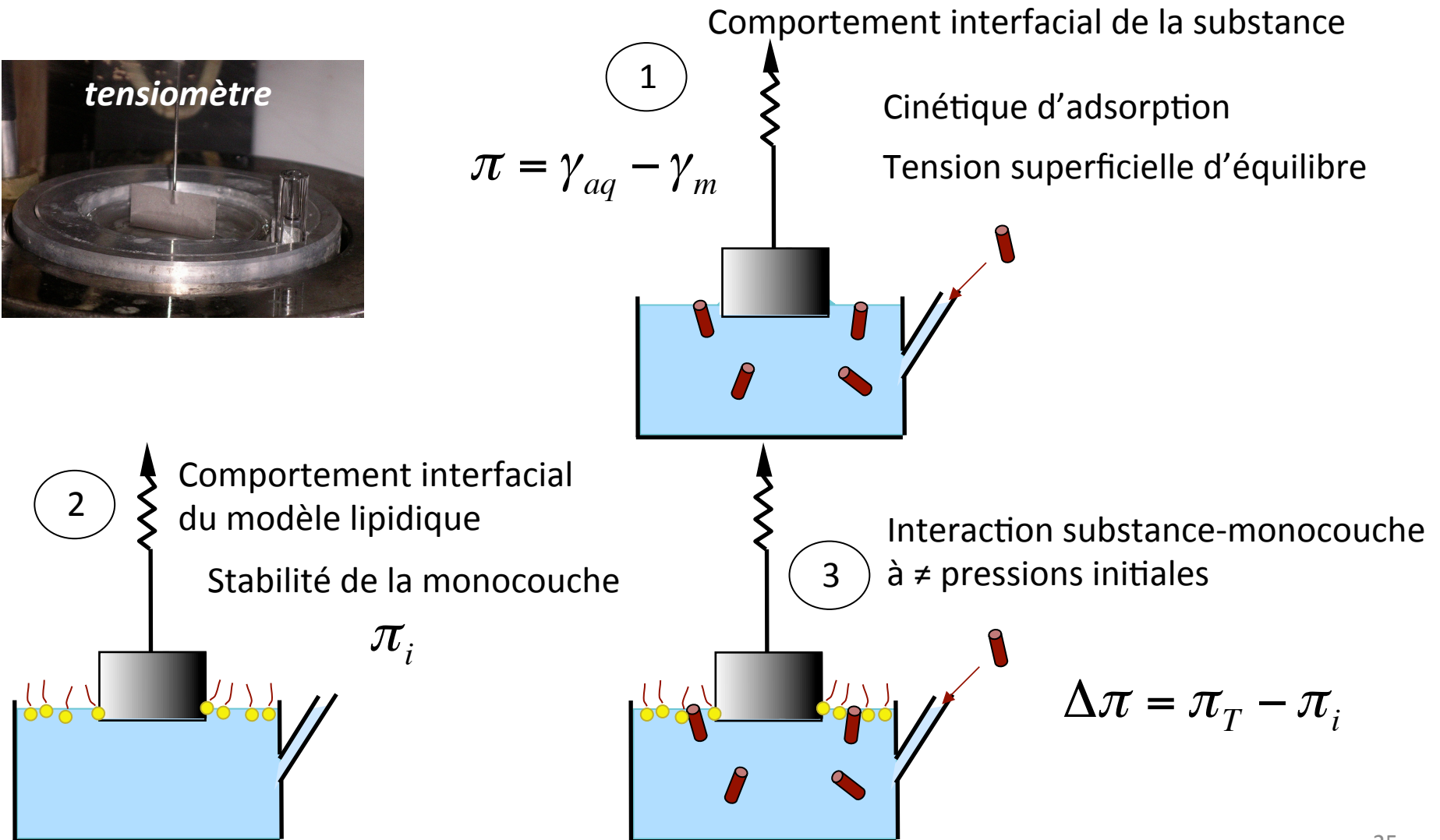
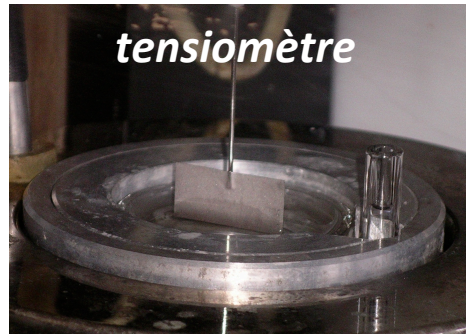


Interaction molécules-membrane SQ-Gem/DOPC-DSPC-CHOL



Modélisation des interactions molécule/membrane

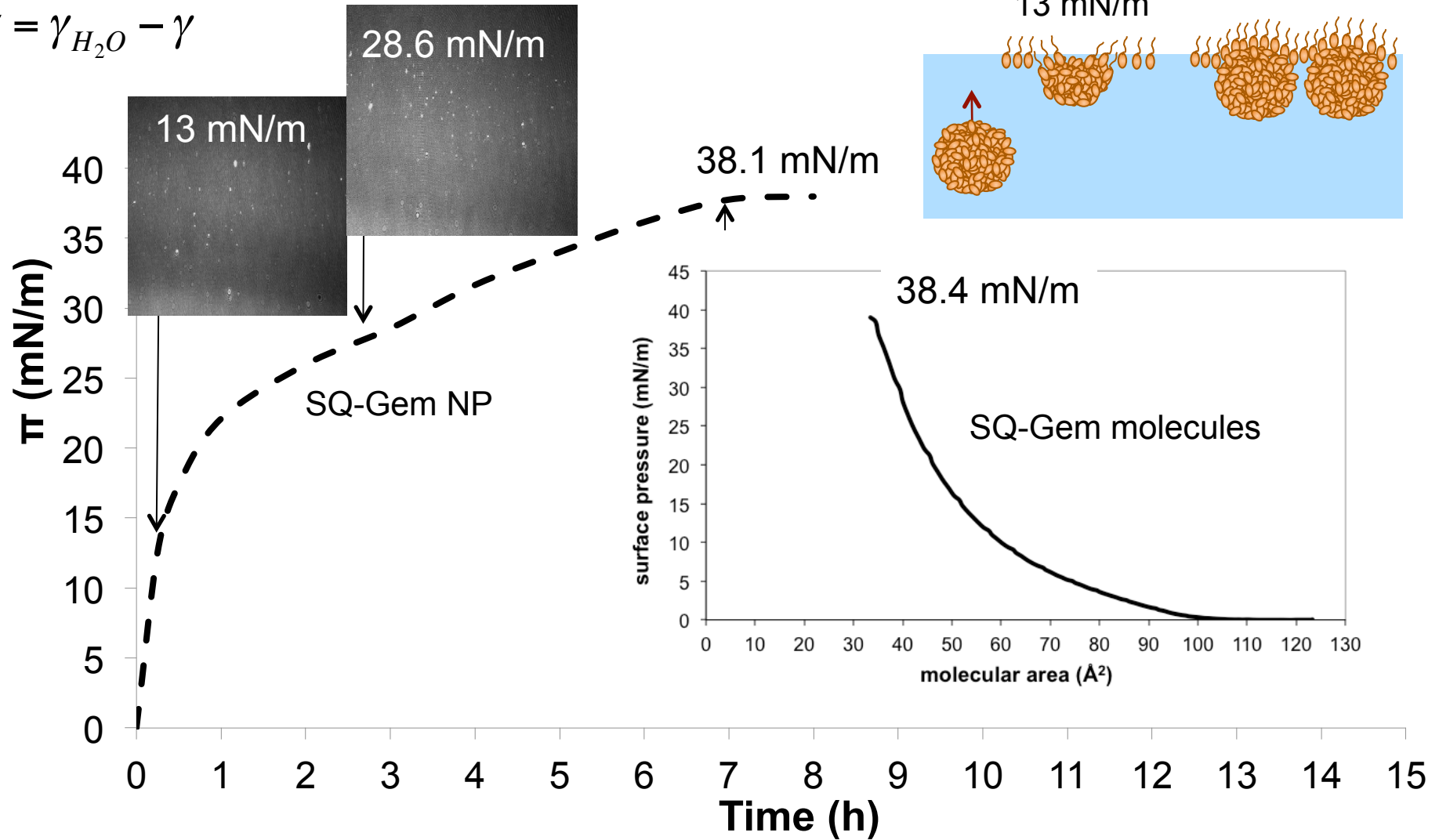
- **Analyse du phénomène d'adsorption-pénétration**



Comportement interfacial des NP de SQ-Gem

[SQ-Gem] = 3.9×10^{-5} M

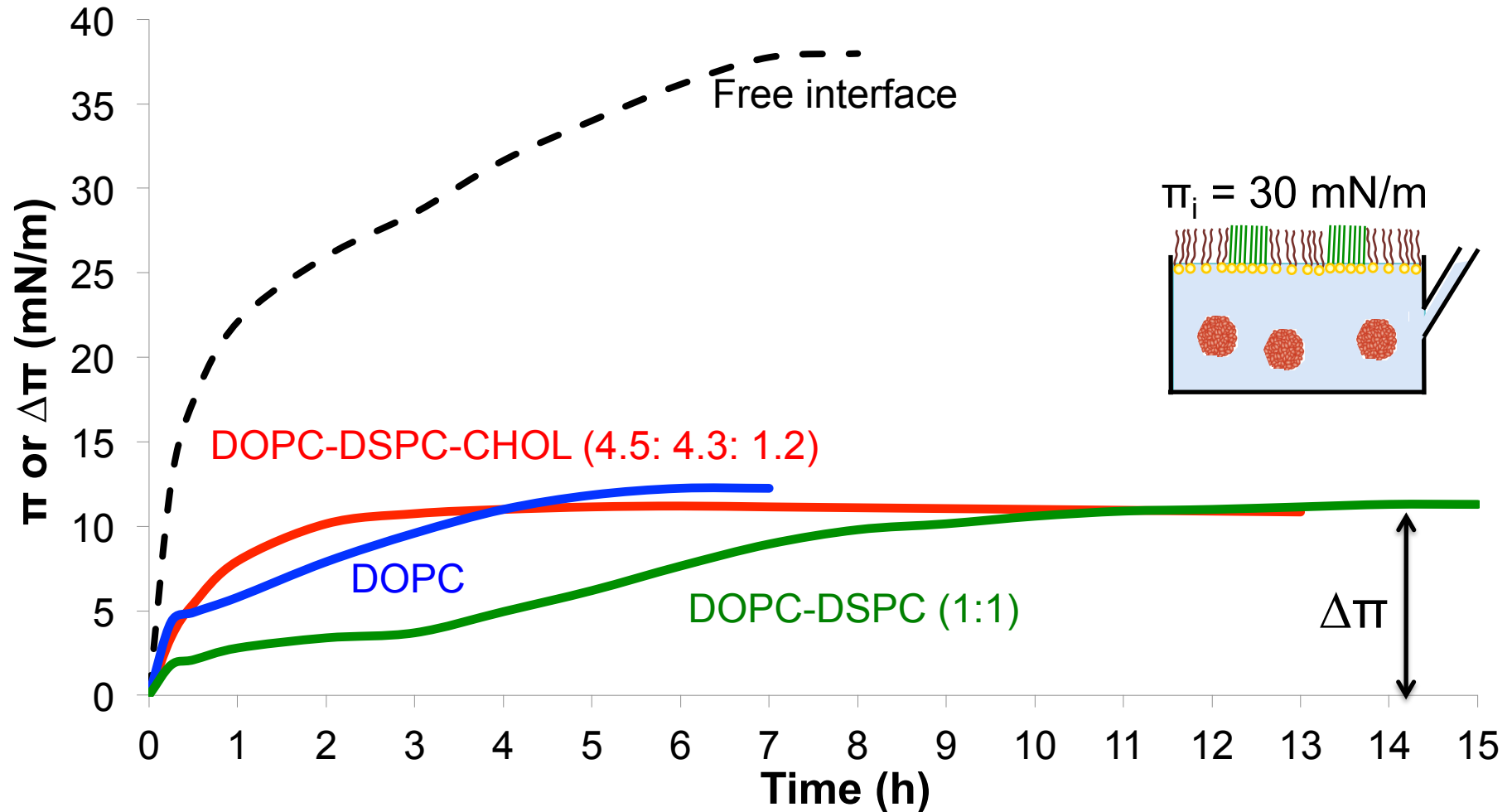
$$\pi = \gamma_{H_2O} - \gamma$$



Ambike et al., *Langmuir* 2011

Interaction des NP avec des monocouches lipidiques

[SQ-Gem] = 3.9×10^{-5} M

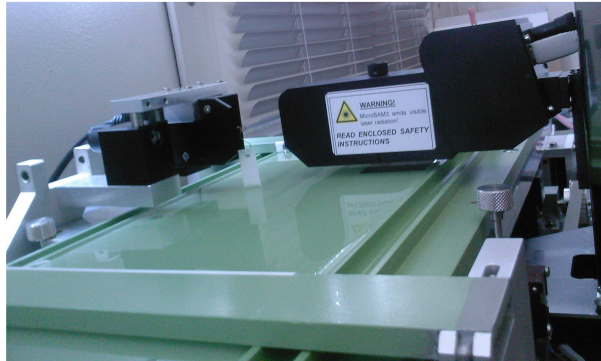


DOPC: dioleoylphosphatidylcholine
DSPC: distearoylphosphatidylcholine

Ambike et al., *Langmuir* 2011

Comportement de SQ-Gem en mélange avec les lipides

- **Analyse de l'interaction de SQ-Gem avec chaque lipide**



$$\Delta G_{EXC} = \int_0^{\pi} \Delta A_{EXC} d\pi$$

– Pour une monocouche contenant 20% de SQ-Gem, à 30 mN/m:

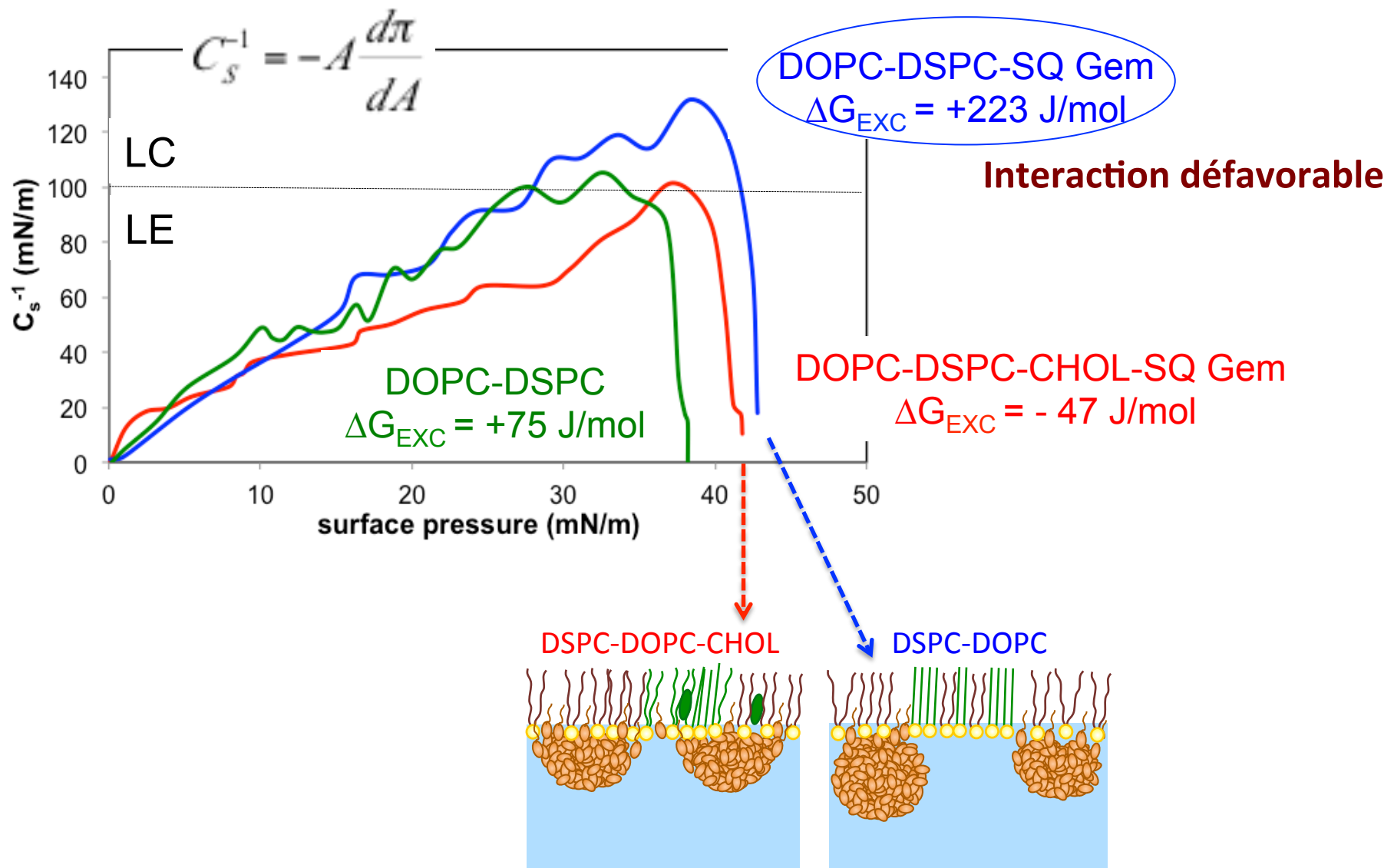
- $\Delta G_{EXC} (DOPC) = - 930 \text{ J/mol}$

- $\Delta G_{EXC} (DSPC) = - 20 \text{ J/mol}$

- $\Delta G_{EXC} (CHOL) = + 310 \text{ J/mol}$

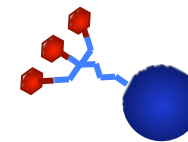
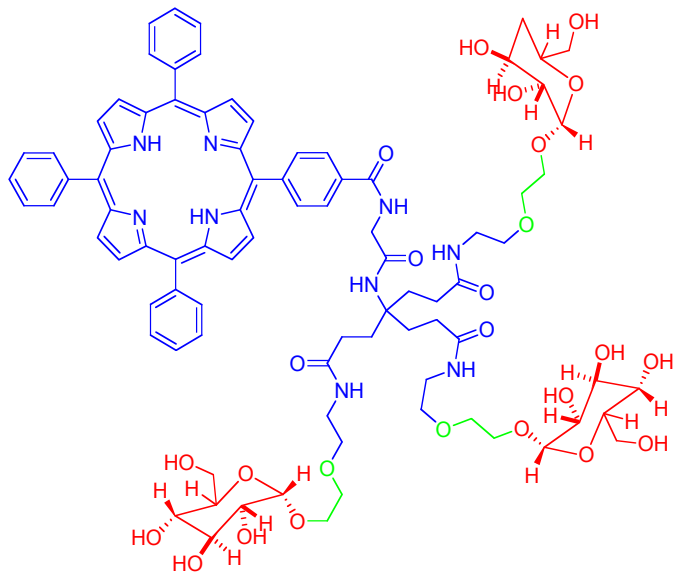
Interaction défavorable

Organisation des monocouches mixtes SQ-Gem-lipides

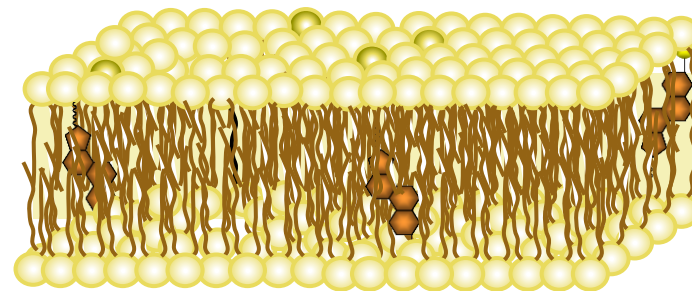


Ambike et al., *Langmuir* 2011

Interaction non spécifique molécule-membrane Porphyrines/SOPC-SOPE-SOPS-CHOL

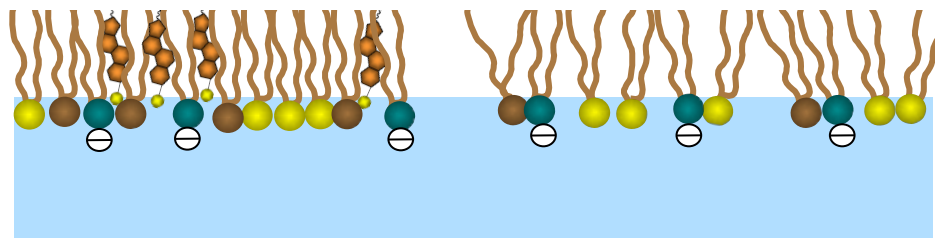
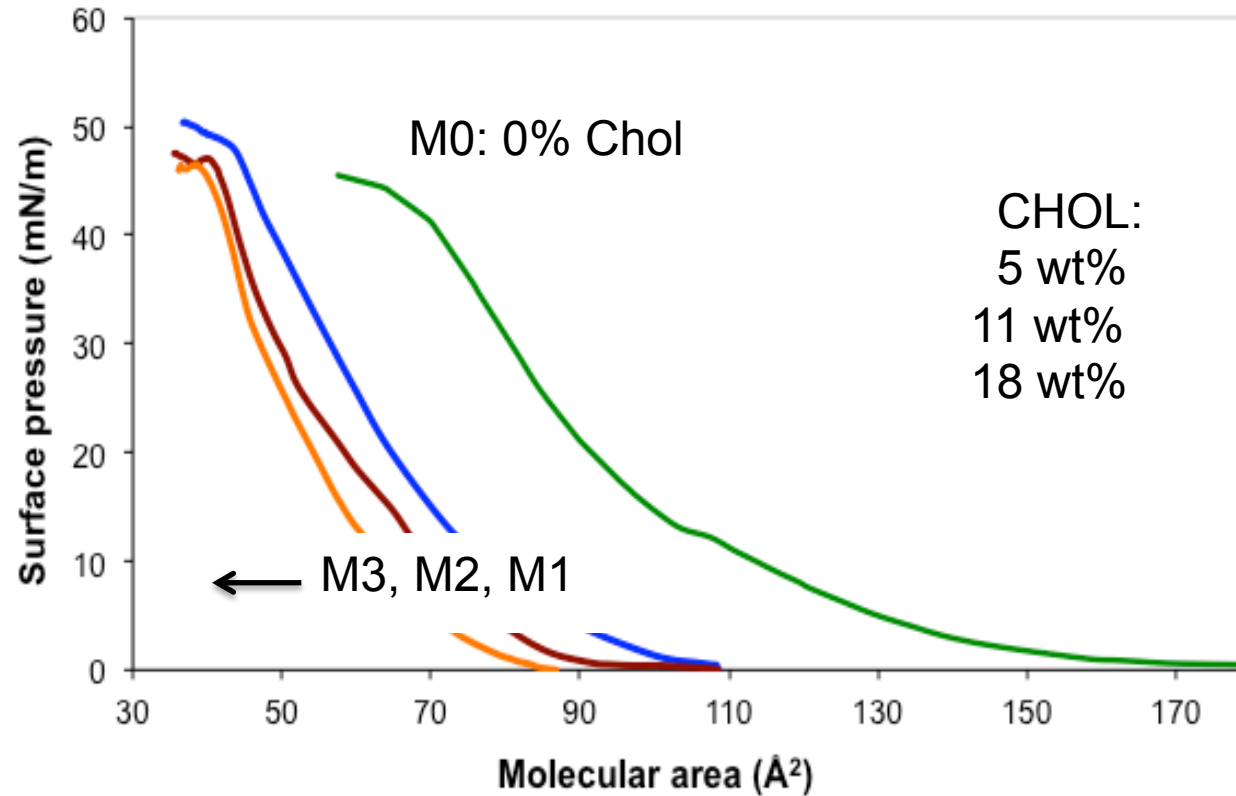


Diffusion passive?

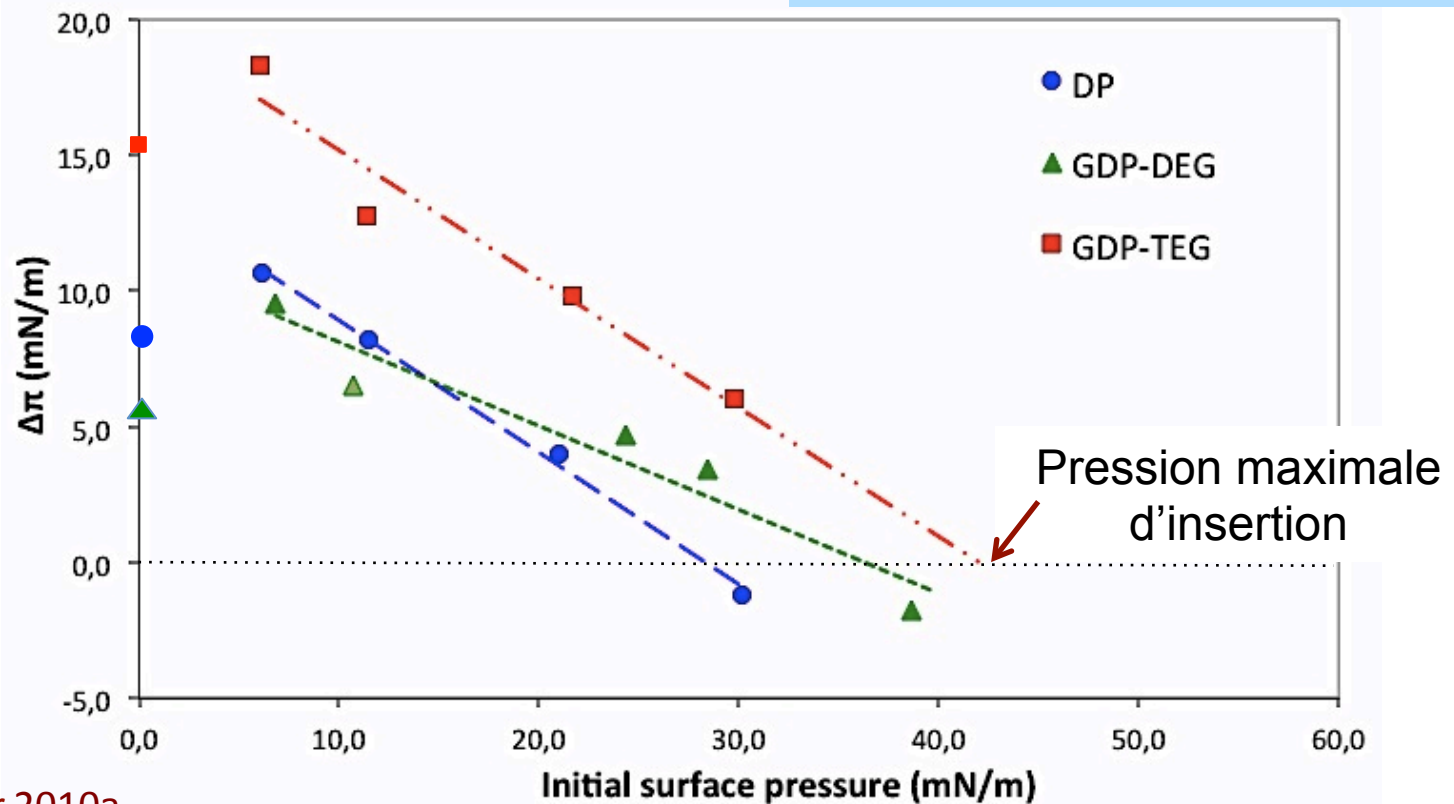
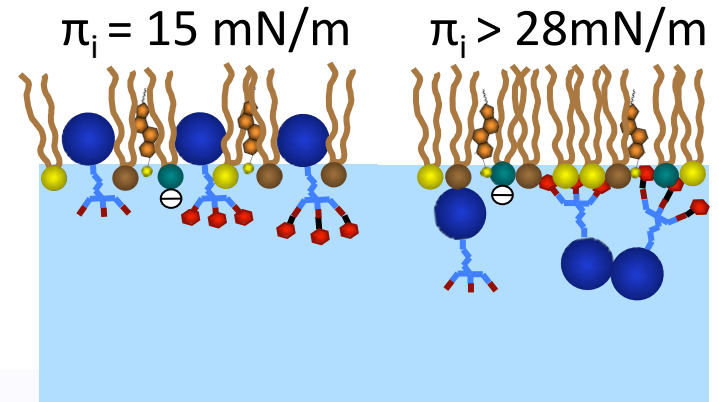
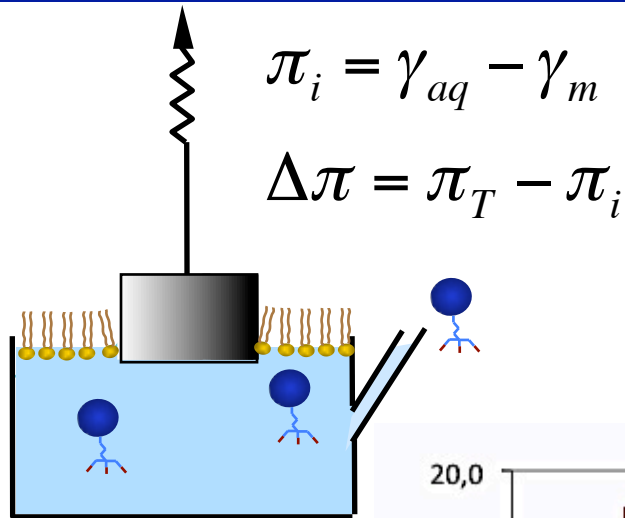


Propriétés interfaciales des lipides membranaires

- Mélange de phospholipides (SOPC, SOPE, SOPS) avec cholestérol



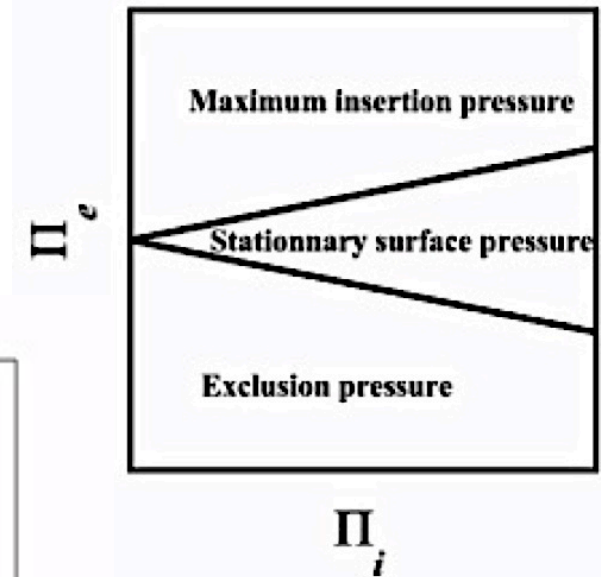
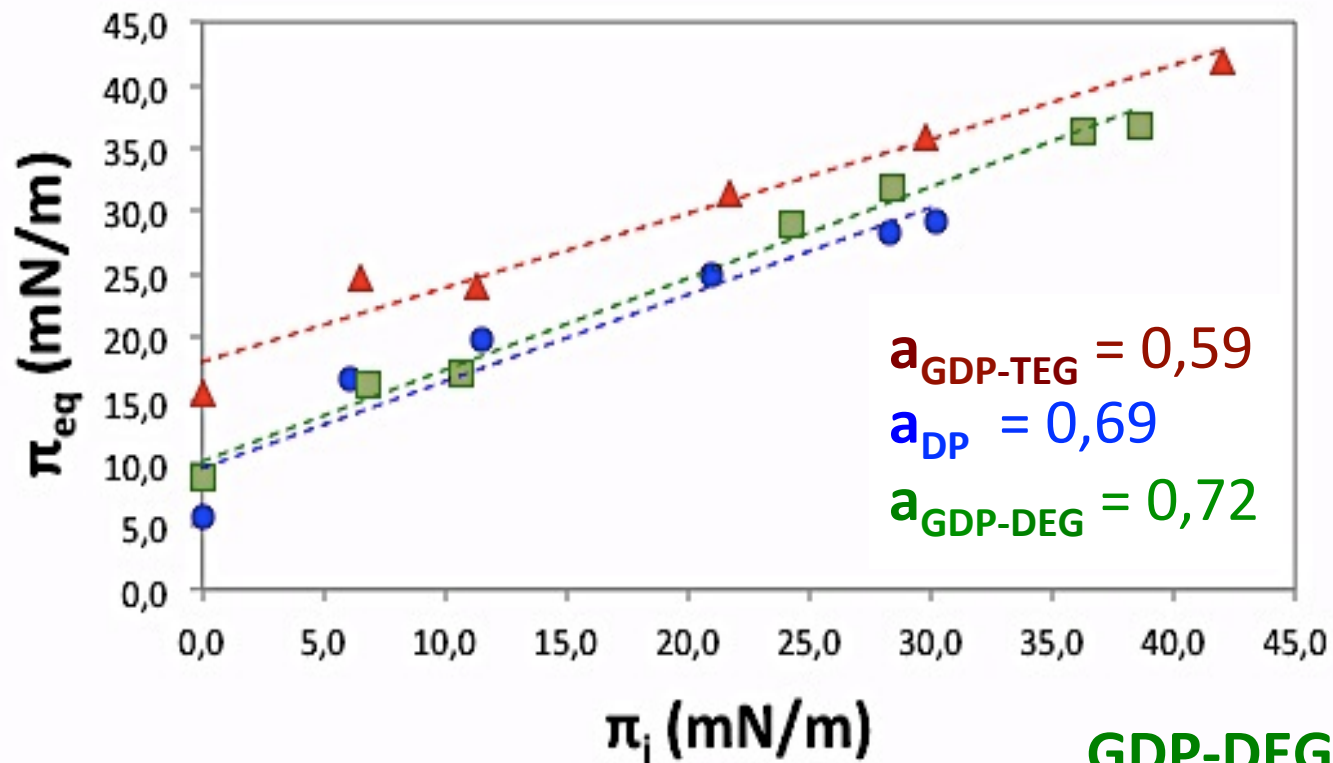
Interaction des porphyrines / monocouche M3



Interaction des porphyrines / monocouche M3

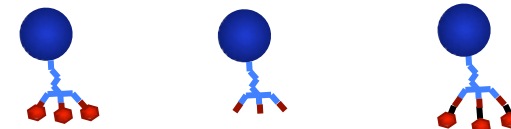
$$\Pi_e = \pi_T = a\Pi_i + b$$

SOPC-SOPE-SOPS-CHOL (36/34/12/18)

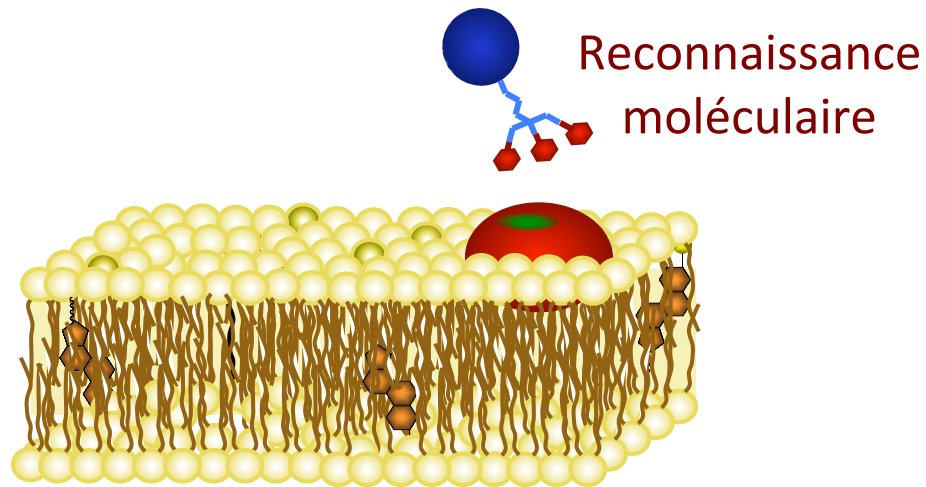


Calvez, Langmuir 2011

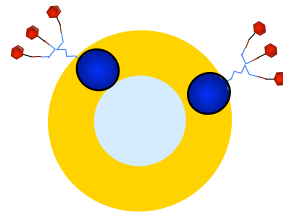
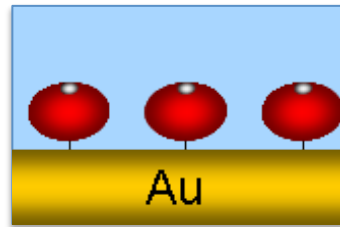
GDP-DEG > DP > GDP-TEG



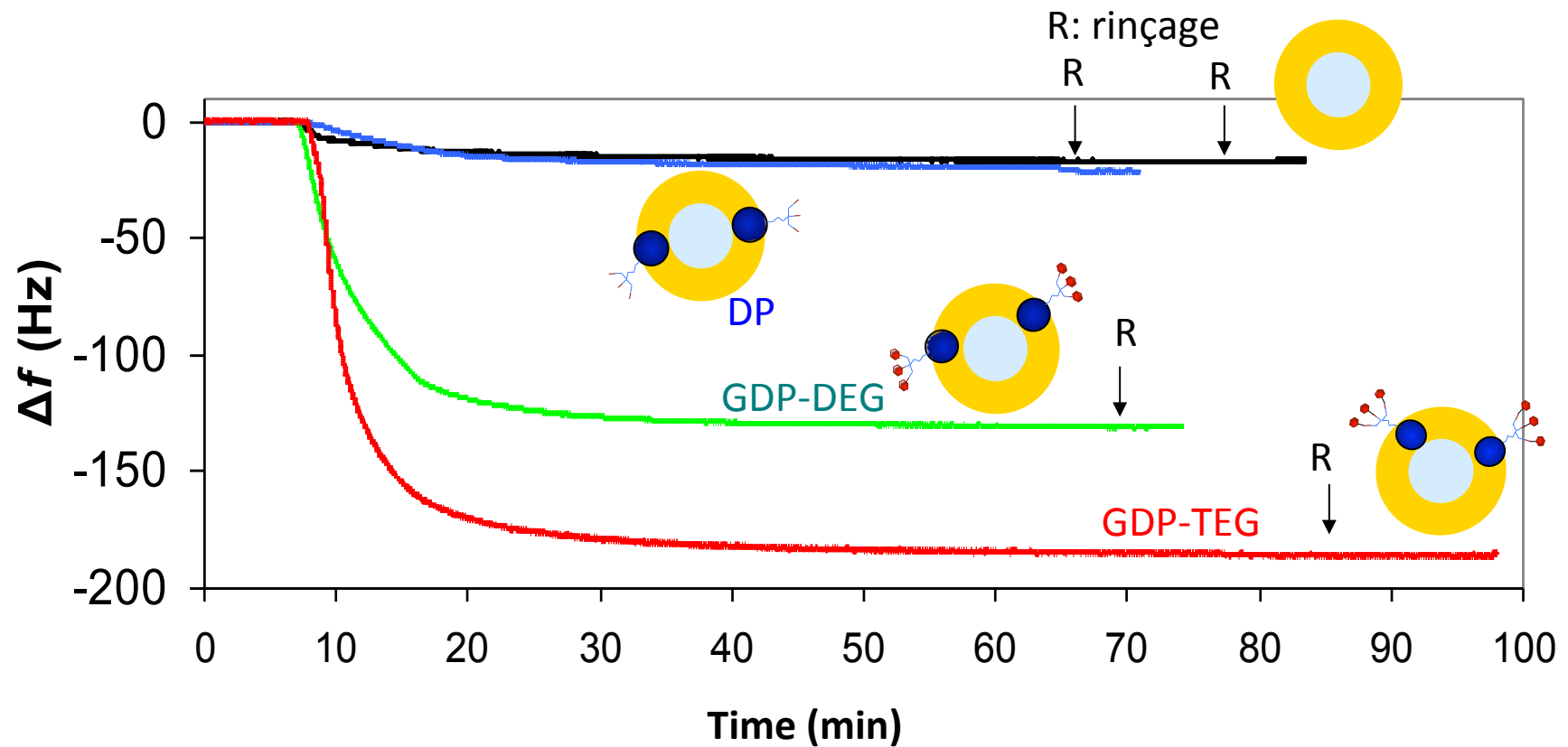
Interaction spécifique molécule-membrane Porphyrines/SOPC-SOPE-SOPS-CHOL-Con A



Interaction spécifique porphyrines-Concanavalline A

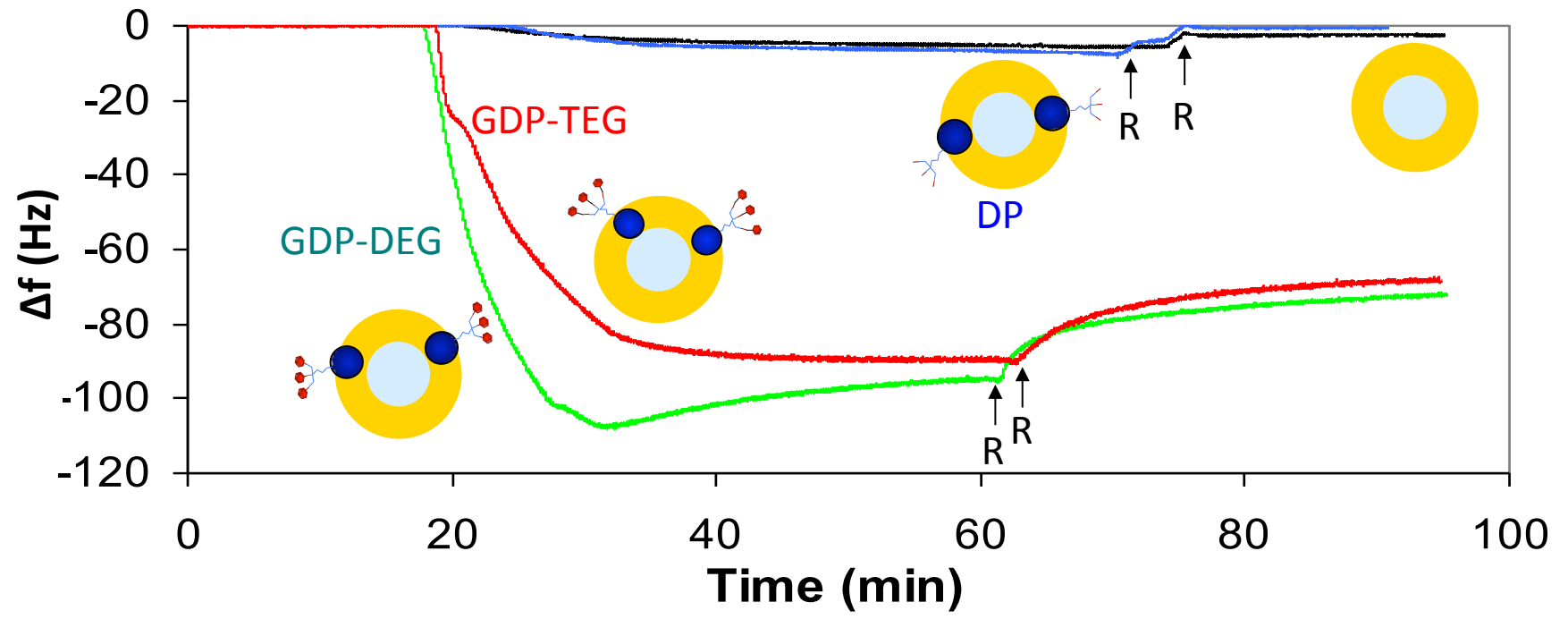
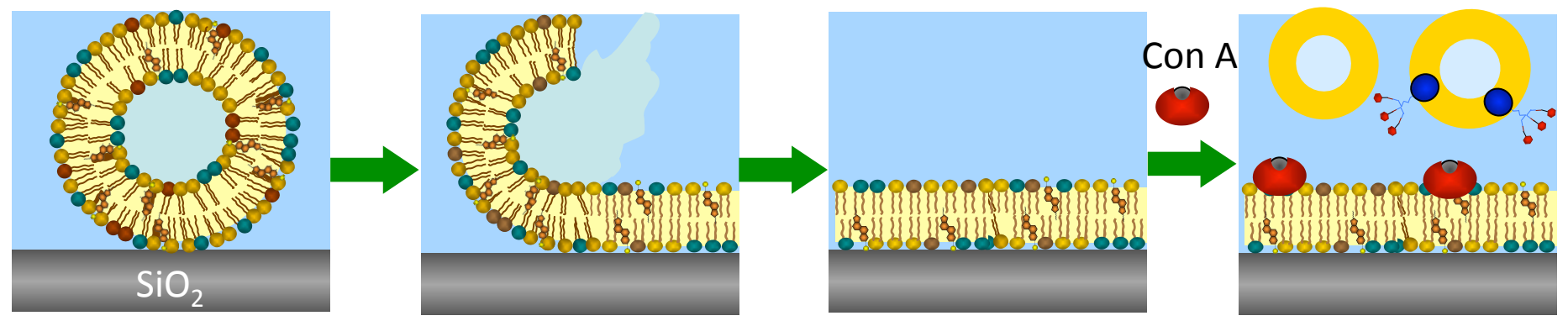


$$\Delta m = -\frac{C}{n} \Delta f \quad \text{SAUERBREY}$$





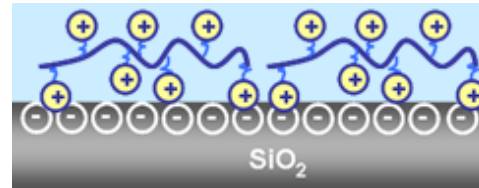
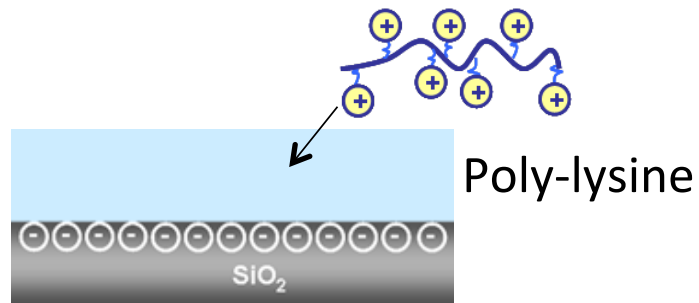
Interaction porphyrine/bicouche-Con A



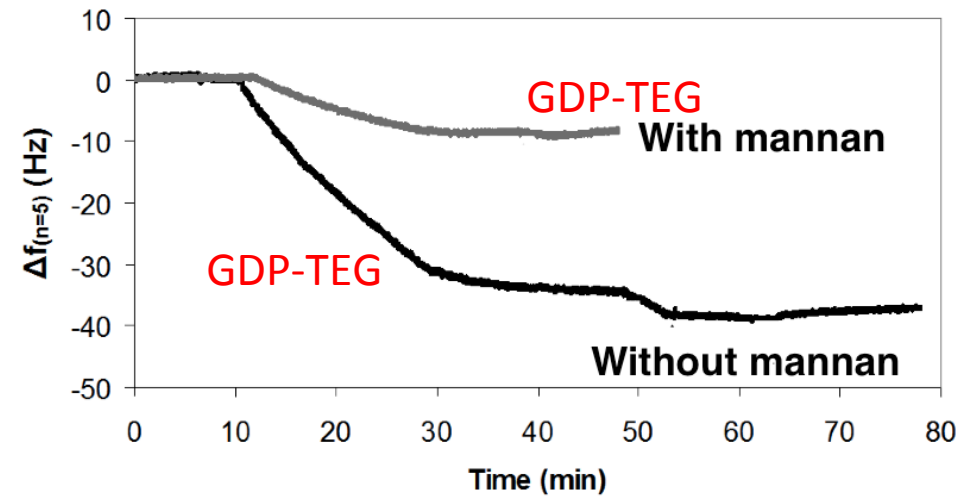
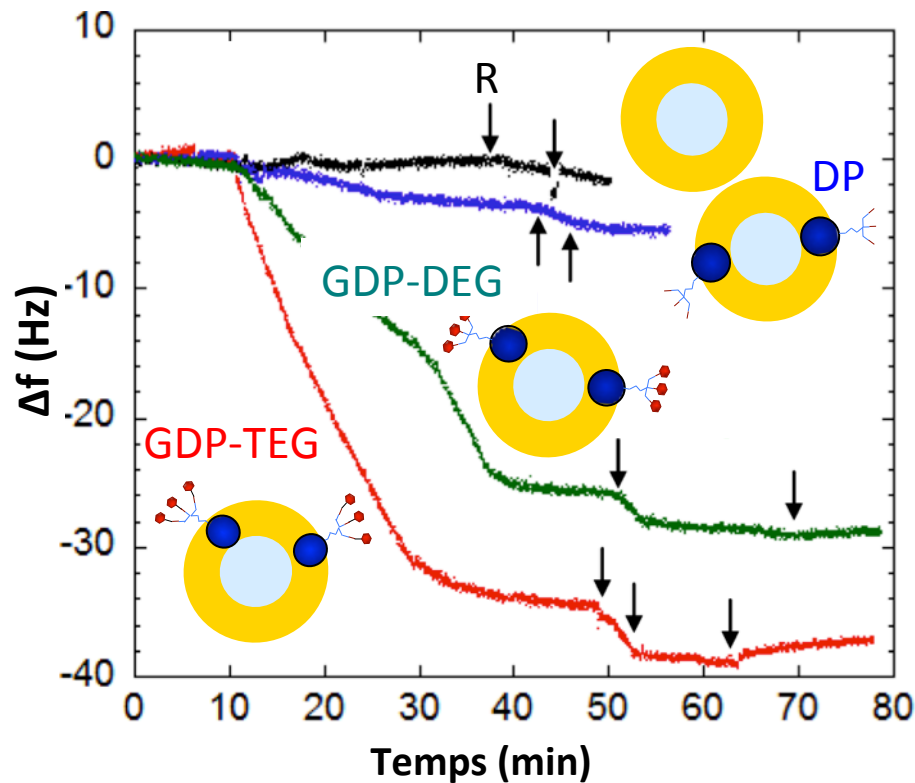
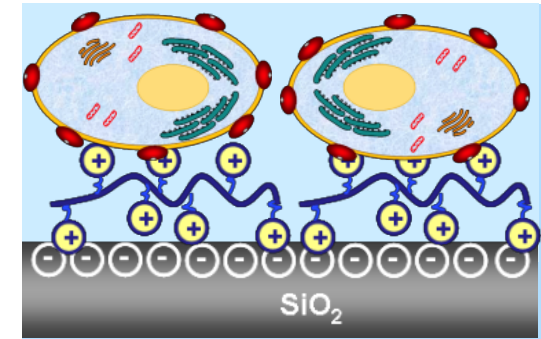


Interaction porphyrines/cellules Y79

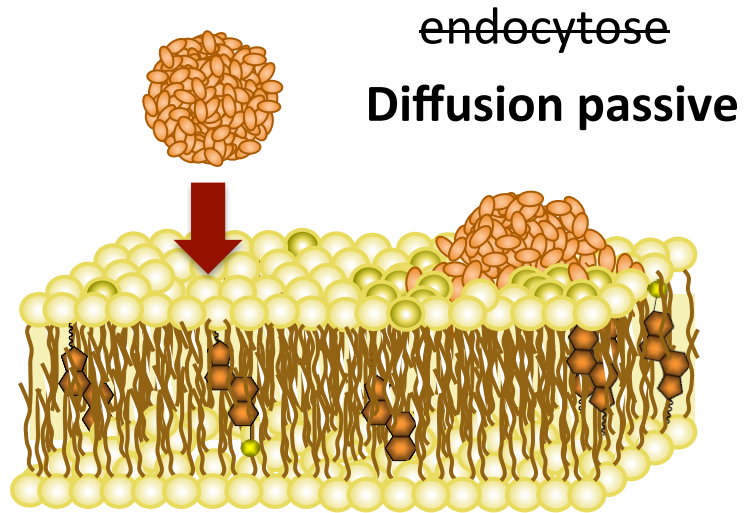
Modification de surface



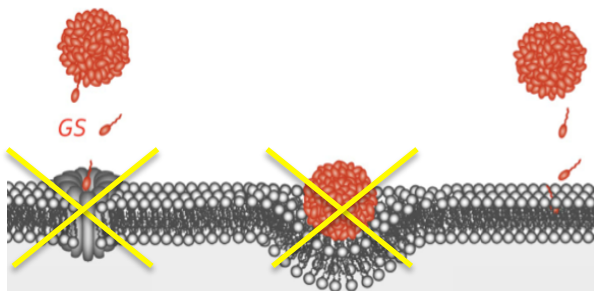
Dépôt cellulaire



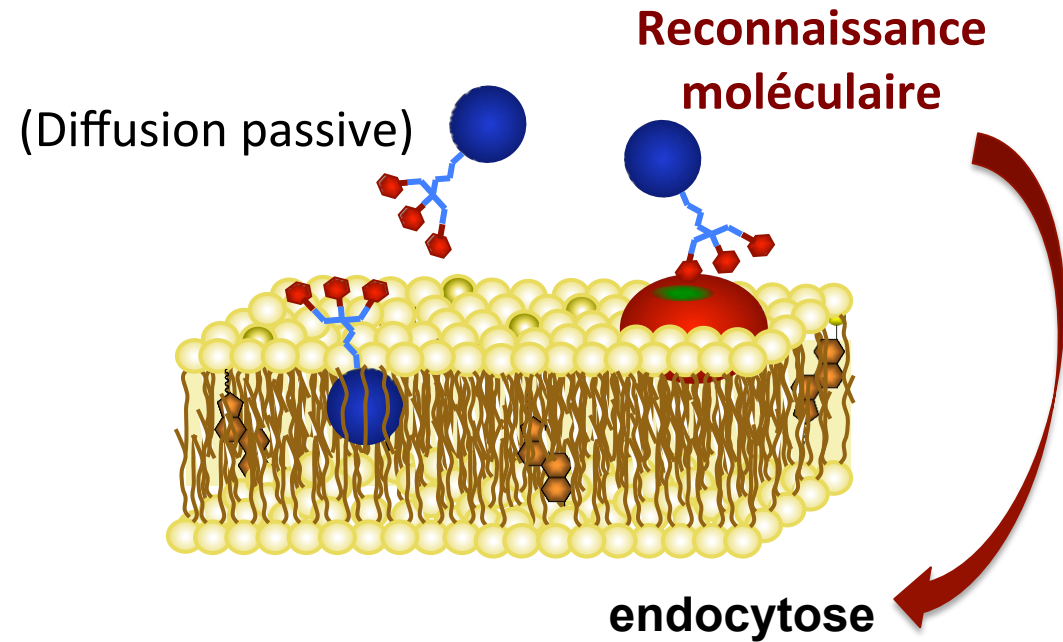
Conclusion



SQ-Gem/ DOPC-DSPC-CHOL



Bildstein et al, *Soft Matter*, 2010



Porphyrines/ SOPC-SOPE-SOPS-CHOL

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