université PARIS-SACLAY | FACULTÉ DE PHARMACIE

Institut Galien PARIS-SACLAY

Assemblages supramoléculaires pour le domaine biomédical

M2 Pharmacotechnie et Biopharmacie

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Objectifs

- Identifier les **systèmes supramoléculaires**
- Appréhender les mécanismes qui sous-tendent **l'auto-assemblage**
- Considérer l'intérêt des assemblages supramoléculaires pour **le domaine biomédical**
- Etudier des **exemples** et proposer **des applications**

Déroulement de la séance

Introduction : l'échelle supramoléculaire

I] Assemblages supramoléculaires: de quoi parle-t-on ?

II] Systèmes supramoléculaires: *an overview*

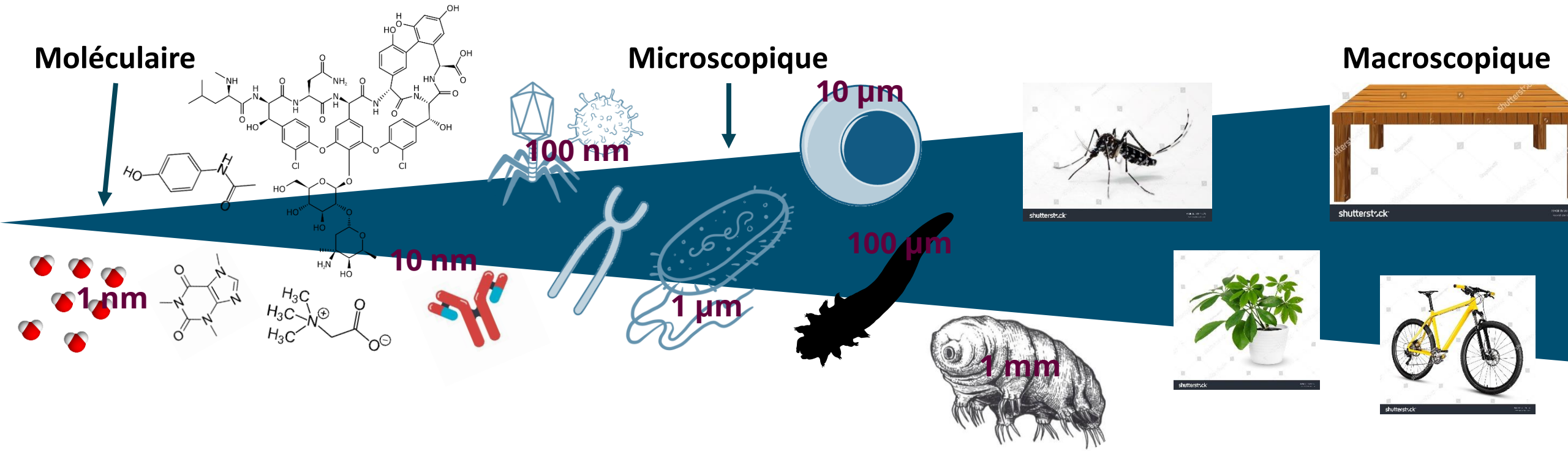
Travail en groupes sur des exemples

III] Vers les applications pour le domaine biomédical

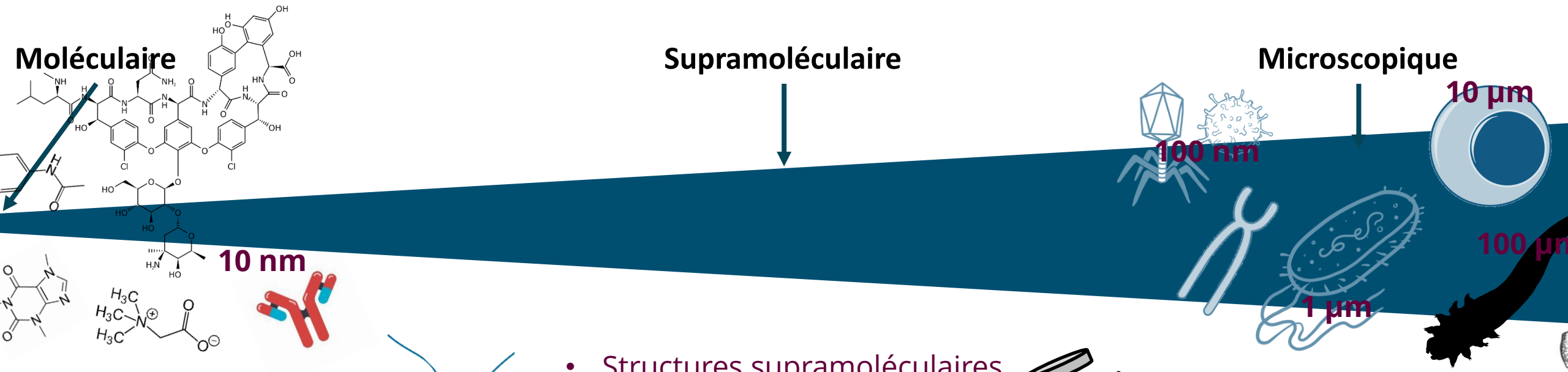
Conclusion

Introduction : l'échelle supramoléculaire ?

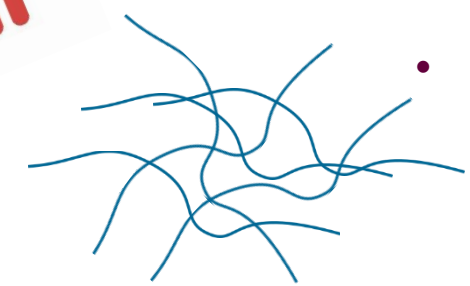
Introduction : l'échelle supramoléculaire ?

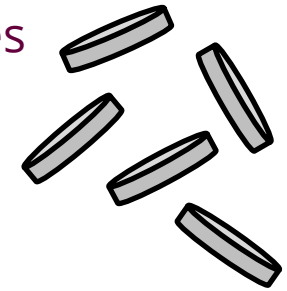


Introduction : l'échelle supramoléculaire ?



- Structures supramoléculaires
- Assemblages

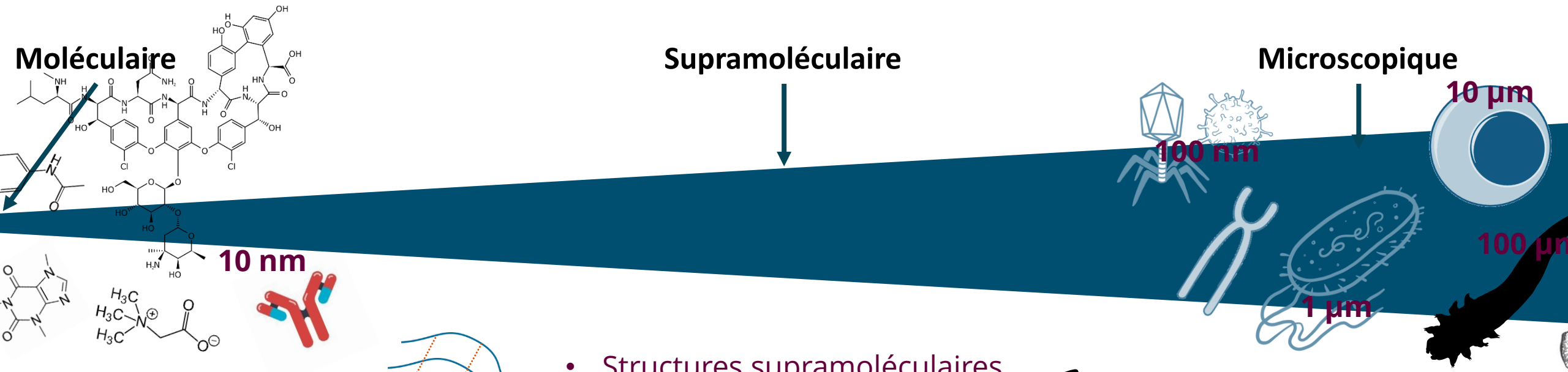




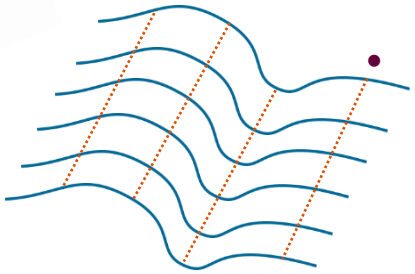
Macromolécules

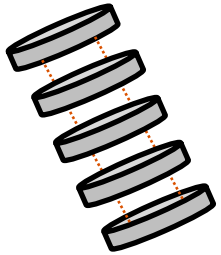
Petites molécules (LMWG)

Introduction : l'échelle supramoléculaire ?



- Structures supramoléculaires
- Assemblages
- Structure quaternaire
- Liaisons intermoléculaires





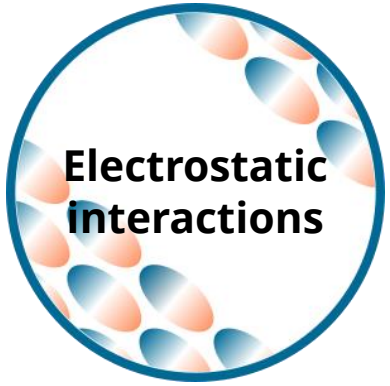
Macromolécules

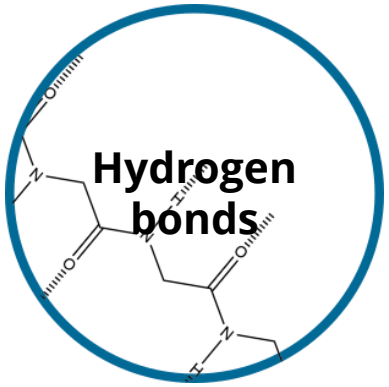
Petites molécules (LMWG)

Introduction : l'échelle supramoléculaire ?

Interactions supramoléculaires

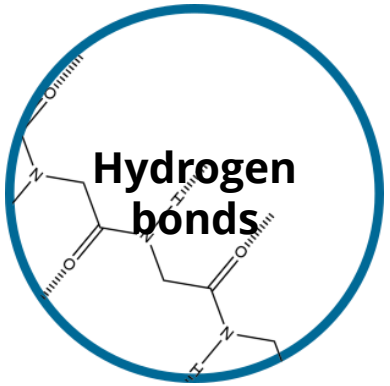
= Interactions faibles ≠ liaisons covalentes



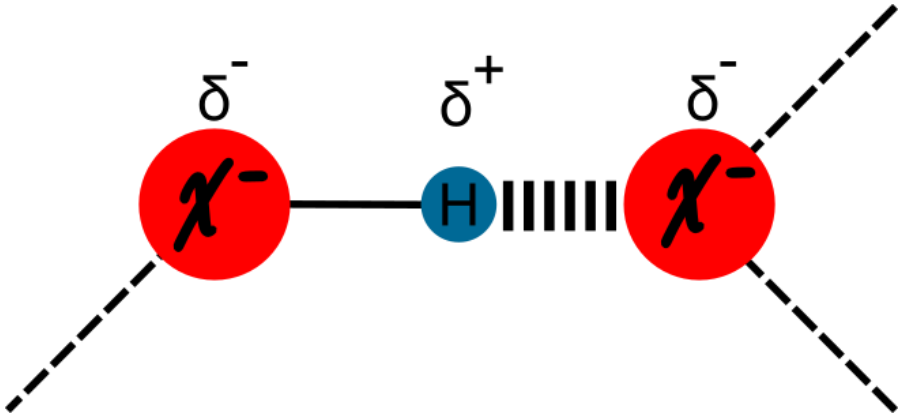


Introduction : l'échelle supramoléculaire ?

Interactions supramoléculaires



Liaisons hydrogène



Liaison **très directive**,

Régulière (longueur, angles)

⇒ structures très organisées

Ex: structure secondaire des protéines

Groupes chimiques donneurs : alcools, phénols, acides carboxyliques, amides, amines …

Groupes chimiques accepteurs : acides carboxyliques, amides, urées, uréthanes …

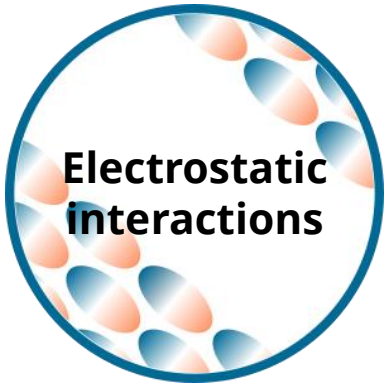
Energie d'interaction comprise entre la liaison covalente et les interactions électrostatiques

Sensible à la **température**, au **pH**, à la **solvatation**

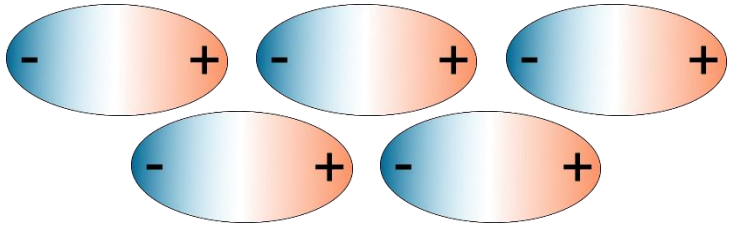
Ex: Matériaux autoréparants

Introduction : l'échelle supramoléculaire ?

Interactions supramoléculaires



Interactions électrostatiques/ioniques



- Zwitterions
- Nano-objets (+) / Nano-objets (–)
- Domaine (+) / domaine (-)

Force de Van der Waals

Keesom

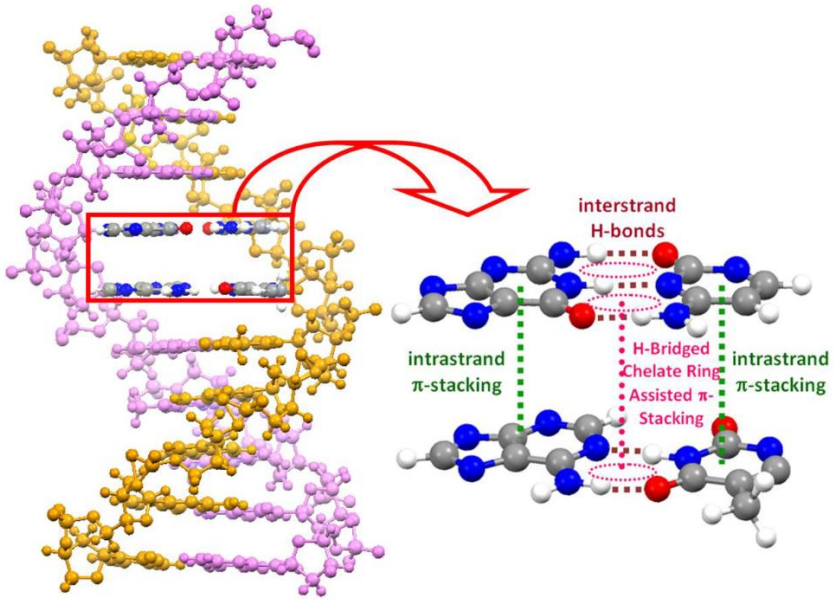
Energie d'interaction plus faible, moins directive, facilement écrantée

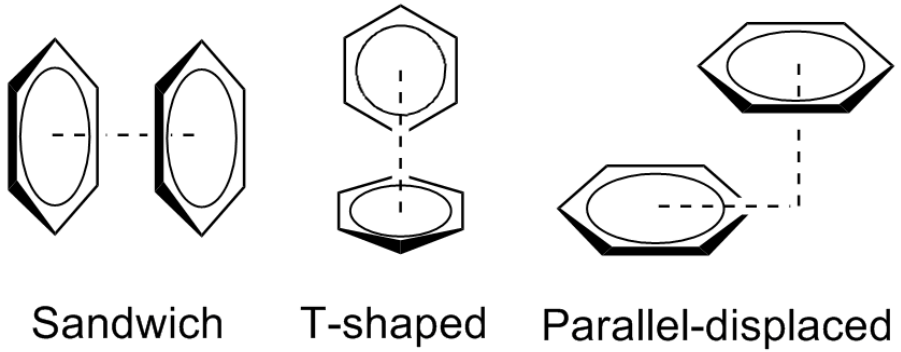
Sensible aux **ions**, au **pH**, aux **métaux**

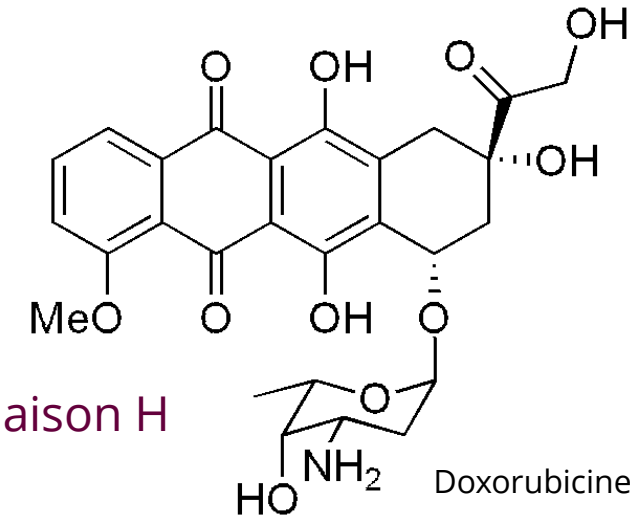
Introduction : l'échelle supramoléculaire ?

Interactions supramoléculaires

Π-stacking « empilements pi »

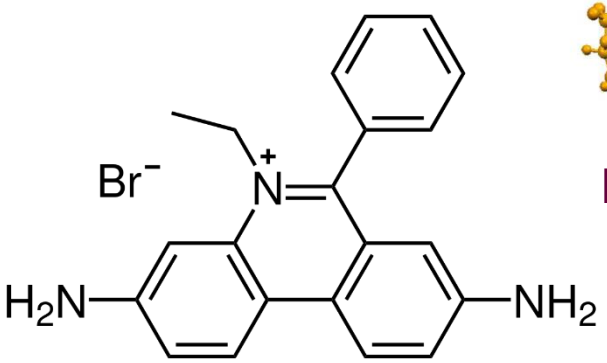






Doxorubicine

Energie d'interaction du même ordre que la liaison H



Bromure d'éthidium

Site de liaison pour les **intercalateurs**

Karabıyık, H.; Sevinçek , R.; Karabıyık, H., *Phys. Chem. Chem. Phys.* **2014**,16, 15527-15538

Introduction : l'échelle supramoléculaire ?

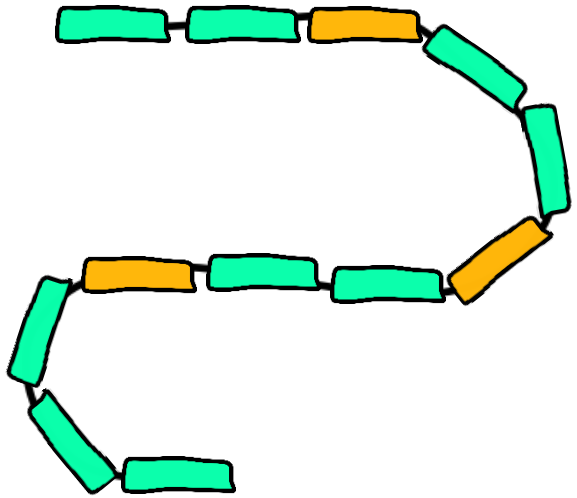
Interactions supramoléculaires

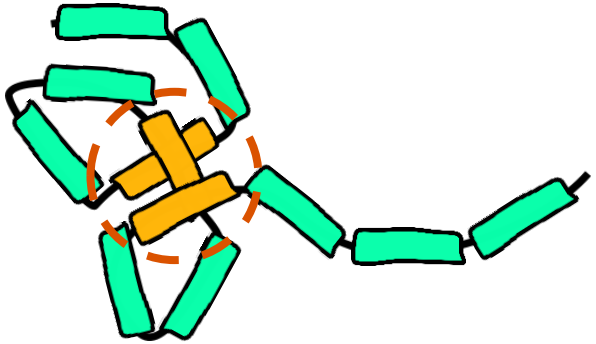
Interactions hydrophobes – Effet hydrophobe

Effet considéré dans les milieux biologiques

Milieu aqueux = solvant polaire protique

Minimisation spontanée de l'énergie libre





Systèmes amphiphiles

Equilibre Hydrophobie/Hydrophilie

Ex: Repliement des protéines – Structure tertiaire

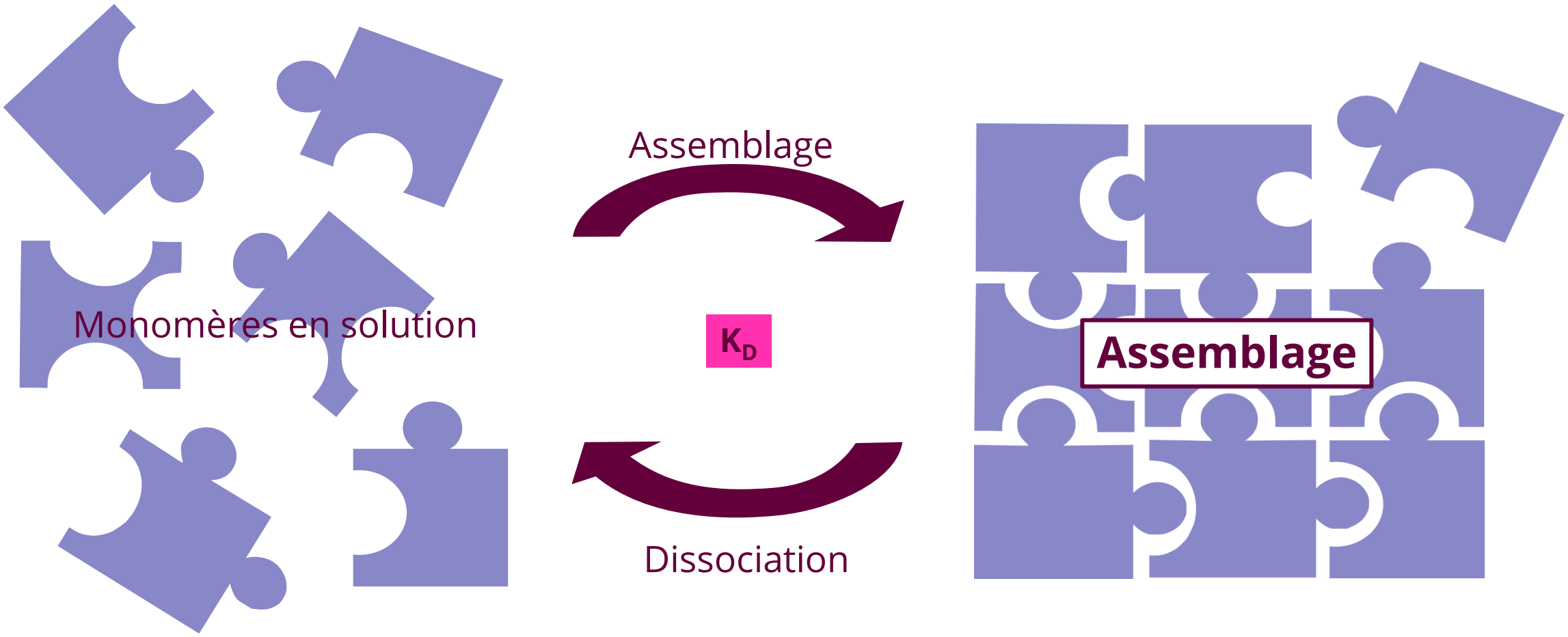
I] Assemblages supramoléculaires

I] Assemblages supramoléculaires

« Assembly » = Structure produced by putting together its parts

Adapted from Cambridge dictionnary

I] Assemblages supramoléculaires

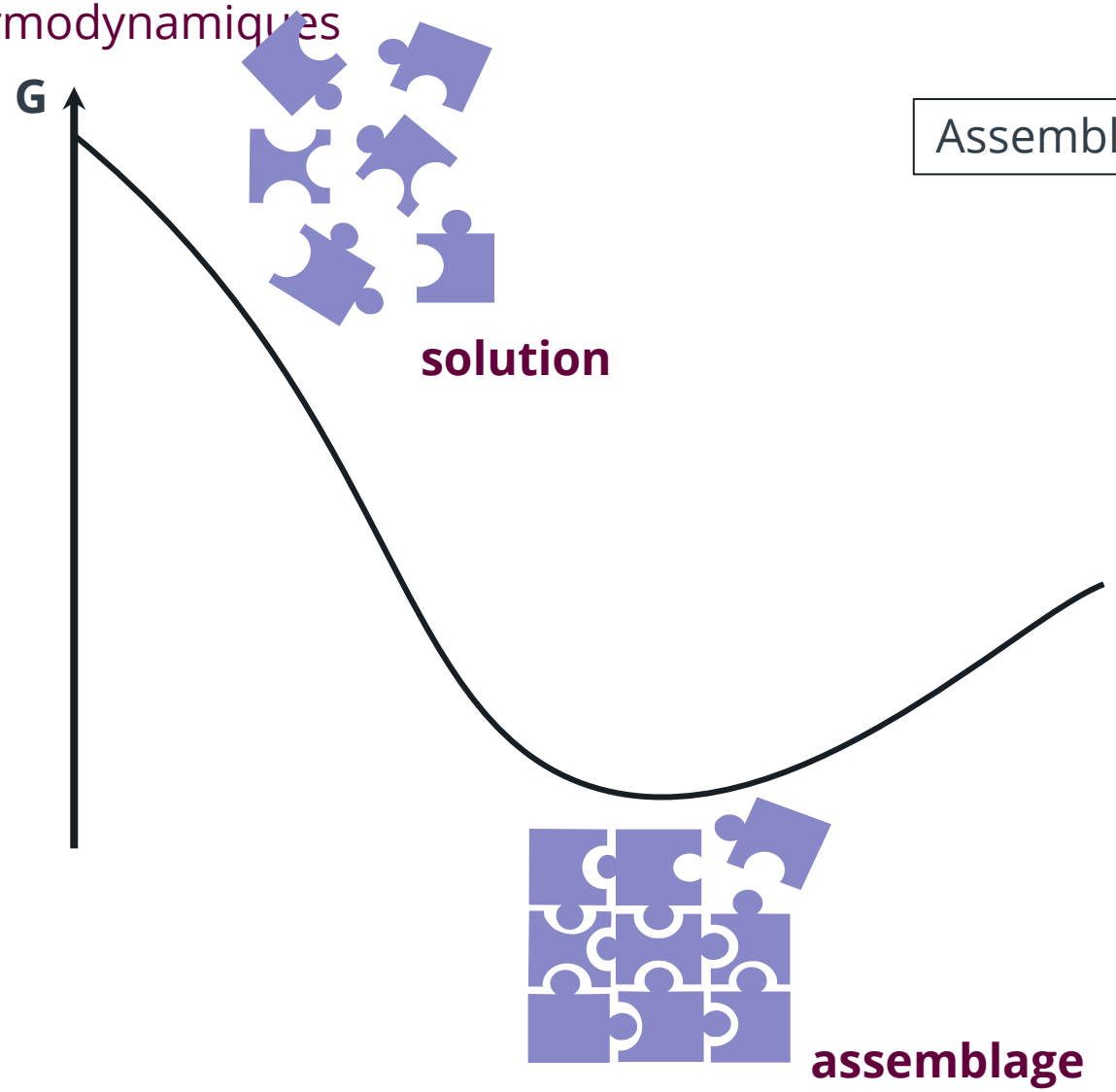


Auto-assemblage (« self-assembly ») = 1 seul composé dans la structure

Co-assemblage (« coassembly ») ≥ 2 composés dans la structure

I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques



Assemblage thermodynamiquement favorable ?

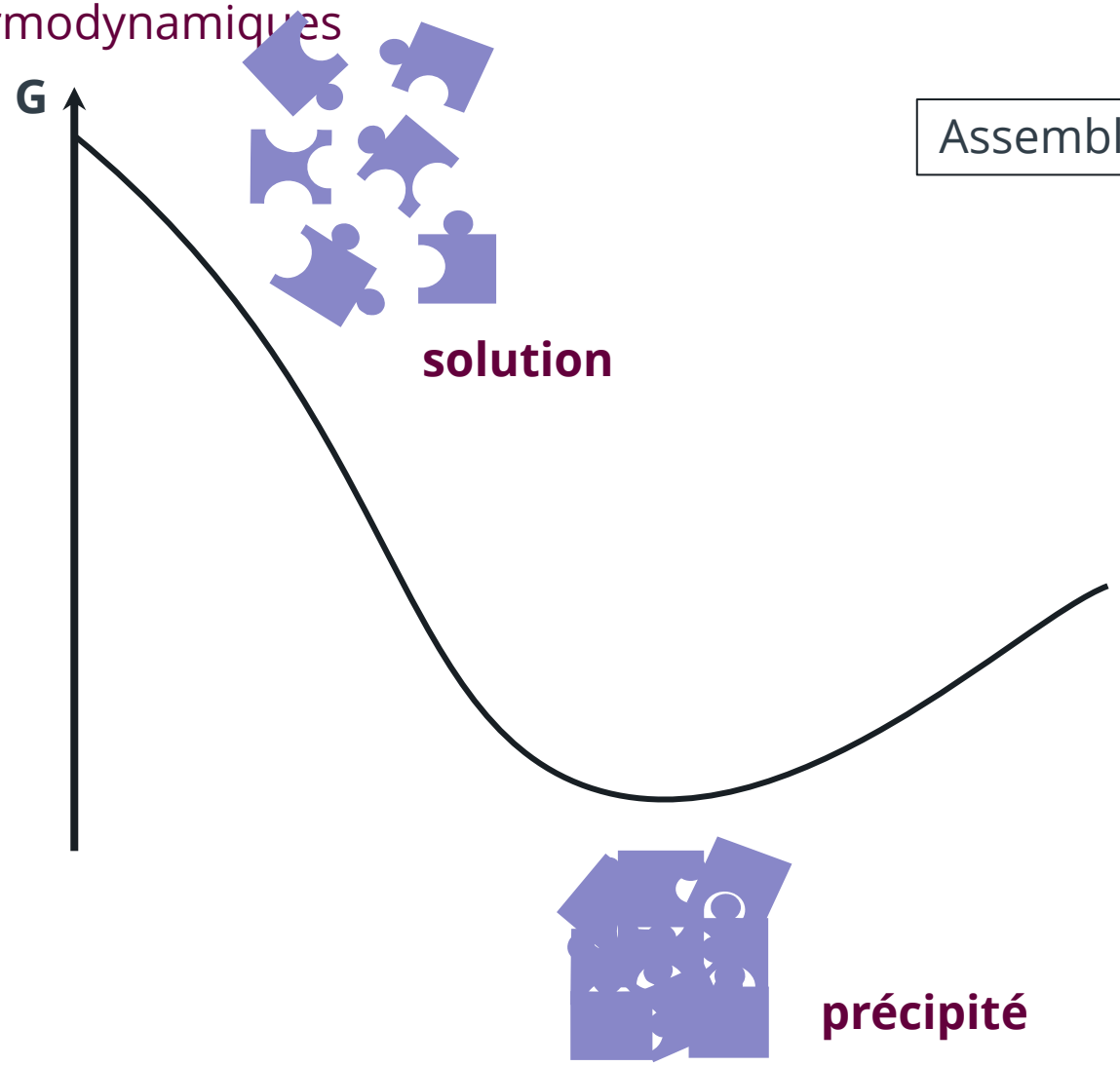
Impossible car:

Placement spécifique

Orientation spécifique

I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques



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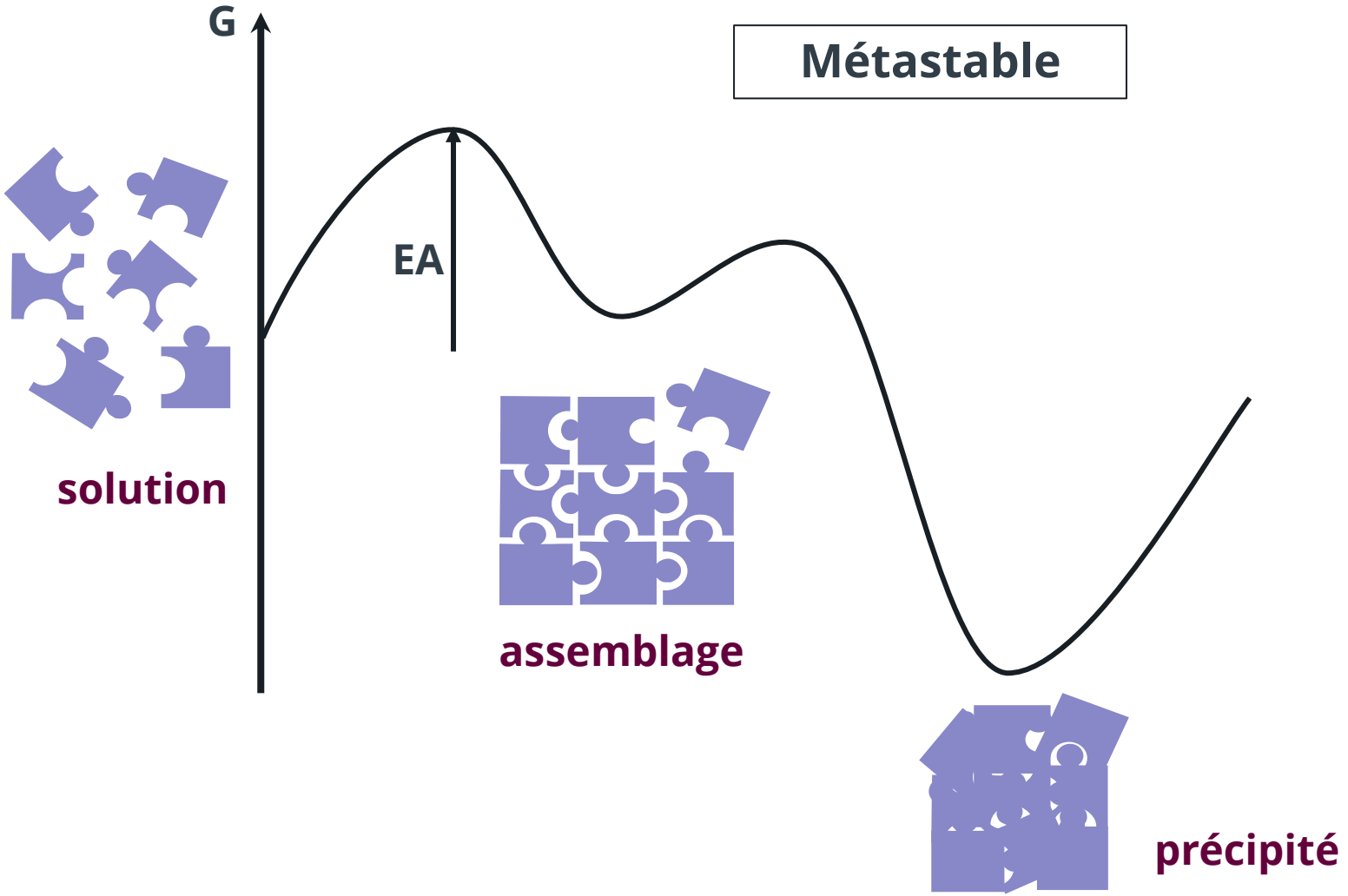
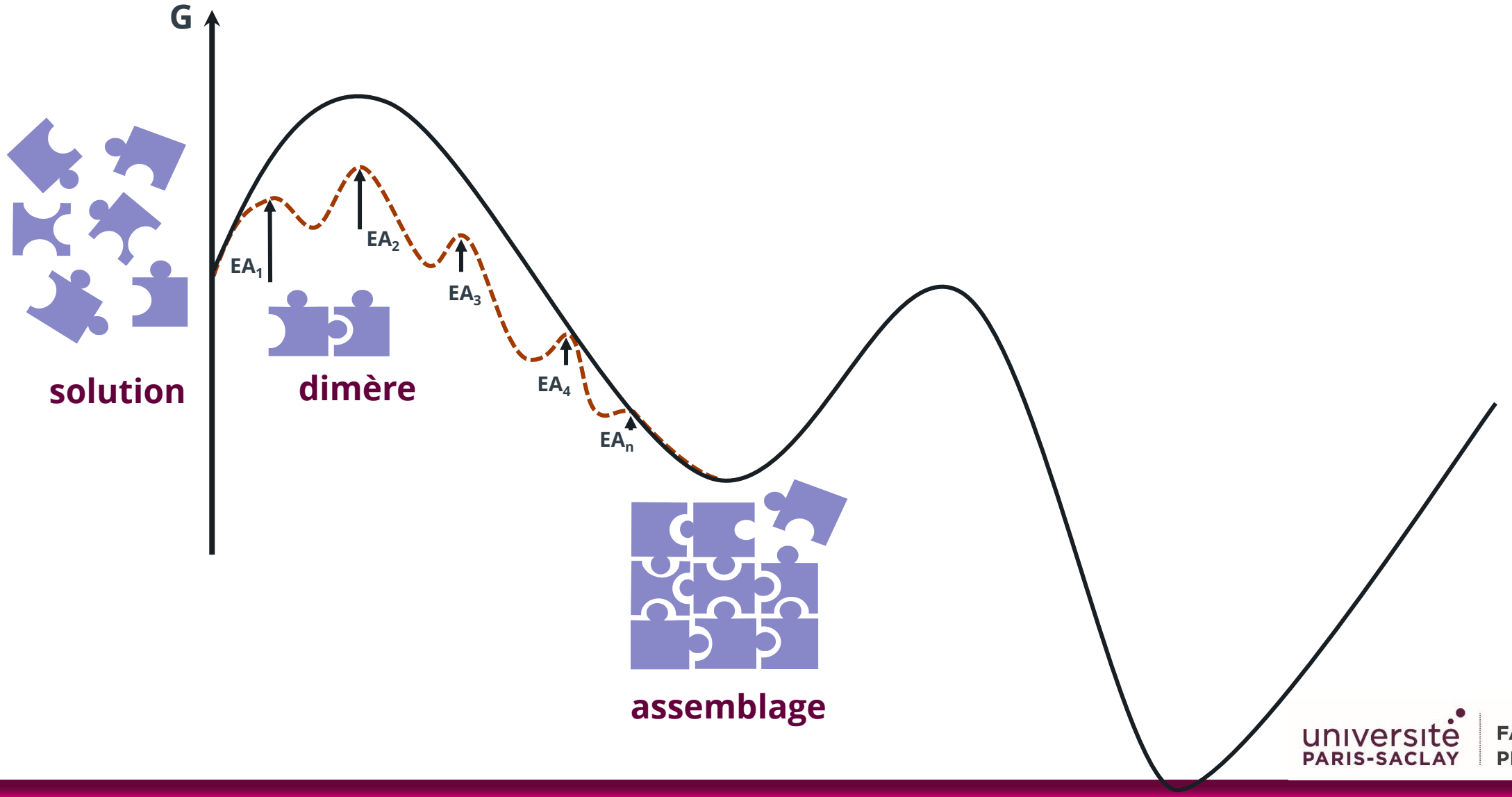
I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques



I] Assemblages supramoléculaires

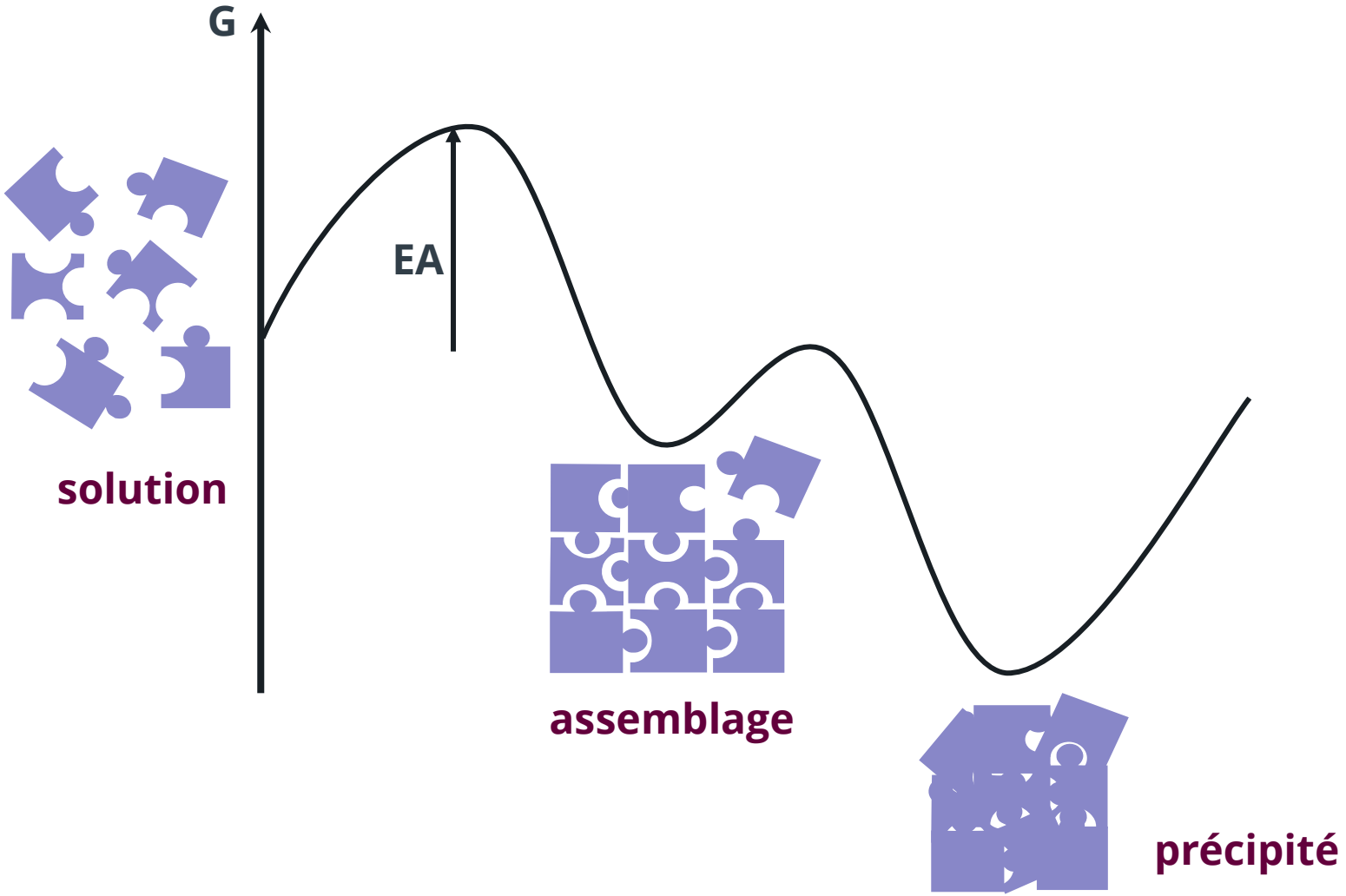
I.1) Aspects thermodynamiques



I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques

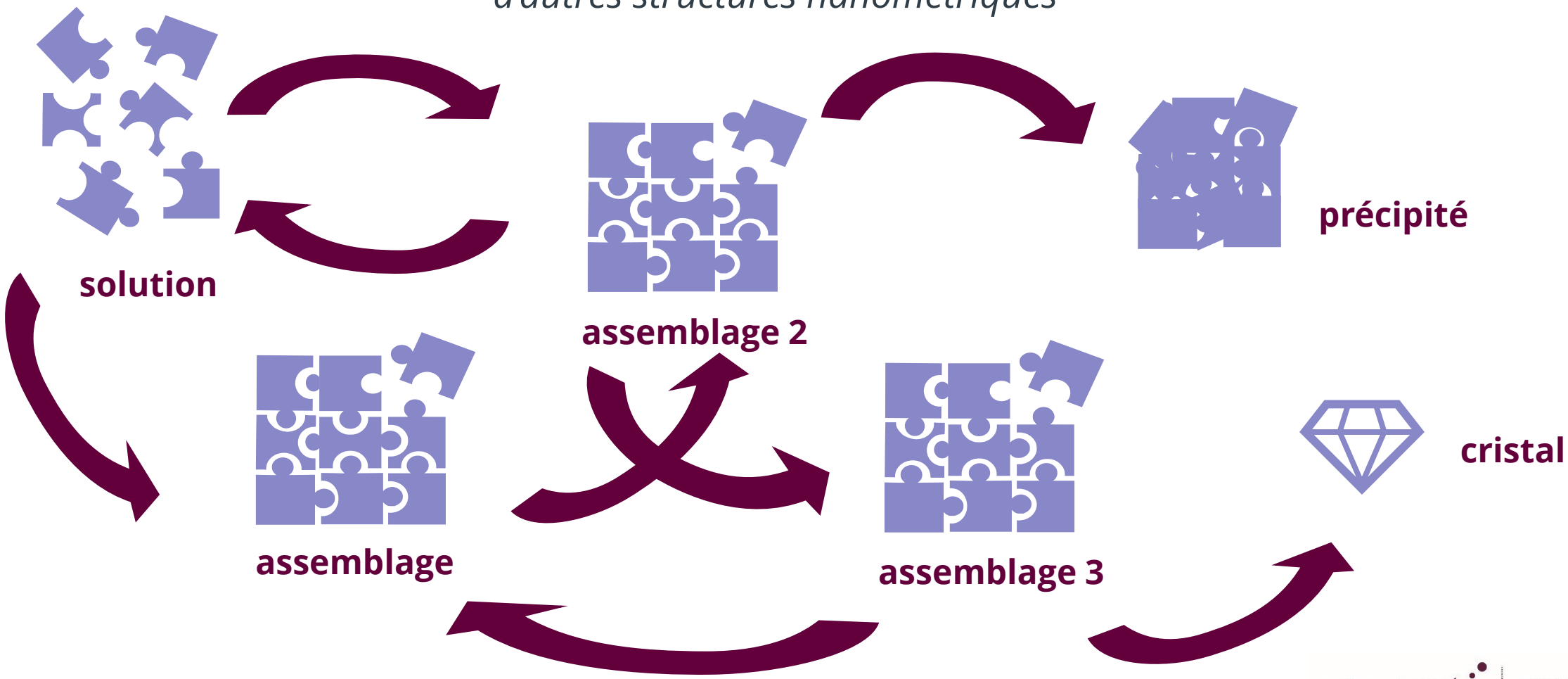
Nécessite un apport d'énergie !



I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques

D'autres états d'énergie peuvent exister
= d'autres structures nanométriques

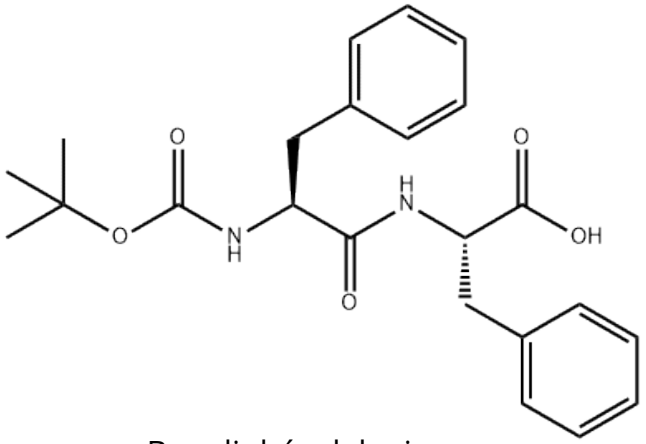


Équilibres thermo-dynamiques réversibles, ou non

I] Assemblages supramoléculaires

I.1) Aspects thermodynamiques

Ex: petite molécule



Boc-diphénylalanine

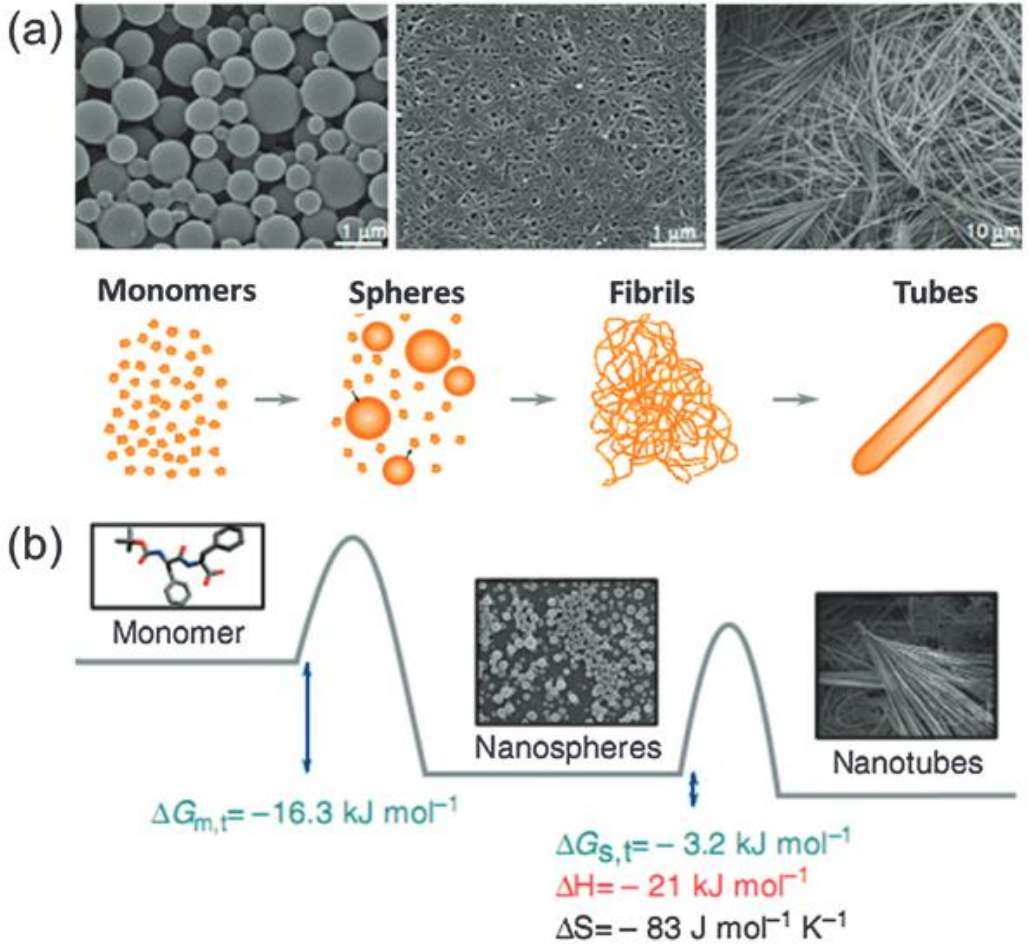
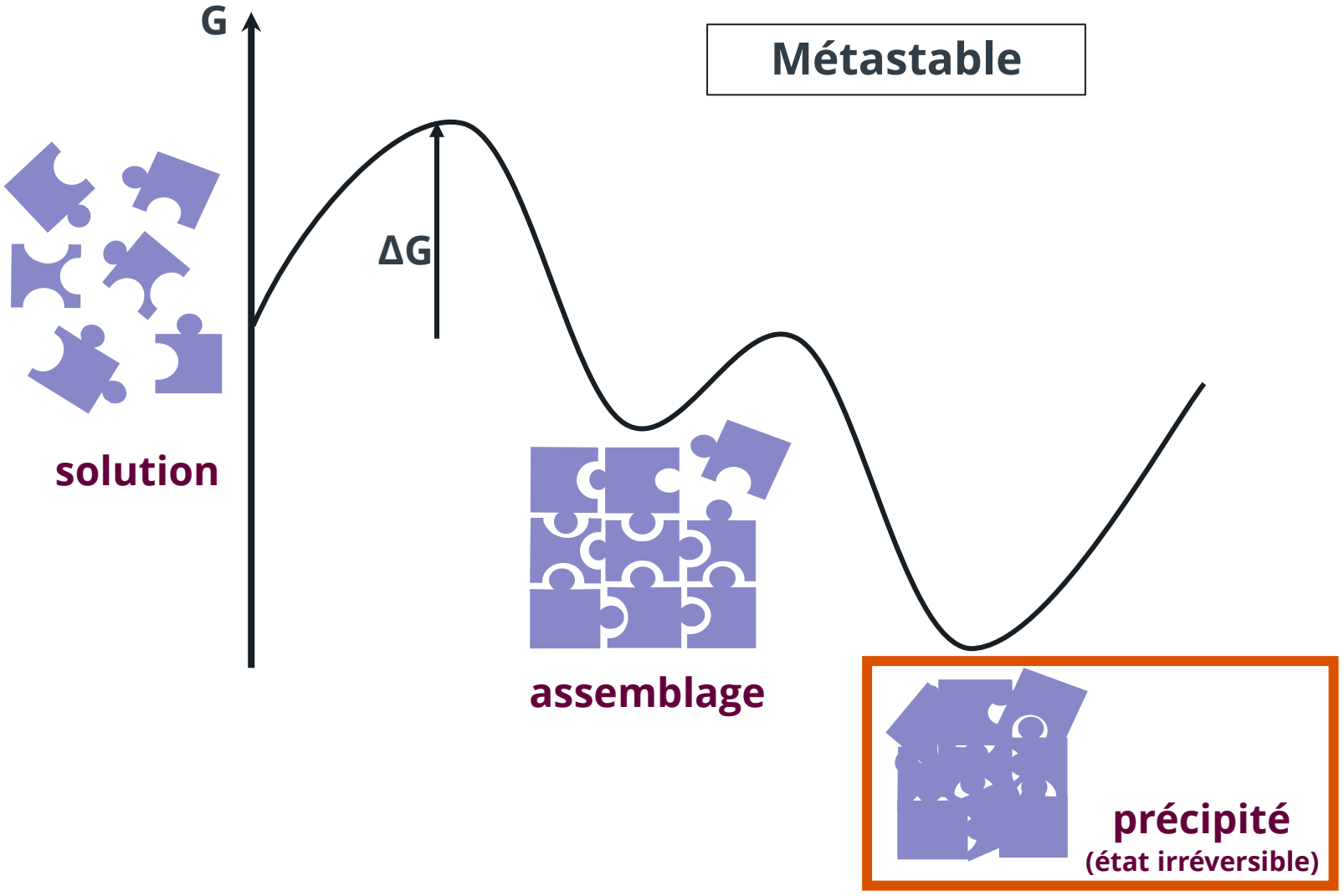


Fig. 2 (a) SEM images and schematic depiction of structural transitions and (b) free energy changes during the phase transition observed in the Boc-FF system.

Wang *et al., Chem. Soc. Rev.*, **2016**, 45 (20), 5589-5604
Levin *et al., Chem. Nat. Commun.*, **2014**, 5, 5219

I] Assemblages supramoléculaires

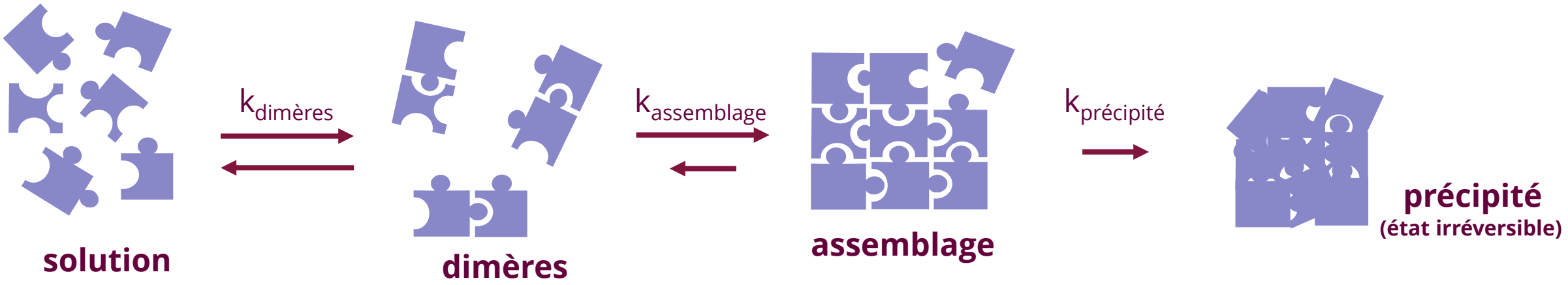
I.2)



=> Aspects cinétiques

I] Assemblages supramoléculaires

I.2) Aspects cinétiques



Etat cinétiquement piégé

I] Assemblages supramoléculaires

I.2) Aspects cinétiques

Assemblages supramoléculaires = Assemblages dynamiques

Exemple de l'actine

- Protéine bi-globulaire
- Rôle dans la structure cellulaire
- Rôle dans la motilité cellulaire

Ex: Contraction musculaire, Mitose, Macrophages

I] Assemblages supramoléculaires

I.2) Aspects cinétiques

Assemblages supramoléculaires = Assemblages dynamiques

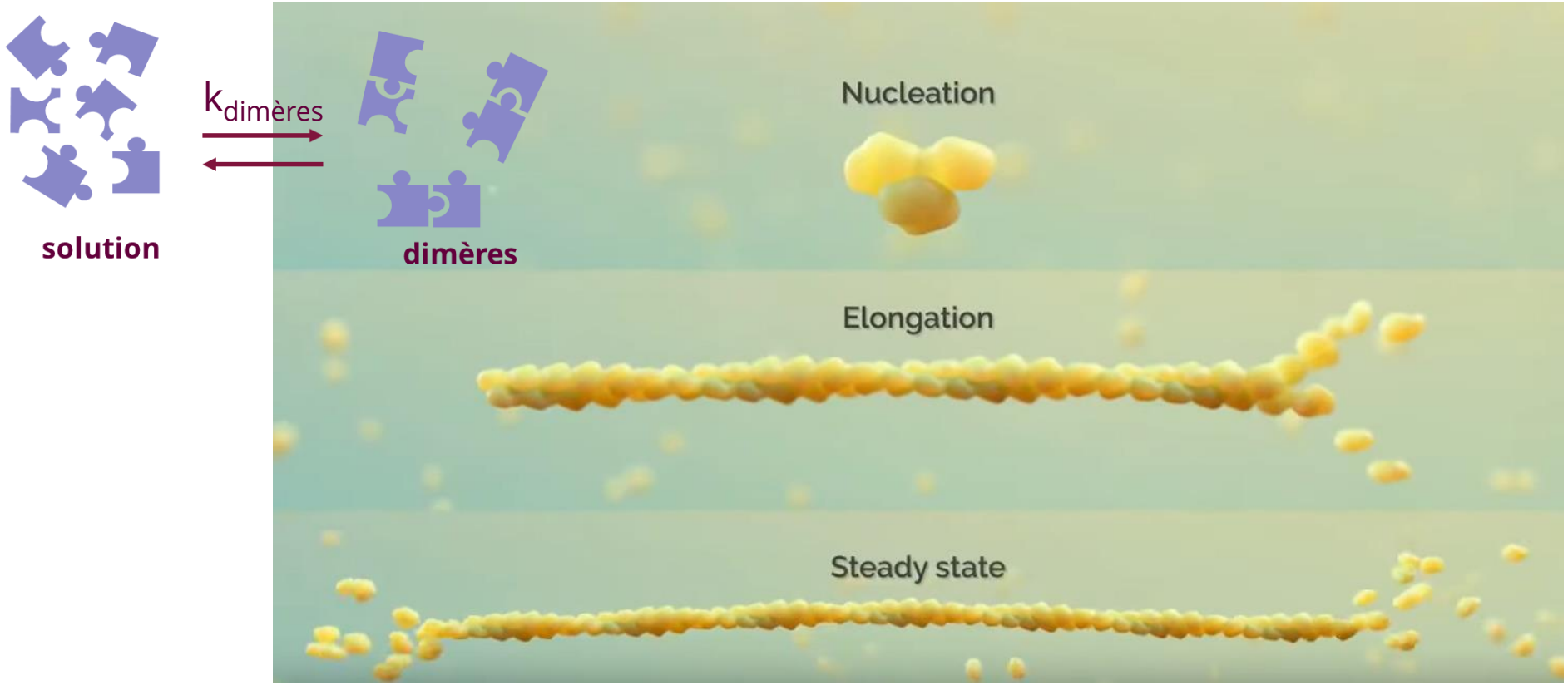
Vidéo sur l'assemblage de l'actine :

https://youtu.be/gDb8ENGOrvw?t=91

I] Assemblages supramoléculaires

I.2) Aspects cinétiques

Assemblages supramoléculaires = Assemblages dynamiques

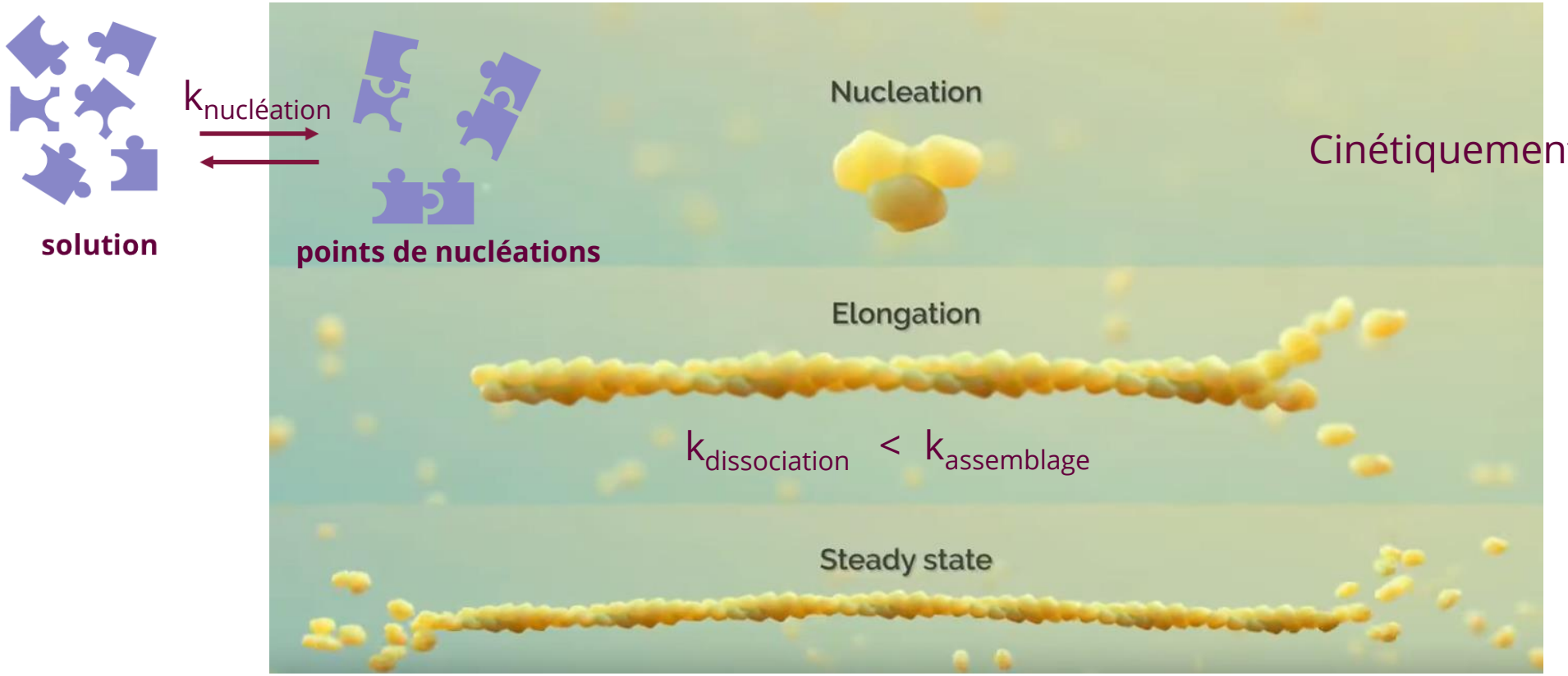


https://youtu.be/gDb8ENGOrvw?t=91 sur l'actine

I] Assemblages supramoléculaires

I.2) Aspects cinétiques

Assemblages supramoléculaires = Assemblages dynamiques



Cinétiquement déterminante

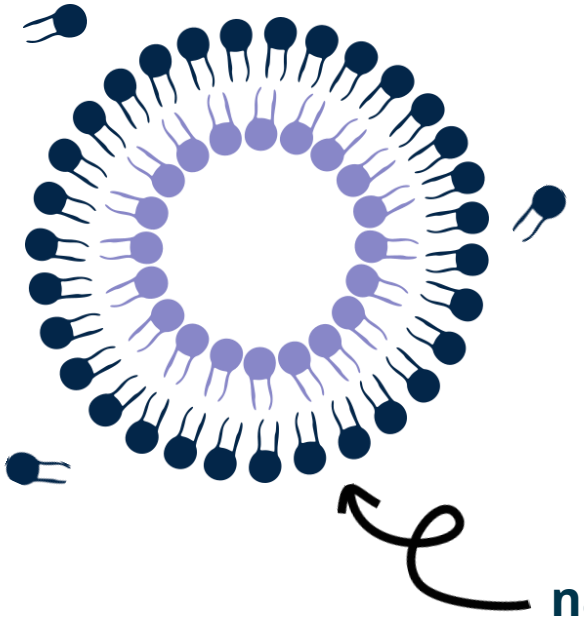
$k_{dissociation} = k_{assemblage}$

https://youtu.be/gDb8ENGOrvw?t=91 sur l'actine

I] Assemblages supramoléculaires

I.2) Aspects cinétiques

Assemblages supramoléculaires = Assemblages dynamiques

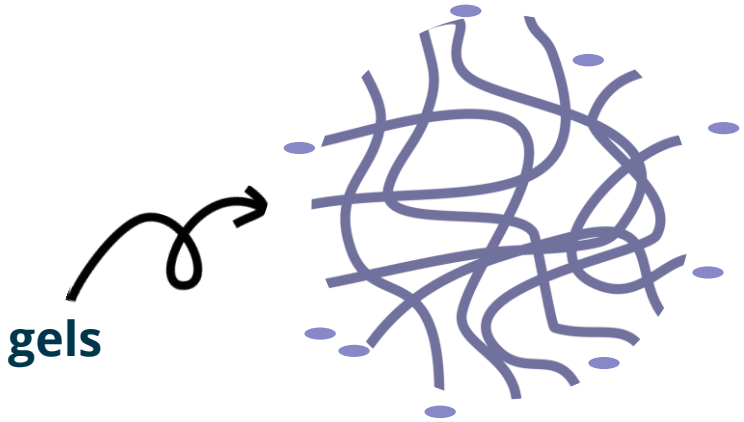


nanoparticules

-> Adaptabilité spatiale et temporelle

-> Régénération

-> Dégradabilité



gels

Nouveaux objets supramoléculaires pour le domaine biomédical

I] Assemblages supramoléculaires

I.3) Conclusion

K_D constante **thermodynamique**

État métastable

$k_{assemblage}$ et $k_{dissociation}$ constantes **cinétiques**

État cinétiquement piégé

auto-assemblage
co-assemblage

dégradation

équilibre dynamique

interactions supramoléculaire

nucléation

II] Systèmes supramoléculaires: *an overview*

Biosourcé

Bio-inspiré

Biocompatible

Biosourcé

« *Bio-based* » = fabriqué à partir de matières d'origine biologique

=> utiliser directement des systèmes existant dans la nature

Bio-inspiré

« *Bio-inspired* » = biomimétique, imitation technique des processus mis en œuvre par la nature.

=> synthétiser des systèmes fonctionnant de manière similaire à ceux existant dans la nature

Biocompatible

« *Biocompatible* » = qui est toléré par l'organisme

=> point de vue de l'application finale, utilisation possible en contact avec le vivant

https://dictionnaire.lerobert.com

II] Systèmes supramoléculaires: *an overview*

Introduction : Exemples dans le vivant

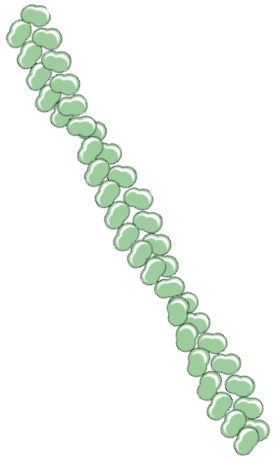
Actine et Micro-tubules

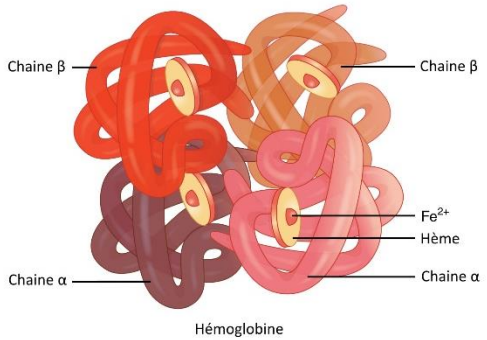
Protéines à sous unités

Vésicules lipidiques

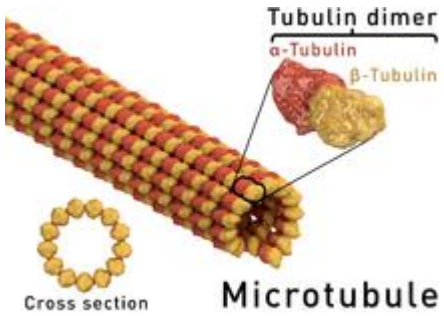
Acides nucléiques (ADN, ARN, …)

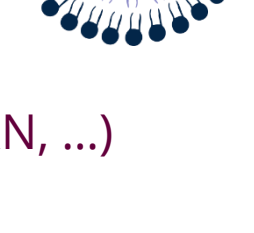
Ligand-récepteur

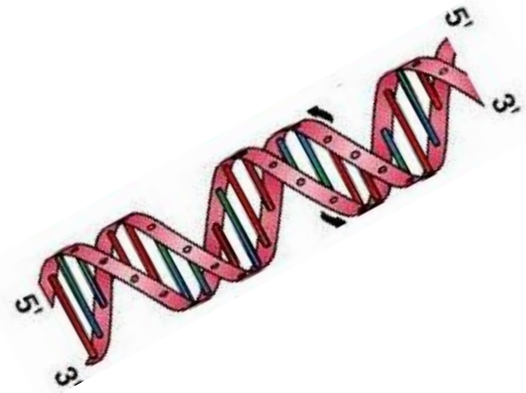




Hémoglobine



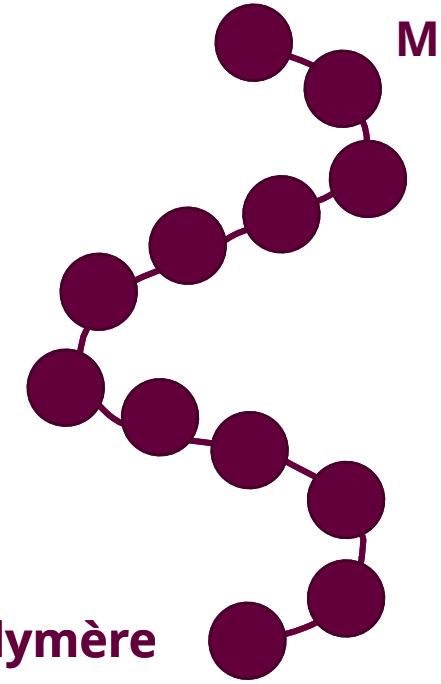




Grandes familles de systèmes supramoléculaires issus de la recherche en nanotechnologies biomédicales

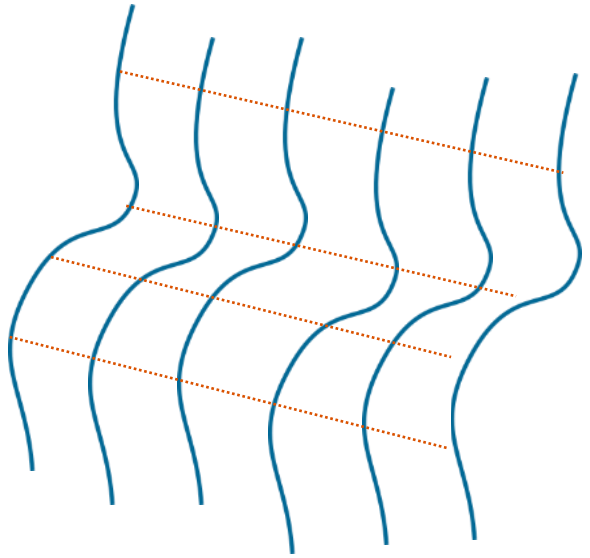
II] Systèmes supramoléculaires: *an overview*

II.1) Polymères (***RAPPEL***)



Monomère

Polymère

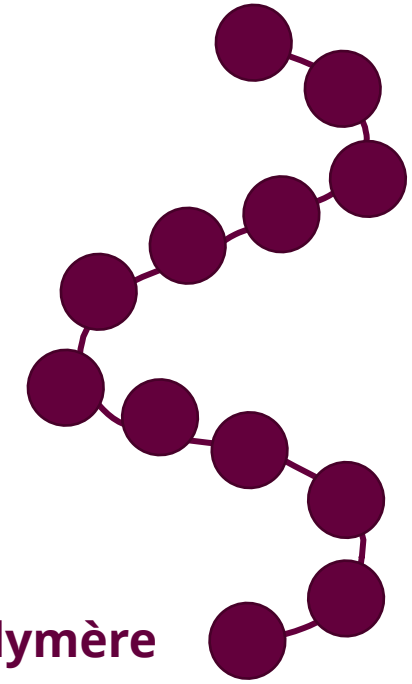


cf Cours sur les polymères F. Agnely

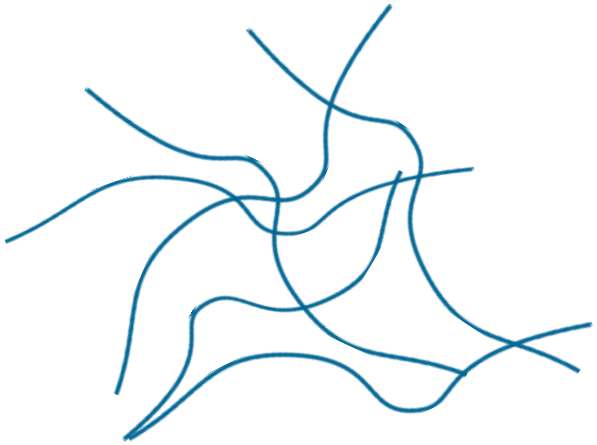
II] Systèmes supramoléculaires: *an overview*

II.1) Polymères (***RAPPEL***)

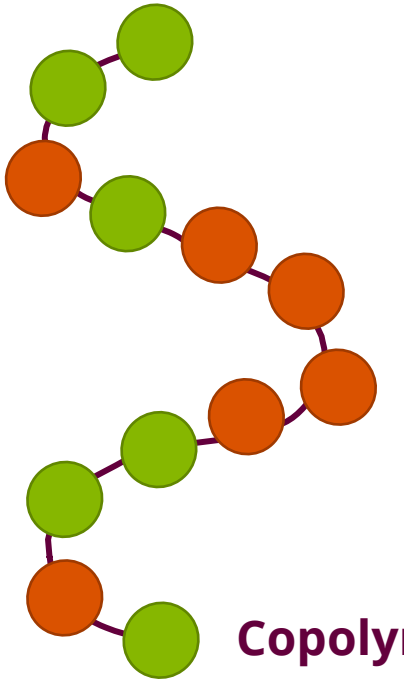
Agir sur les propriétés des polymères



Polymère



Polymères enchevêtrés



Copolymère

Agir sur leur fonctionnalisation

Agir sur leur composition

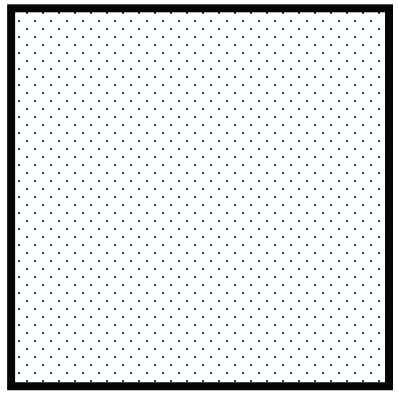
=> Modifier les interactions dominantes et donc les nano-structures

cf Cours sur les polymères F. Agnely

II] Systèmes supramoléculaires: *an overview*

II.2) Milieux colloïdaux et gels de colloïdes

Colloïde = Suspension colloïdale



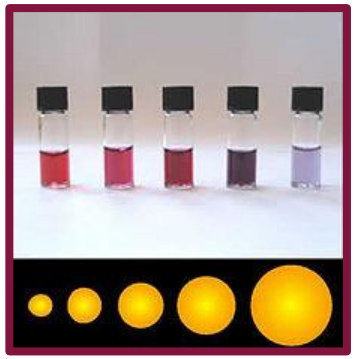
IUPAC definition of "colloidal"

« The term refers to a state of subdivision, implying that the molecules or polymolecular particles dispersed in a medium have at least in one direction a dimension roughly between 1 nm and 1 µm, or that in a system discontinuities are found at distances of that order »

Suspension de particules dont la taille est comprise entre 1nm et 1µm

=> on est bien à l'échelle supramoléculaire

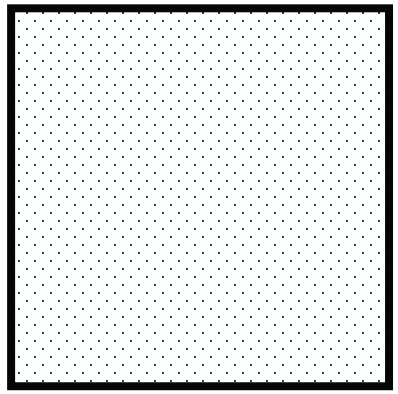
Particules: Métalliques (Au, Ag, Cu…) , inorganiques (SiO_2…), polymères, biomolécules



II] Systèmes supramoléculaires: *an overview*

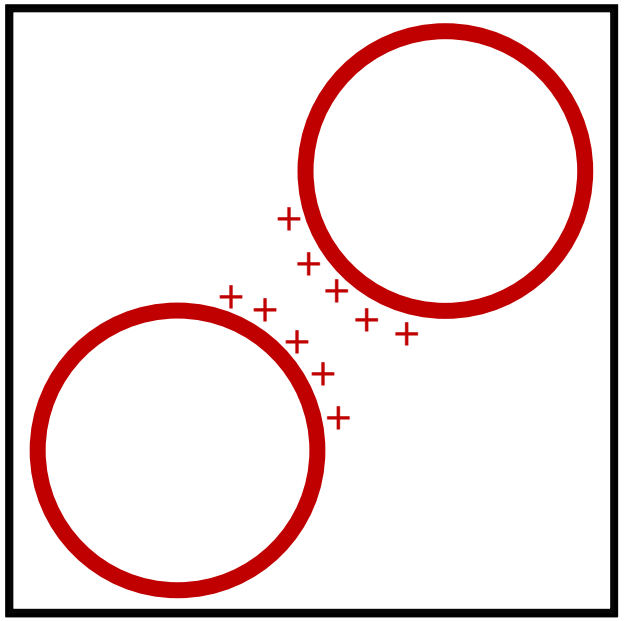
II.2) Milieux colloïdaux et gels de colloïdes

Colloïde = Suspension colloïdale



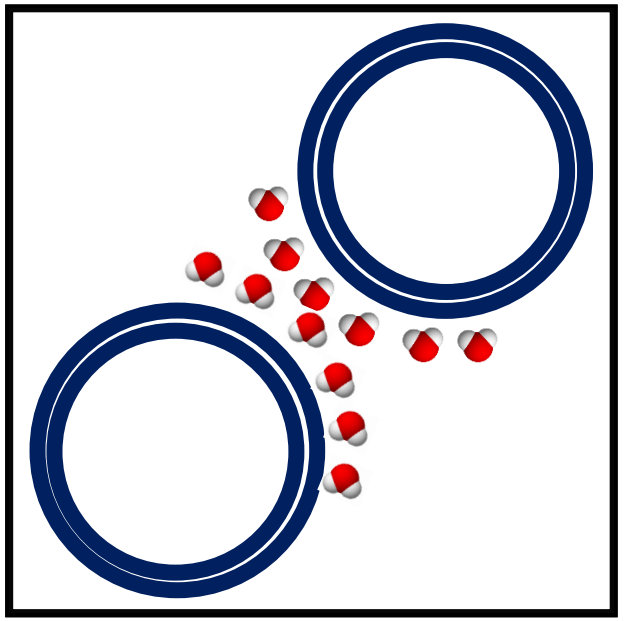
Stabilité colloïdale

Electrostatique



Charge de surface
Potentiel Zeta (ζ)

Stérique

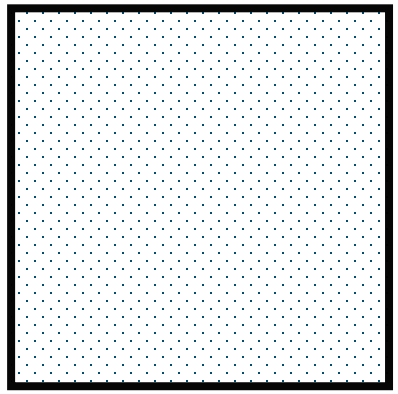


Hydrophilie
Adsorption

II] Systèmes supramoléculaires: *an overview*

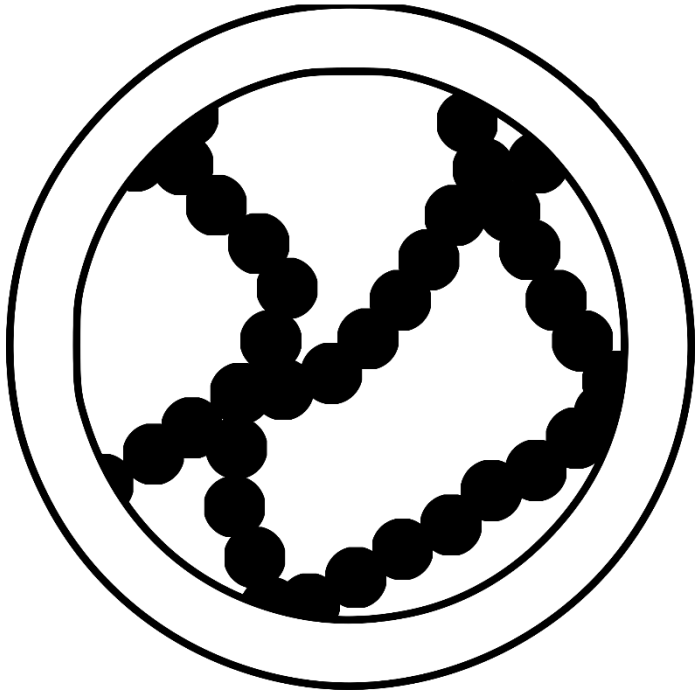
II.2) Milieux colloïdaux et gels de colloïdes

Colloïde = Suspension colloïdale



Stabilité colloïdale +++

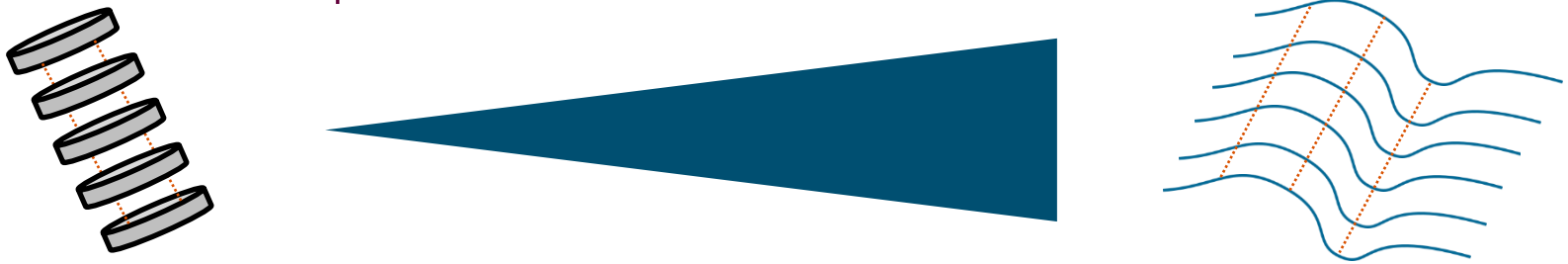
Gels de colloïdes



II] Systèmes supramoléculaires: *an overview*

II.3) *Low Molecular Weight Gelators* (LMWG)

= Gélifiants de bas poids moléculaire



Petites molécules < 3000 Da < **Macromolécules**

Sérendipité

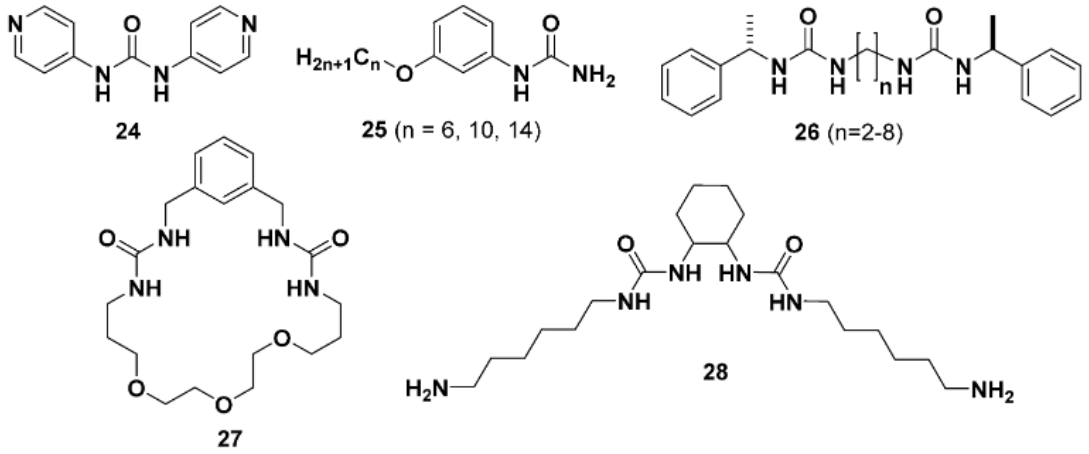
Du *et al.*, *Chem. Rev.*, 2015, **115** (24), 13165-13307

II] Systèmes supramoléculaires: *an overview*

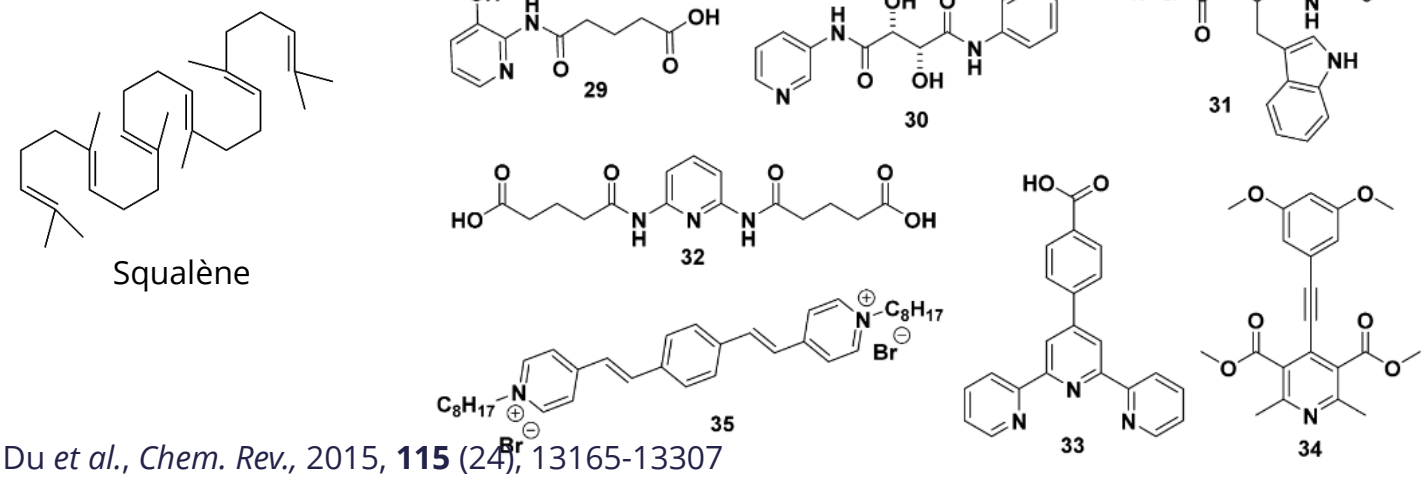
II.3) *Low Molecular Weight Gelators* (LMWG)

Exemples :

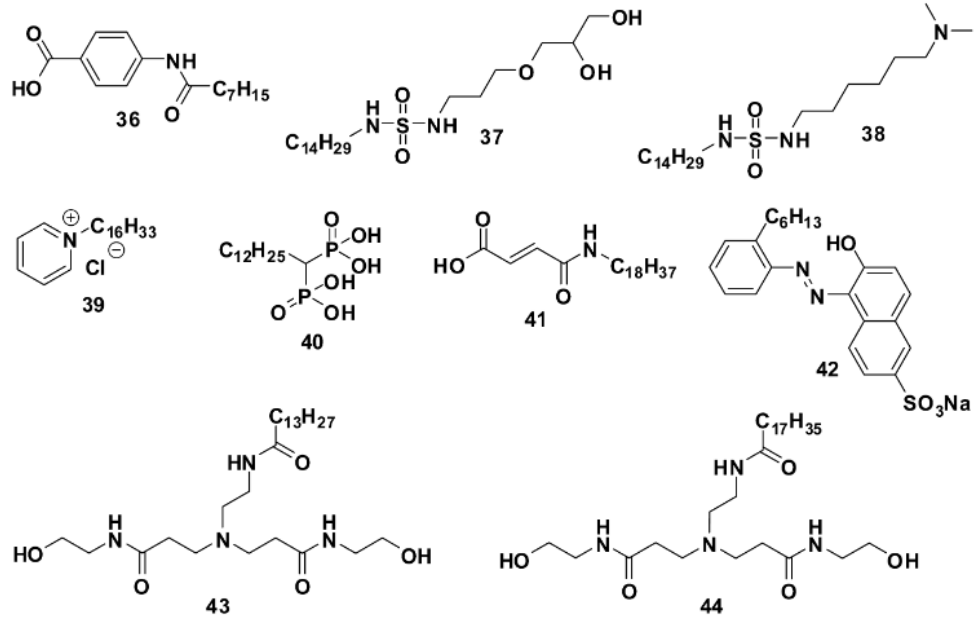
Scheme 8. Representative Molecular Structures of Urea-Containing Hydrogelators

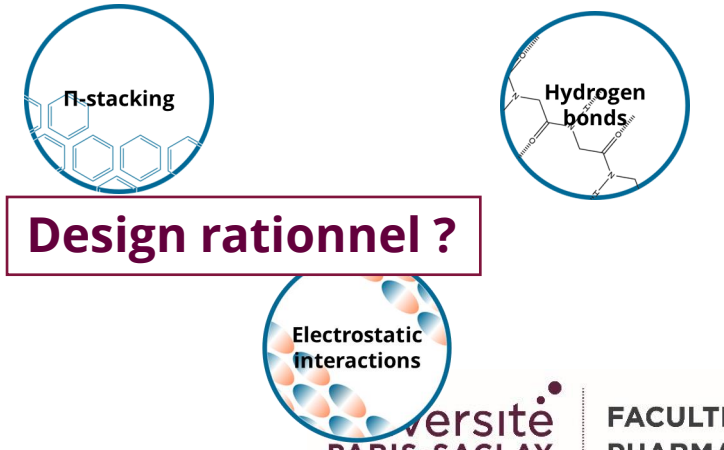


Scheme 9. Representative Molecular Structures of Pyridine-Containing Hydrogelators



Scheme 10. Alkyl-Chain-Containing Hydrogelators





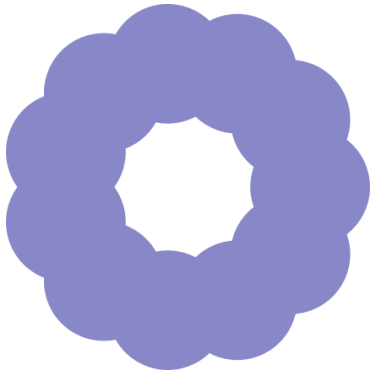
Du *et al.*, *Chem. Rev.*, 2015, **115** (24), 13165-13307

II] Systèmes supramoléculaires: *an overview*

II.4) Systèmes *host-guest*

Inspiré des systèmes protéine-ligand

Guest molecule

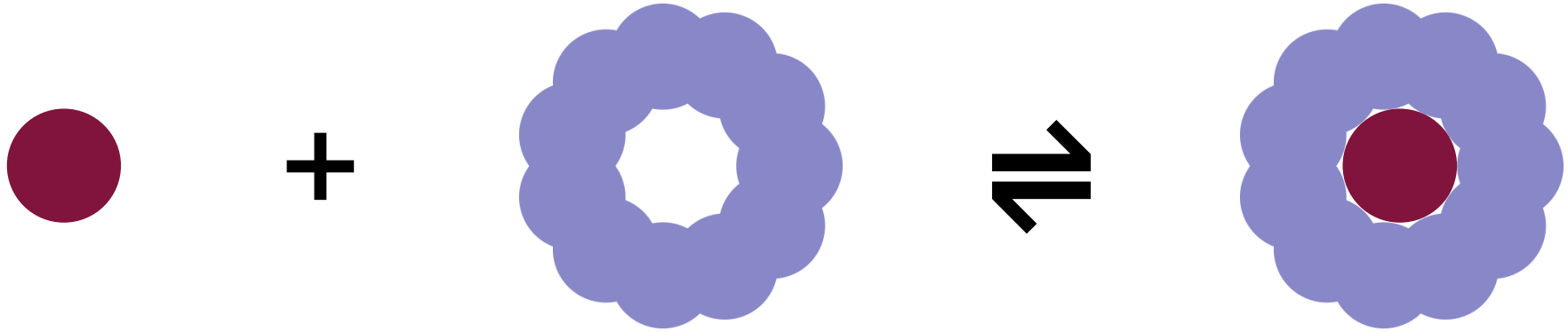


Host molecule

II] Systèmes supramoléculaires: *an overview*

II.4) Systèmes *host-guest*

Inspiré des systèmes protéine-ligand



Guest molecule

Host molecule

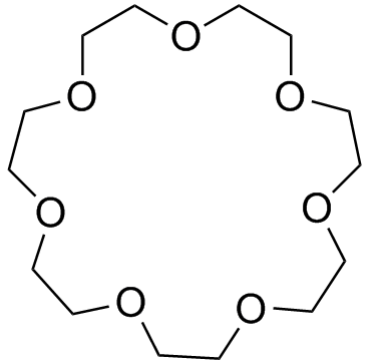
Interaction spécifique

II] Systèmes supramoléculaires: *an overview*

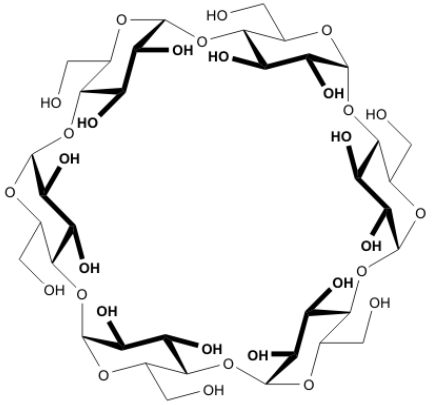
II.4) Systèmes *host-guest*

Inspiré des systèmes protéine-ligand

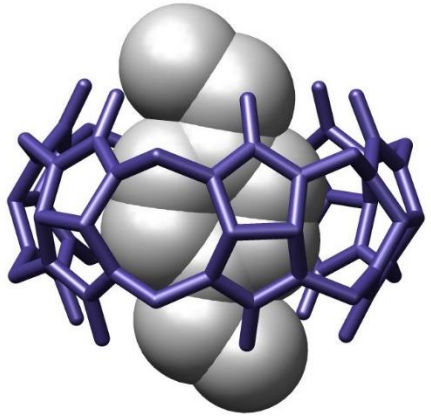
Exemple: éther couronne, cyclodextrine et cucurbiturils



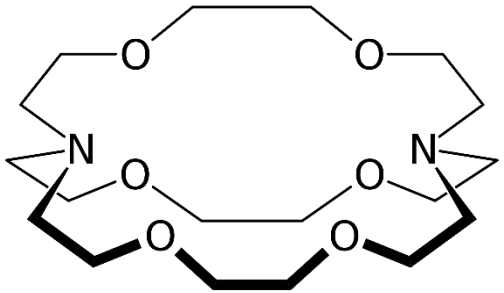
Ether couronne



Cyclodextrine



Host–guest complex with a p-xylylenediammonium bound within a cucurbituril



Cucurbiturile

Donald Cram, Nobel 1987

II] Systèmes supramoléculaires: *an overview*

II.4) Systèmes *host-guest*

Inspiré des systèmes protéine-ligand

Drug delivery systems

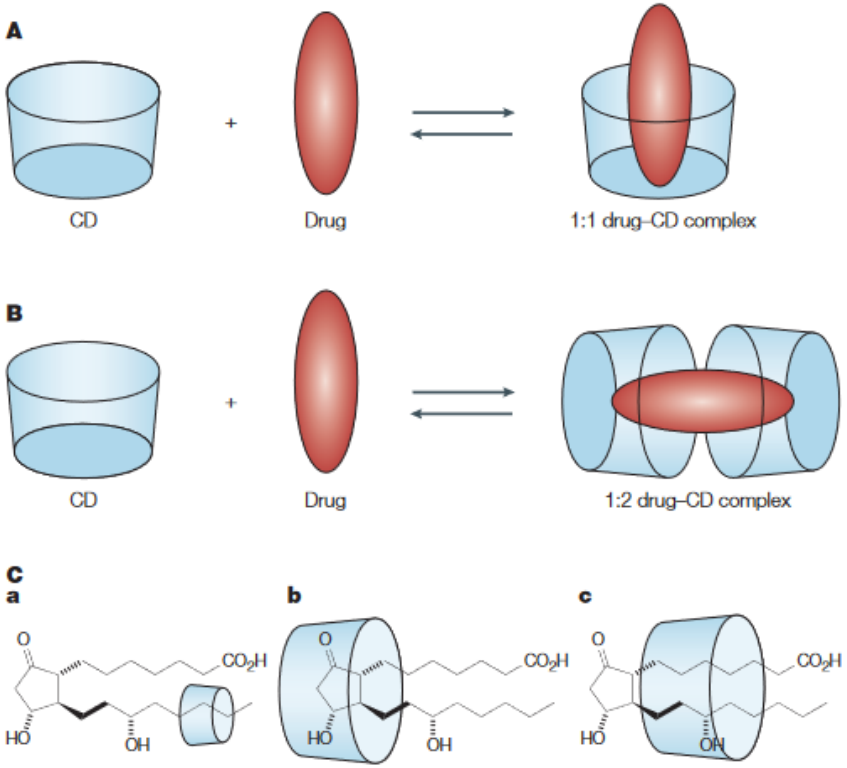
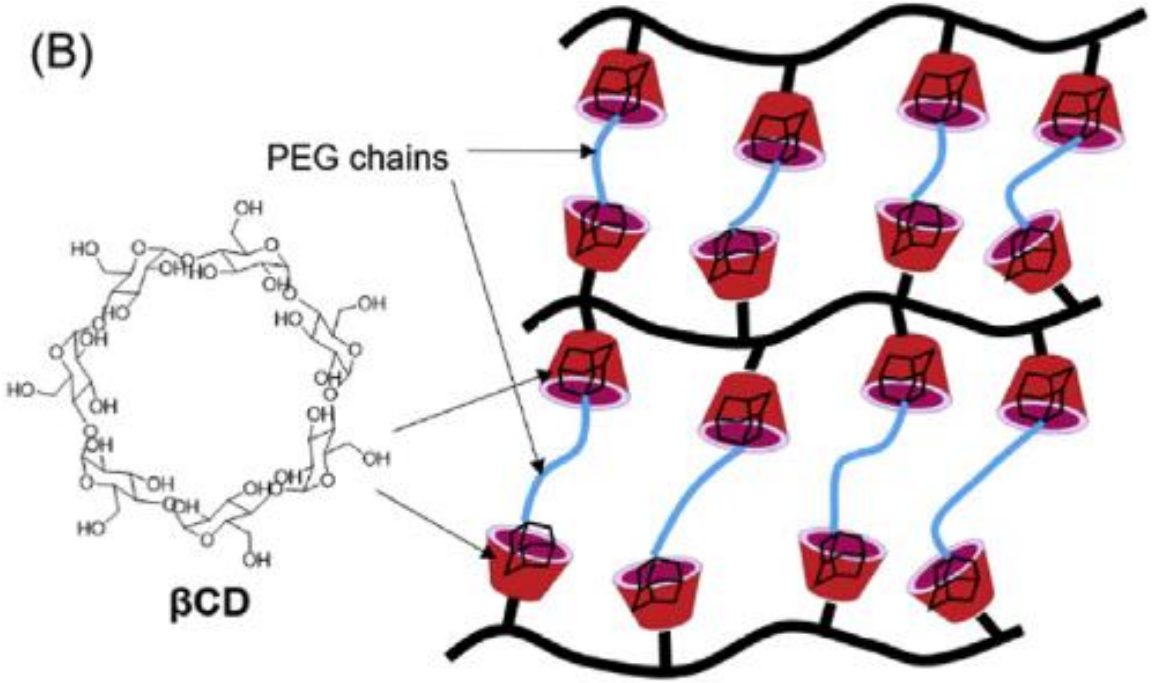


Figure 3 | **Schematic illustration of the association of free cyclodextrin (CD) and drug to form drug–CD complexes. A** | 1:1 drug–CD complex. **B** | 1:2 drug–CD complex. **C** | Proposed models of inclusion complexes between prostaglandin E_2 and (**a**) α-CD, (**b**) β-CD and (**c**) γ-CD.

Selective physical reticulation



Réticulation par interaction host/guest entre cyclodextrine et adamantane

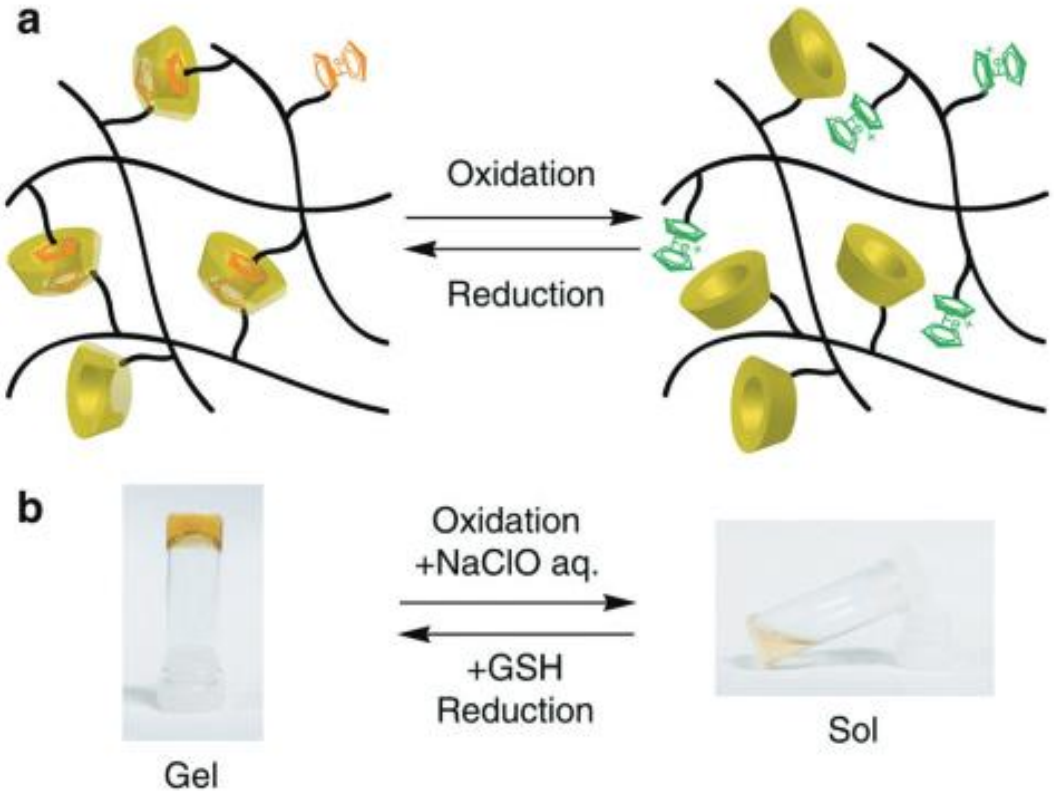
Davis *et al.*, *Nat. Rev. Drug Discoverv*, 2004, **3**, 1023–1035
Lim *et al.*, *Mater. Today Adv.* 2019, **3**, 100021

II] Systèmes supramoléculaires: *an overview*

II.4) Systèmes *host-guest*

Inspiré des systèmes protéine-ligand

Matériaux « intelligents »



Réticulation par reconnaissance host-guest
= gel

↓

Modification de la structure « guest »

↓

Dissociation

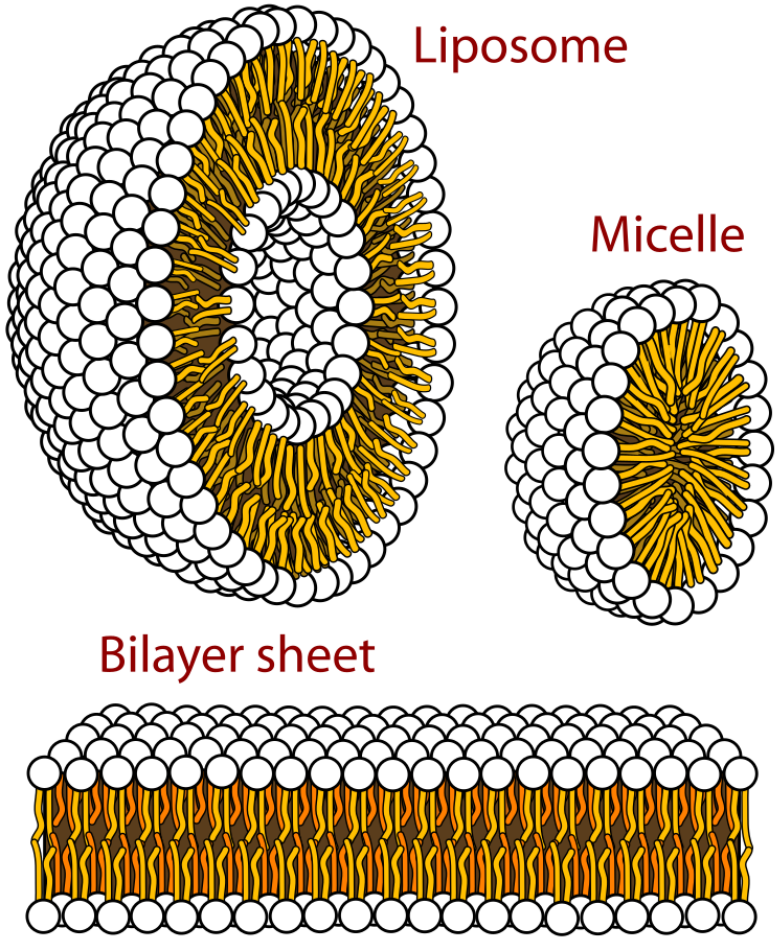
↓

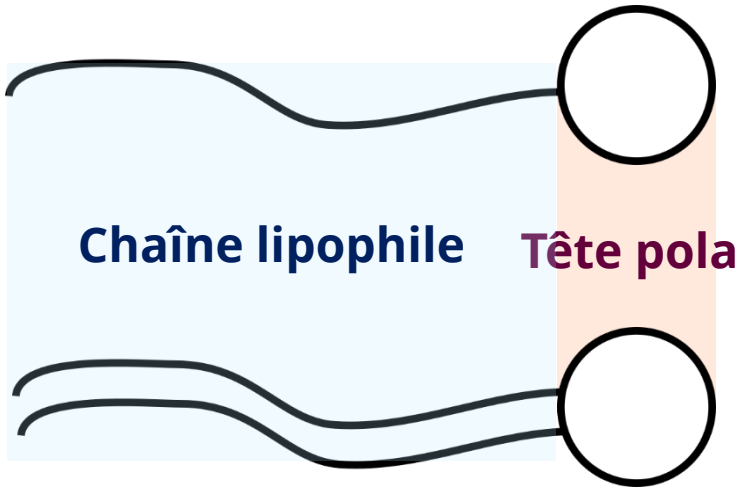
Déstructuration du gel = solution

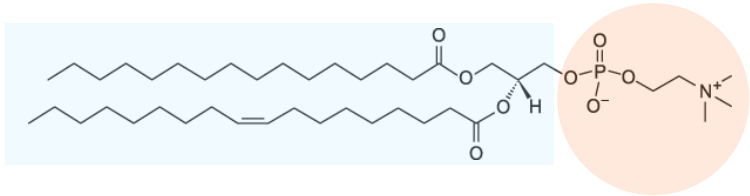
Nakahata *et al., Nat. Commun.*, 2011, **2**, 511

II] Systèmes supramoléculaires: *an overview*

II.5) Particules lipidiques

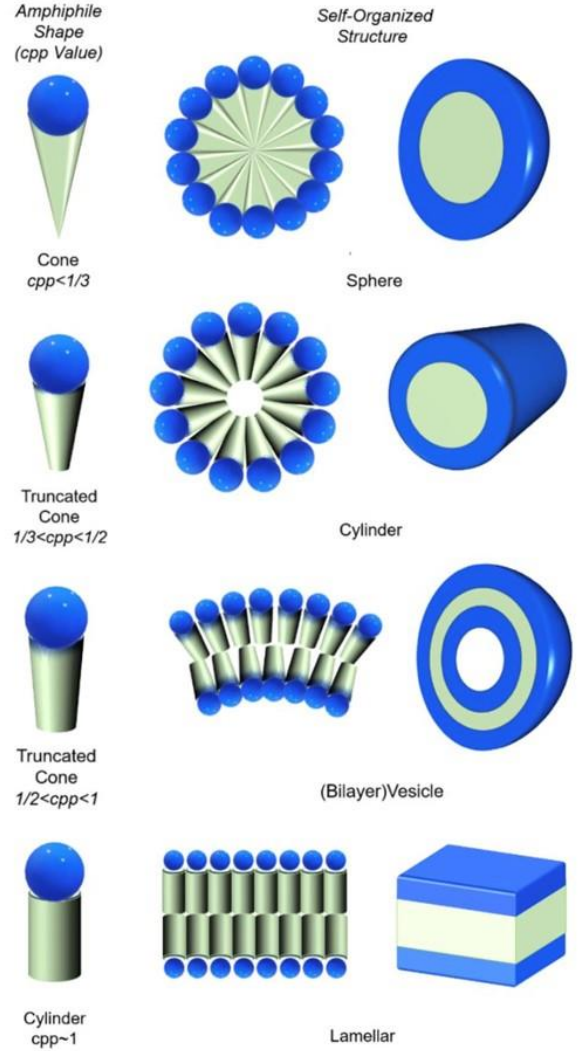






Exemple : phospholipide

Agir sur la charge de surface



Agir le volume stérique

cf Cours sur les liposomes et particules lipidiques

II] Systèmes supramoléculaires: *an overview*

II.6 Programmer l'assemblage supramoléculaire

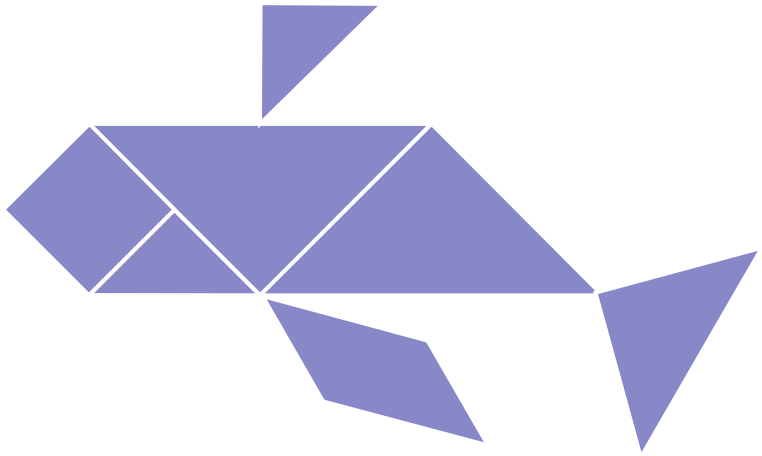
Jusqu'à présent on a joué **sur la stabilité de l'état d'assemblage** qui nous intéressait:

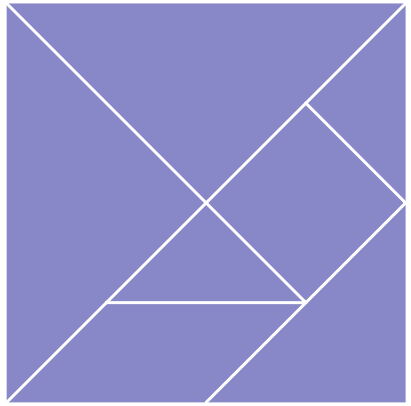
Affinité intermoléculaires	Equilibre hydrophile/hydrophobe	Stabilité interfaciale
K_D des Host-Guest	Repliement des polymères	Colloïdes et particules lipidiques

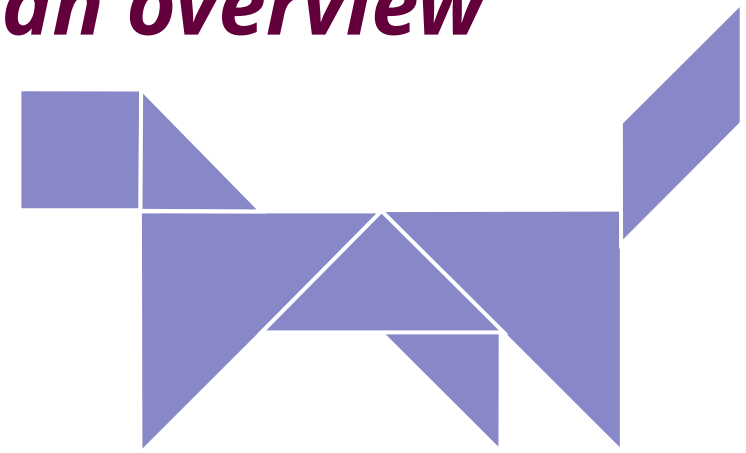
Grâce à ça on peut déjà prédire *a priori* les structures formées

II] Systèmes supramoléculaires: *an overview*

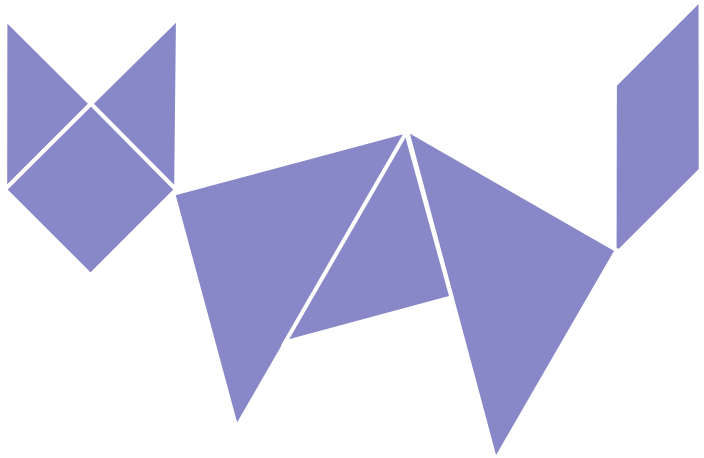
II.6 Programmer l'assemblage supramoléculaire

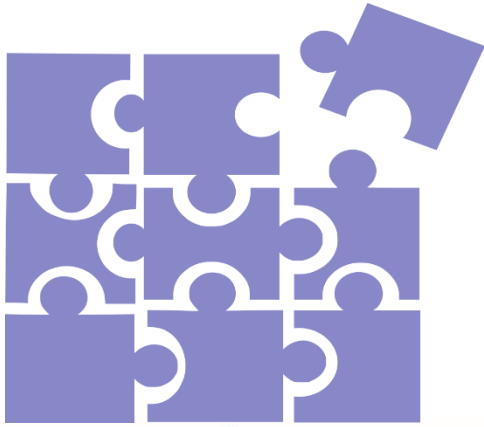






Tangram → Puzzle

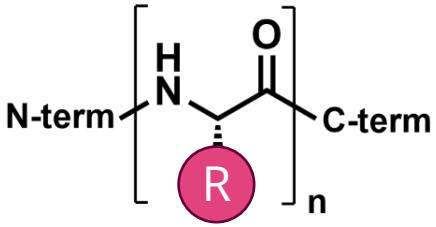




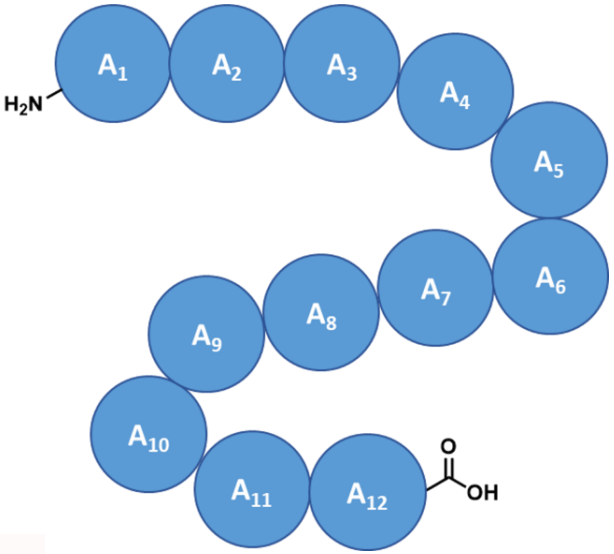
II] Systèmes supramoléculaires: *an overview*

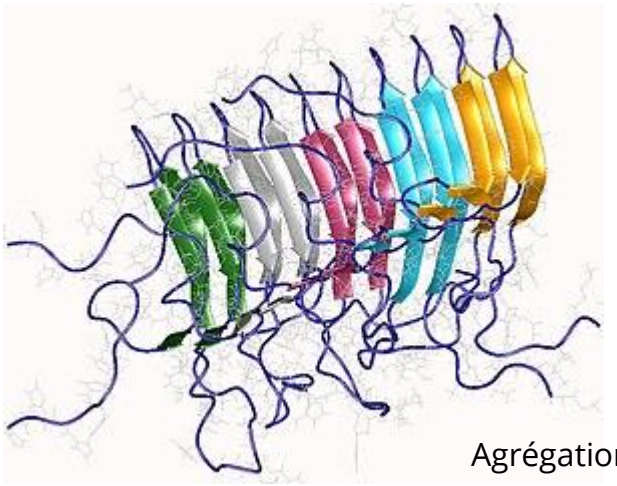
II.6a) Programmer l'assemblage: les peptides

Peptides



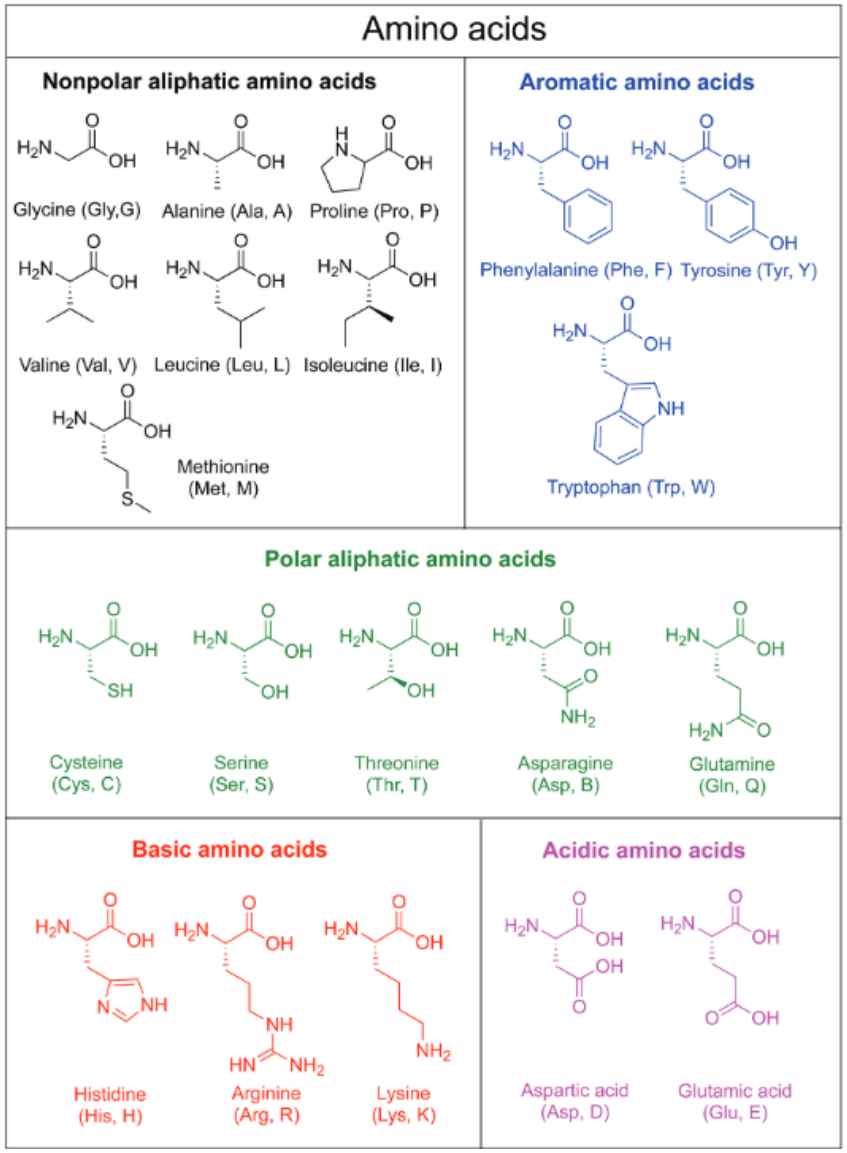
R = Chaîne latérale
(voir table des acides aminés)





Agrégation amyloïde

Bio-inspiration

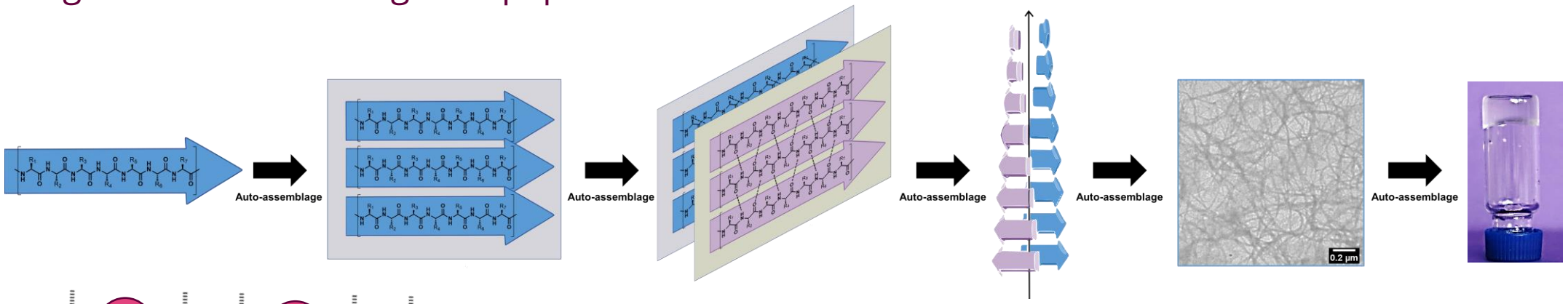


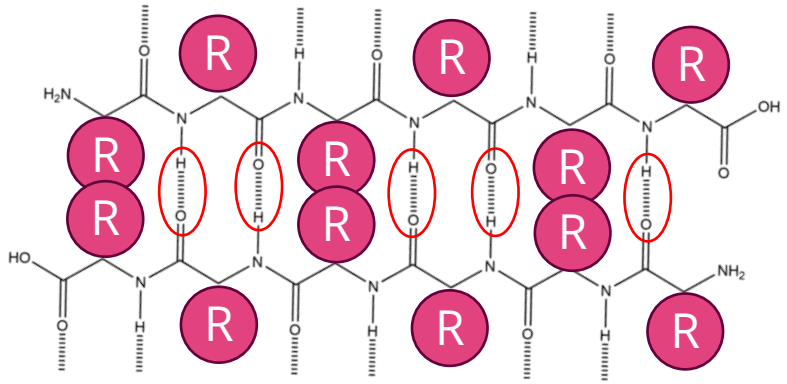
Structure et classification des acides aminés protéinogènes

Das *et al*., *Soft Matter*, 2020, **16** (44), 10065-10095

II] Systèmes supramoléculaires: *an overview*

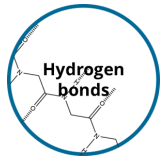
II.6a) Programmer l'assemblage: les peptides

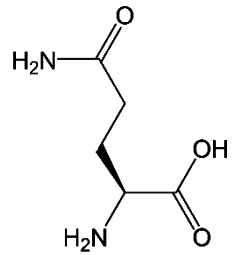




Famille P_{11} : avec des glutamines = liaisons hydrogènes

Ac-**QQ**R**QQQQQ**G**QQ**-NH_2





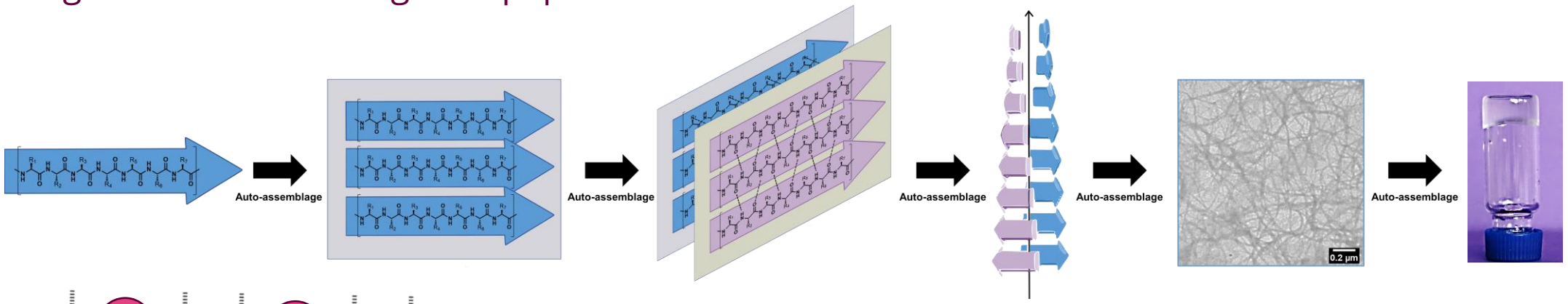
Glutamine

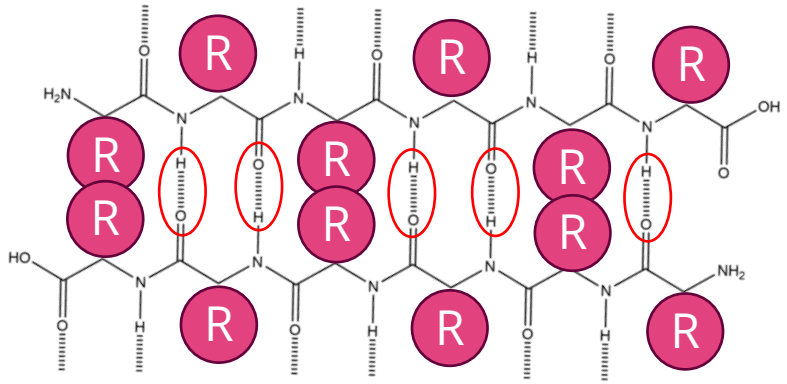
Q – Gln

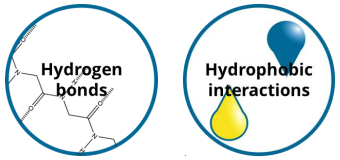
Aggeli *et al.*, *PNAS*, 2001, **98** (21), 11857-11862

II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides



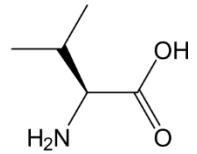




Famille P_{11} : avec des glutamines = liaisons hydrogènes

Famille MAX1 : avec une structure repliée

Structure schématisée du repliement de MAX1 et MAX8

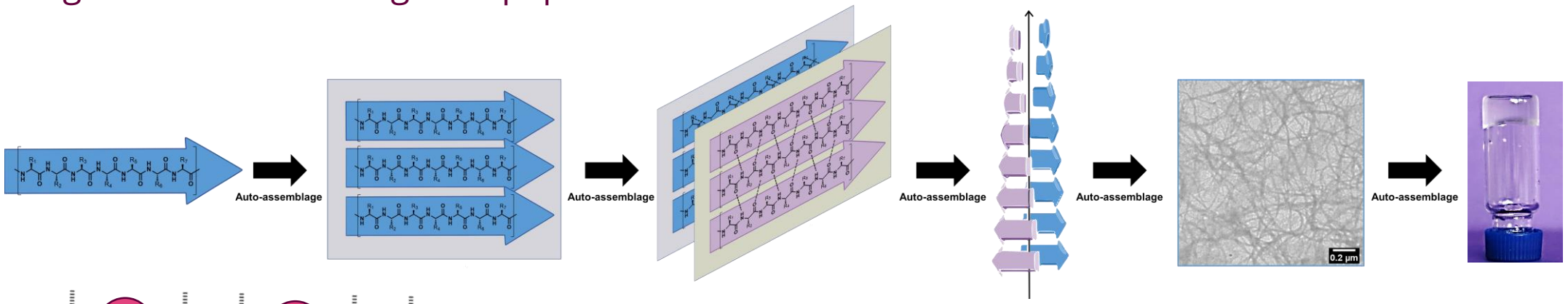


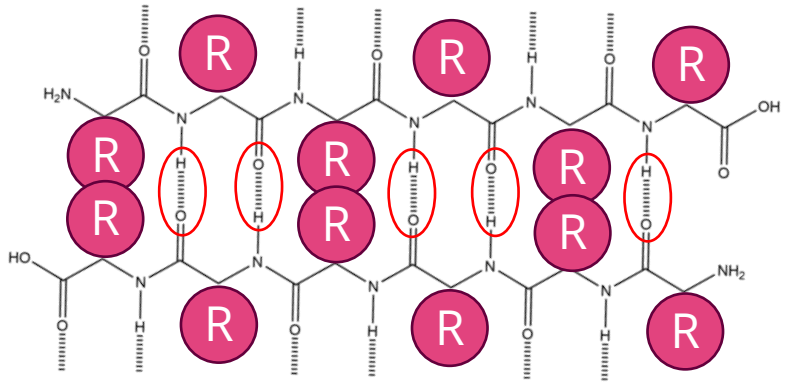
Valine
V – Val

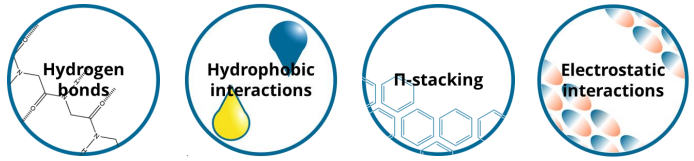
Schneider *et al.*, *J. Am. Chem. Soc.*, 2002, **124** (50), 15030-15037
Hao *et al.*, *Adv. Sci.*, 2022, **9** (11), 2103820

II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides



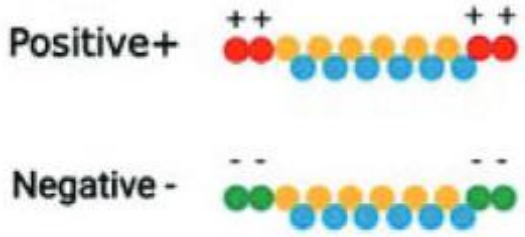




Famille P_{11} : avec des glutamines = liaisons hydrogènes

Famille MAX1 : avec une structure repliée

Famille Multidomain Peptides (MDP)

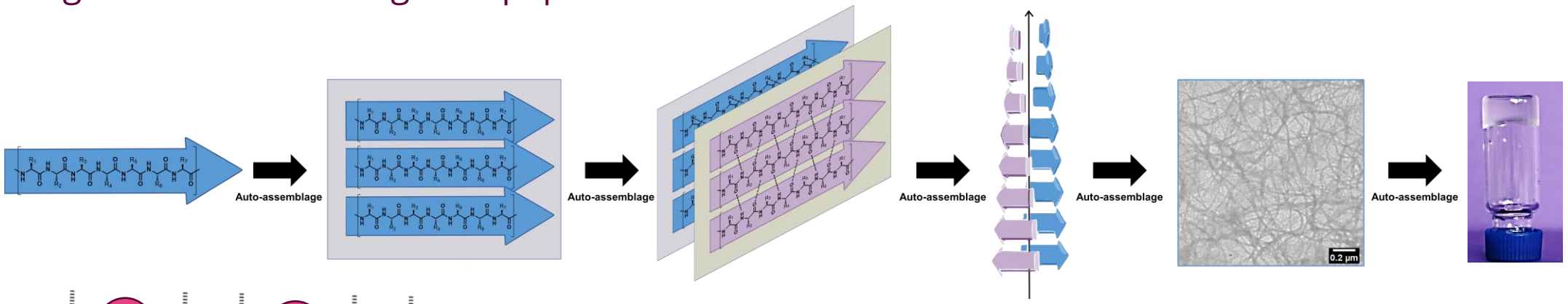


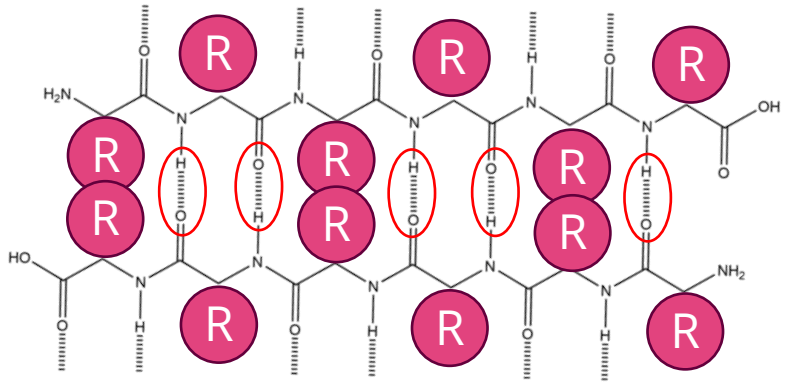
Structure schématisée de multidomain peptides

Schneider *et al.*, *J. Am. Chem. Soc.*, 2002, **124** (50), 15030-15037
Hao *et al.*, *Adv. Sci.*, 2022, **9** (11), 2103820

II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides



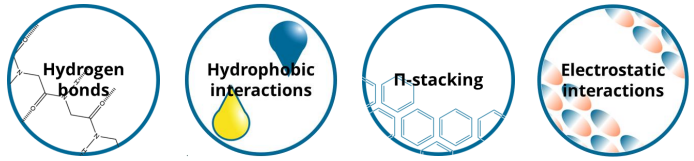


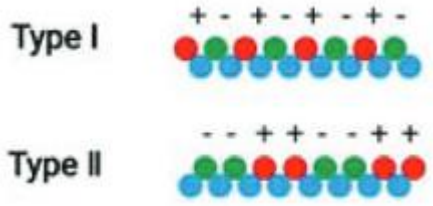
Famille P_{11} : avec des glutamines = liaisons hydrogènes

Famille MAX1 : avec une structure repliée

Famille Multidomain Peptides (MDP)

Famille Peptides amphipathiques

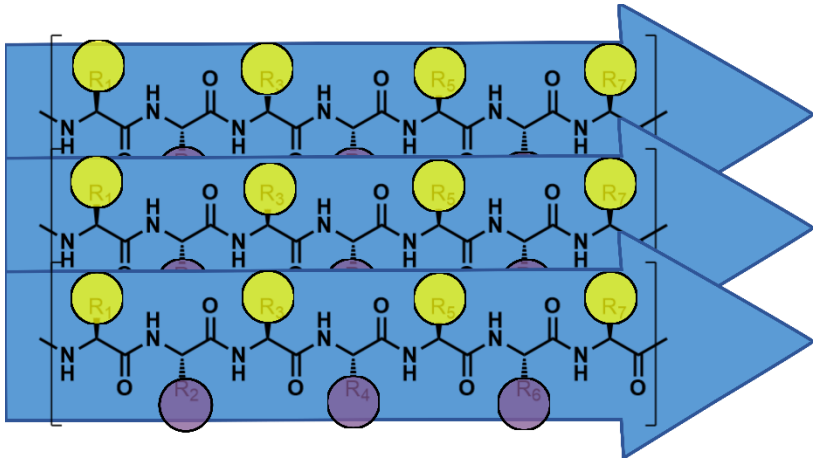




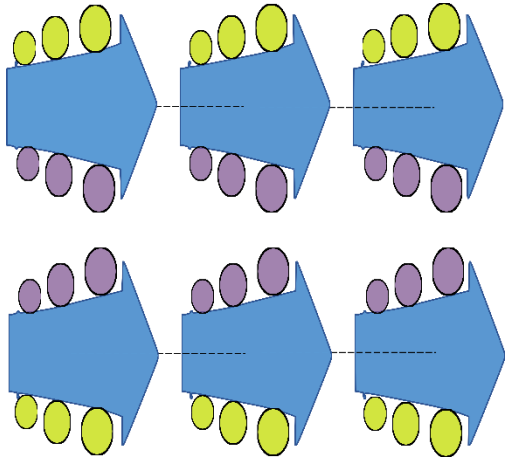
II] Systèmes supramoléculaires: *an overview*

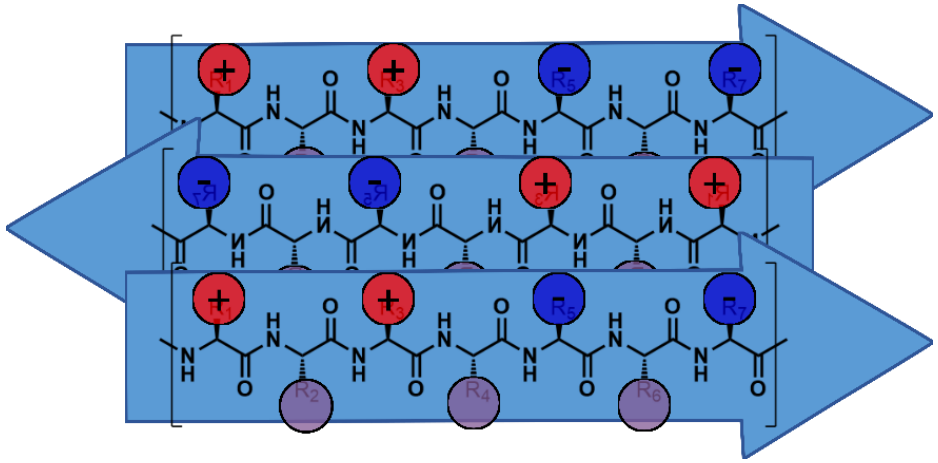
II.6a) Programmer l'assemblage: les peptides

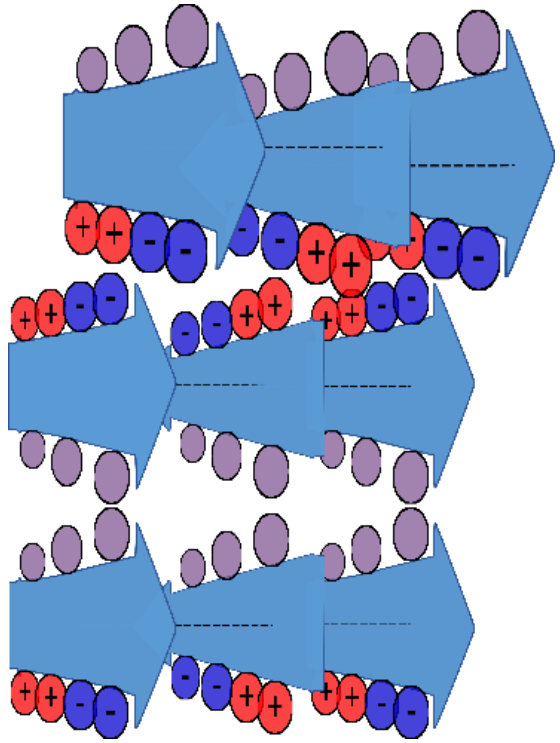
Famille Peptides amphipathiques



Alternance a.a. hydrophile et a.a. hydrophobe

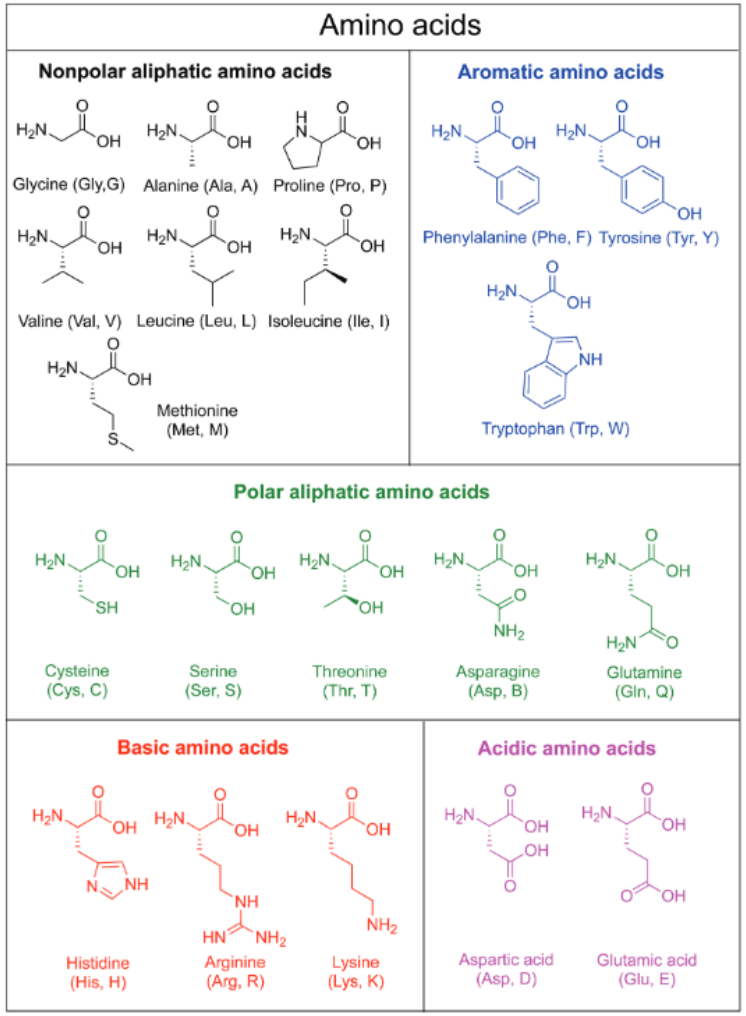






II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

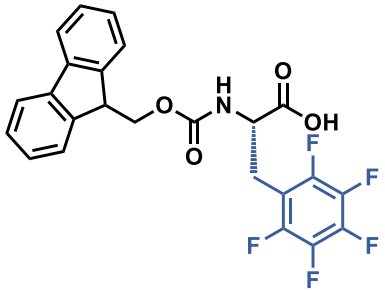


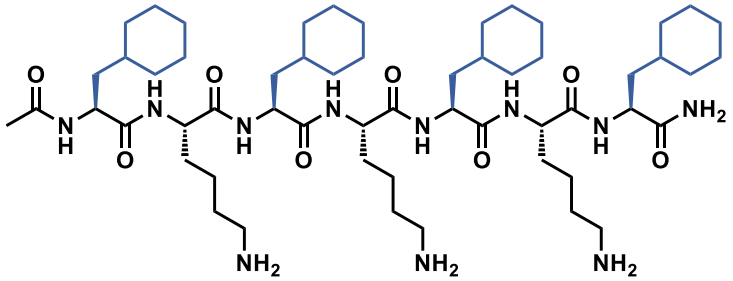
Structure et classification des acides aminés protéinogènes

Das *et al.*, *Soft Matter*, 2020, **16** (44), 10065-10095

=> 20^N possibilités, un peu moins qui s'auto-assemblent

...Mais d'autres acides aminés non-naturels





Et d'autres types de peptides inspirés du collagène, la laminine, la fibroïne, etc...

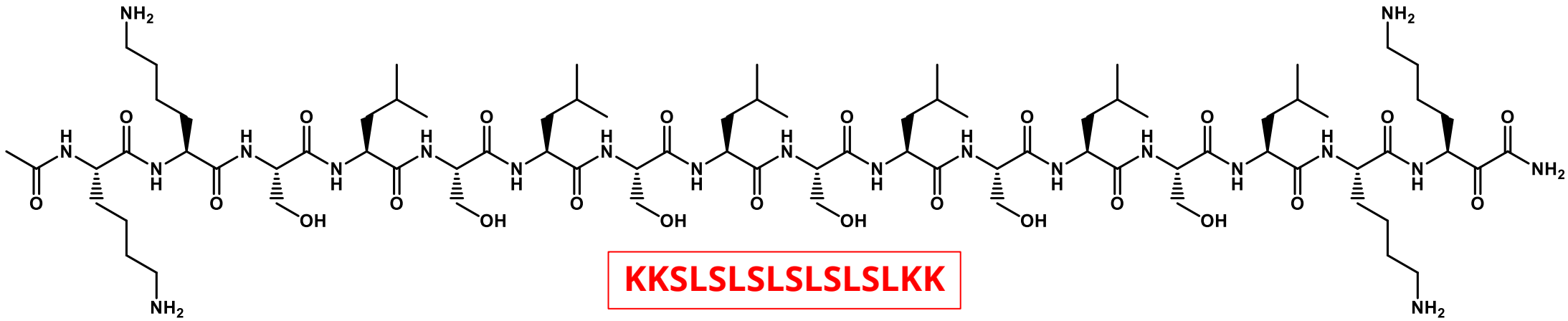
Ex: Forment des matériaux hydrogels similaires à l'ECM

II] Systèmes supramoléculaires: *an overview*

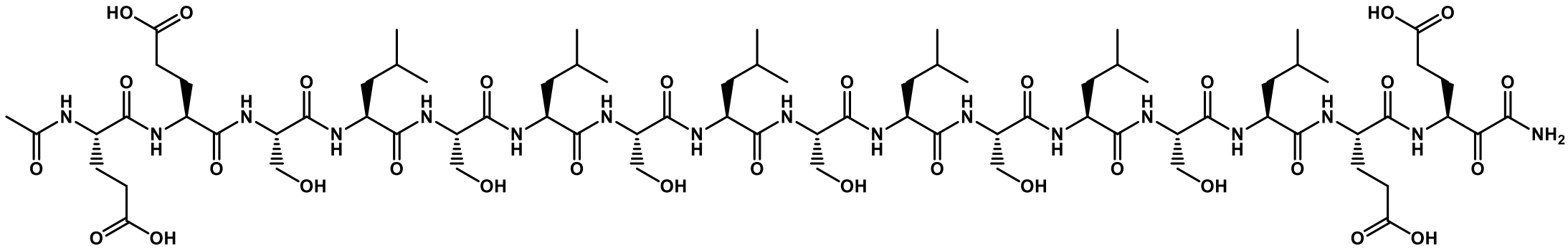
II.6a) Programmer l'assemblage: les peptides

-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al.*, *Adv. Mater.* **2023**, 35, 2210378



KKSLSLSLSLSLSLKK



EESLSLSLSLSLSLEE

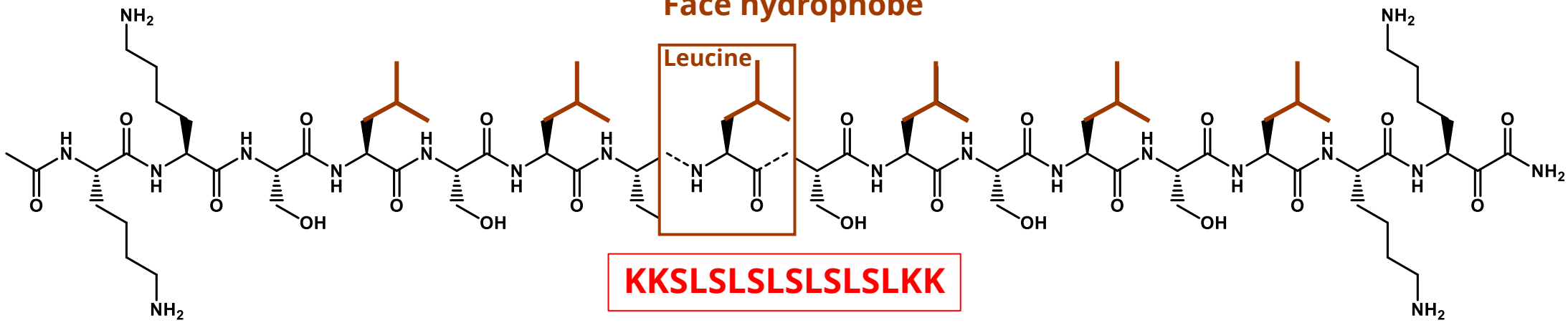
II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

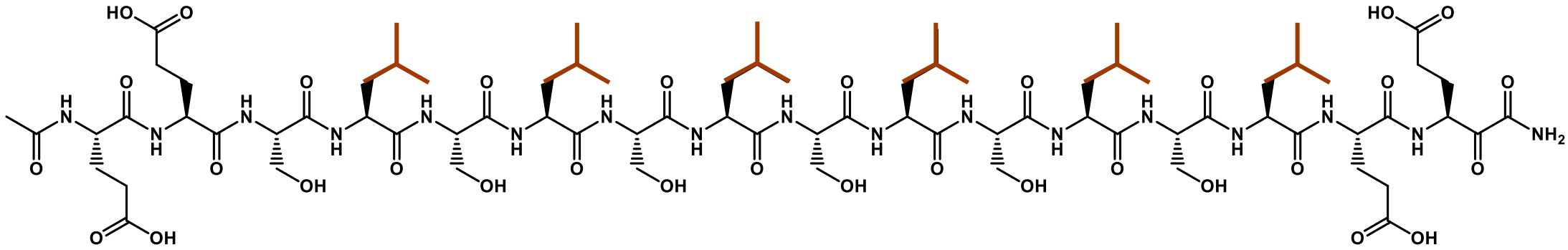
-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al., Adv. Mater.* **2023**, 35, 2210378

Face hydrophobe



KKSLSLSLSLSLSLKK



EESLSLSLSLSLSLEE

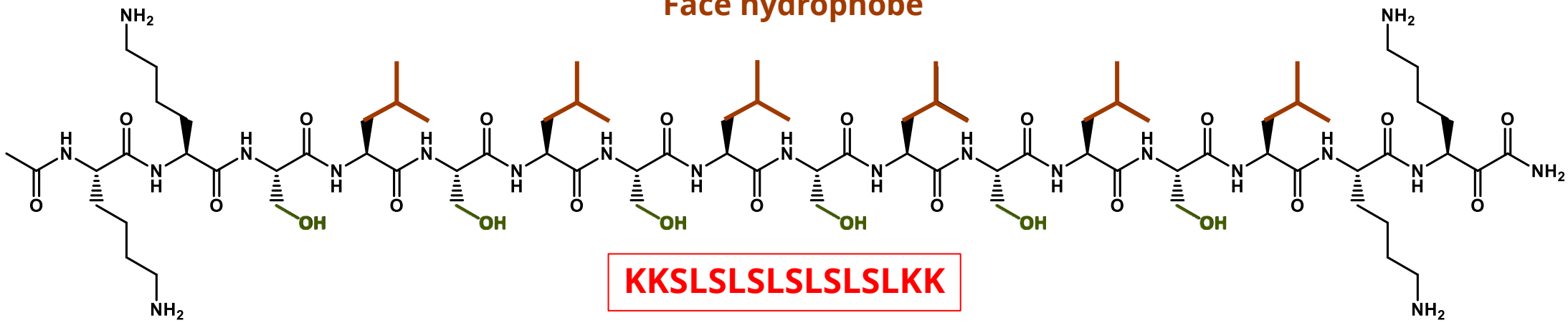
II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

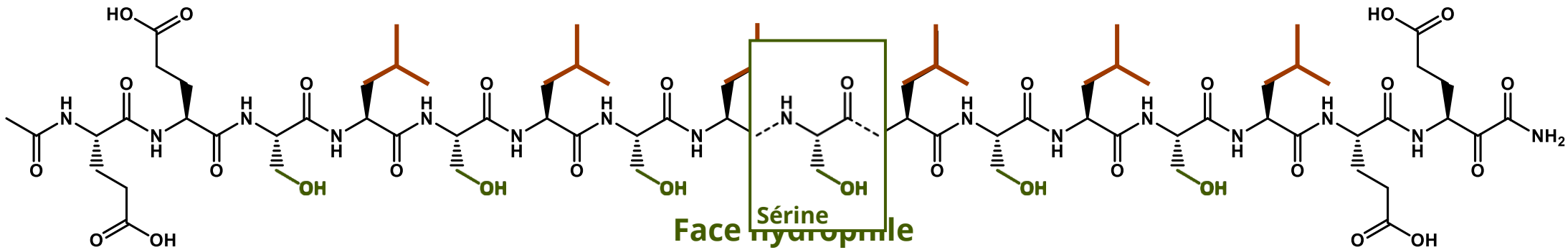
-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al., Adv. Mater.* **2023**, 35, 2210378

Face hydrophobe



KKSLSLSLSLSLSLKK



Face hydrophile

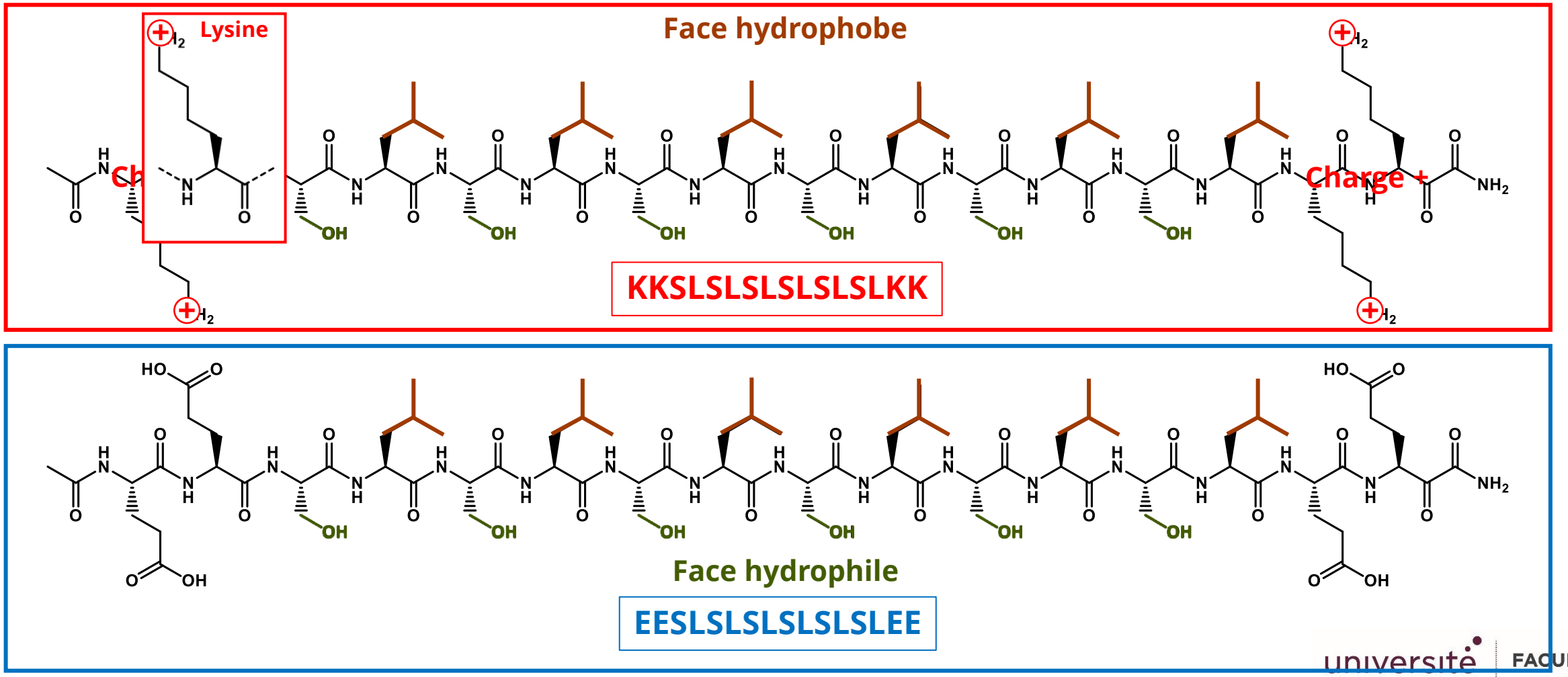
EESLSLSLSLSLSLEE

II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al., Adv. Mater.* **2023**, 35, 2210378

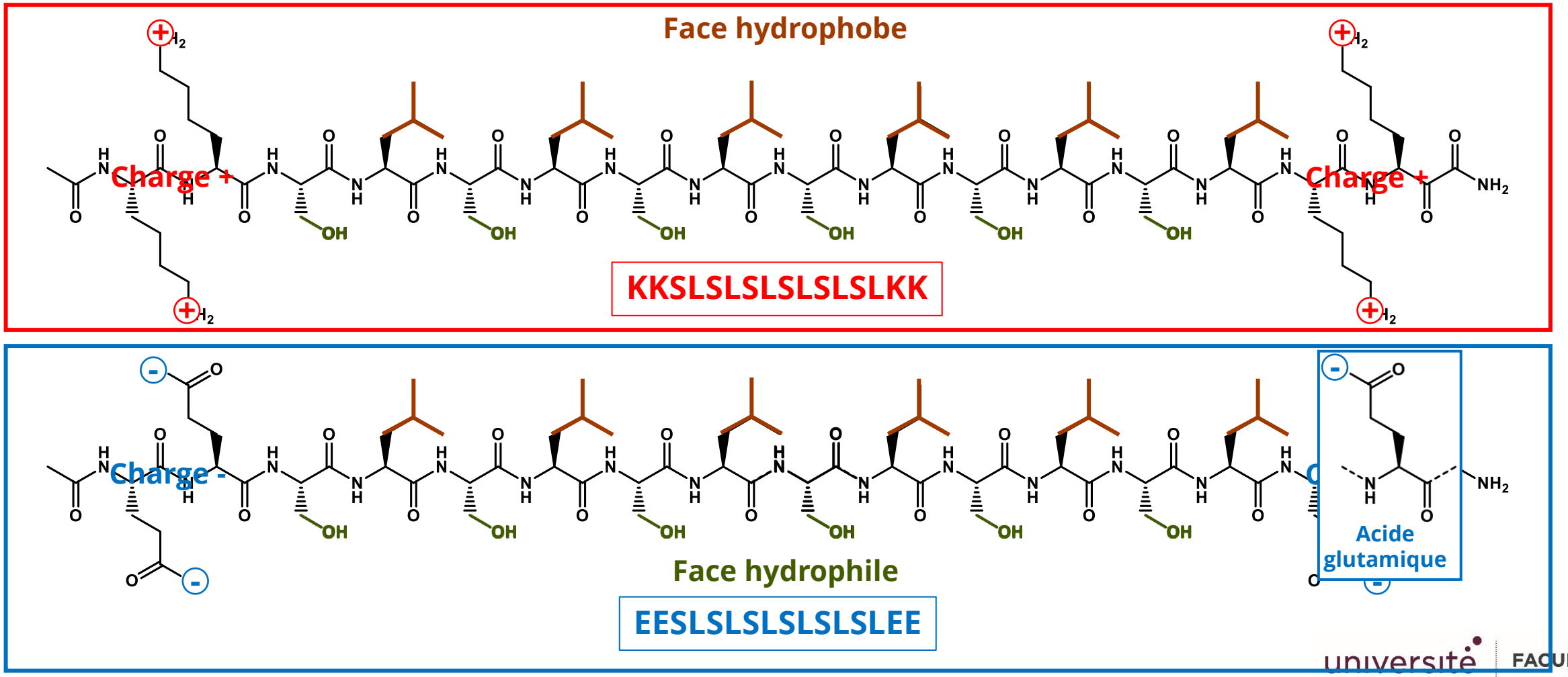


II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al., Adv. Mater.* **2023**, 35, 2210378

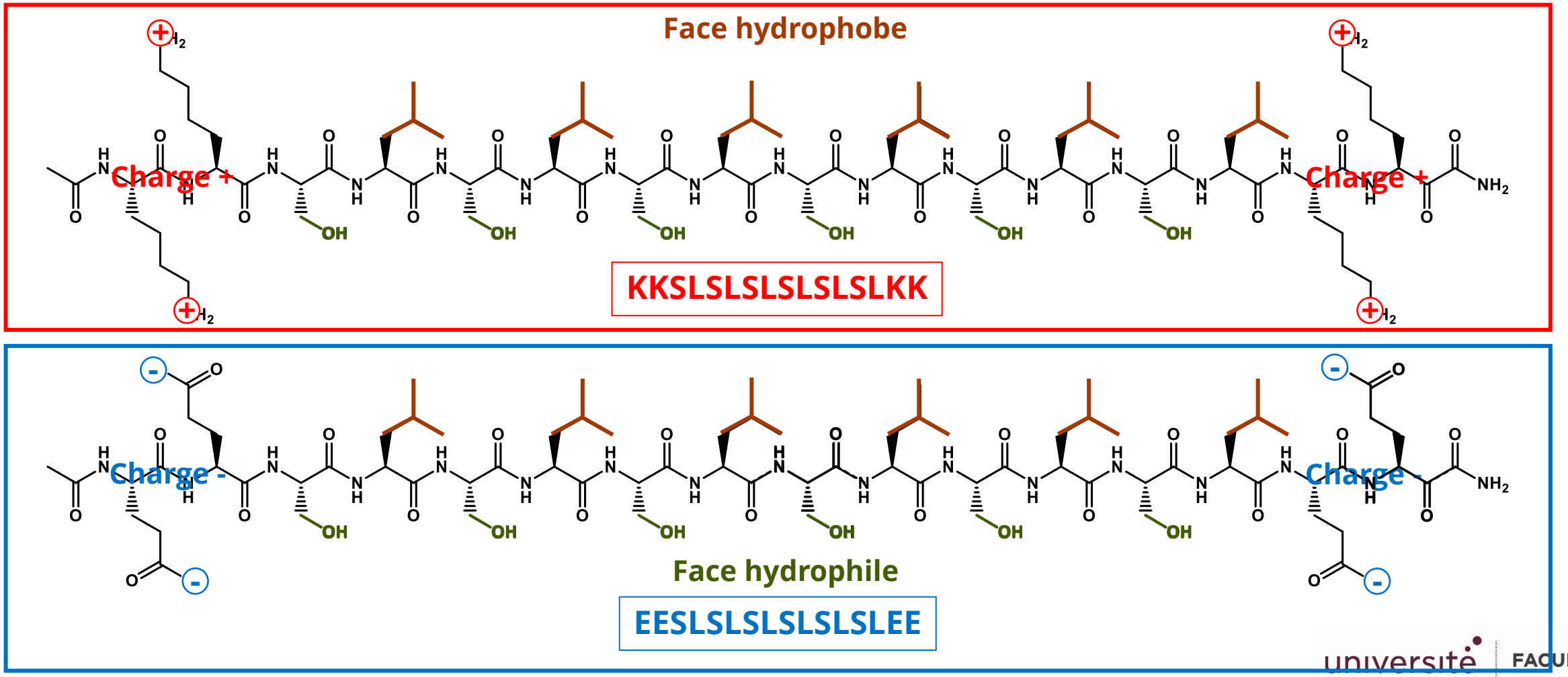


II] Systèmes supramoléculaires: *an overview*

II.6a) Programmer l'assemblage: les peptides

-> Un exemple : Hydrogel de peptides pour l'impression 3D

Farsheed *et al., Adv. Mater.* **2023**, 35, 2210378



II] Systèmes supramoléculaires: *an overview*

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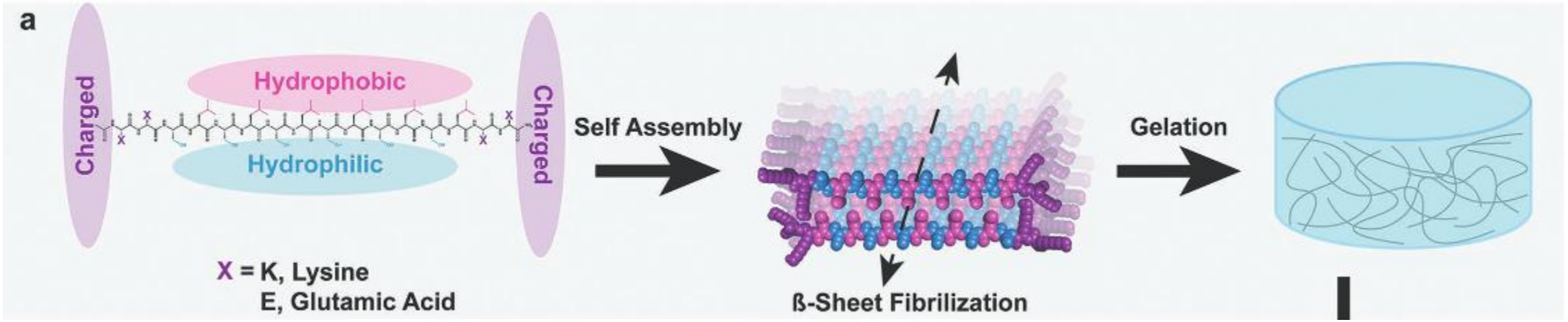

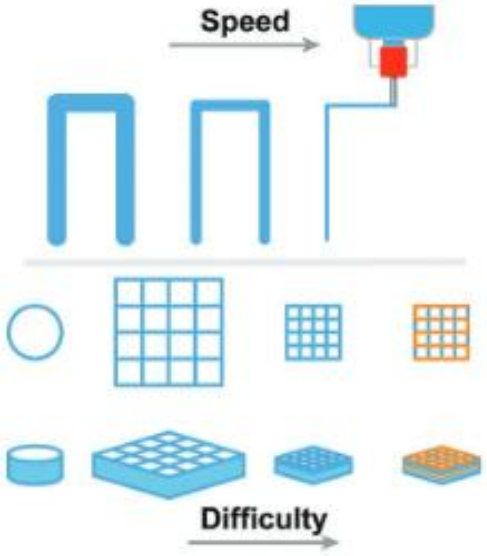

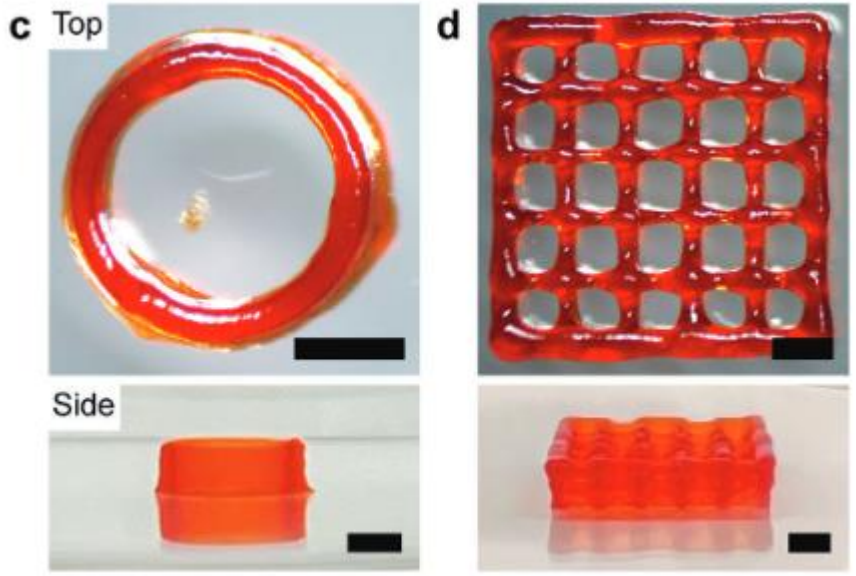

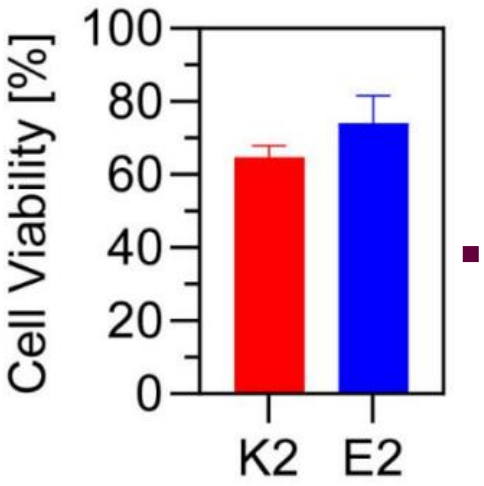

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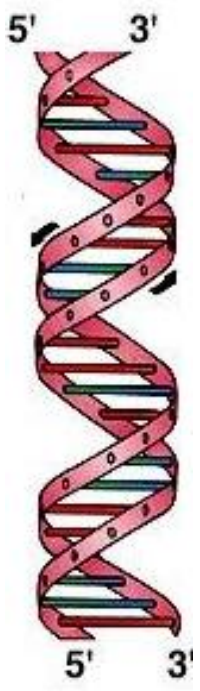
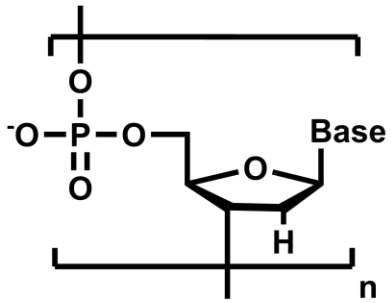
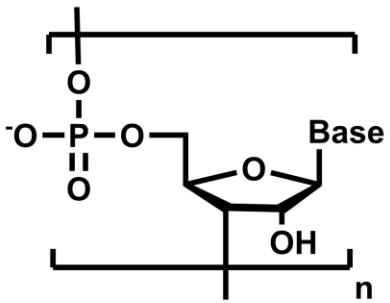
II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques

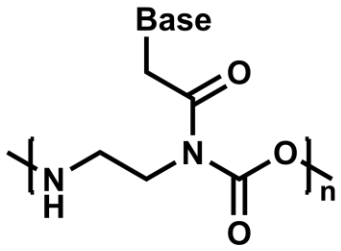




ADN

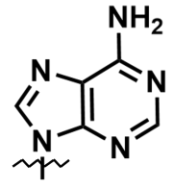
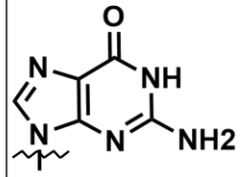
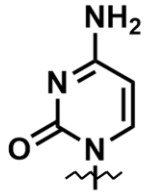
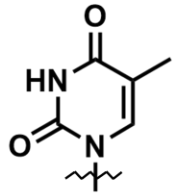
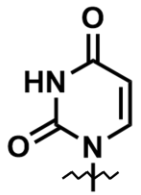


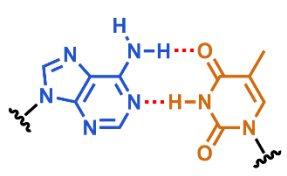
ARN



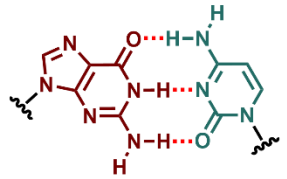
*aeg*PNA

Bases nucléiques:

Adénine	Guanine	Cytosine	Thymine	Uracile
				
Purines		Pyrimidines		

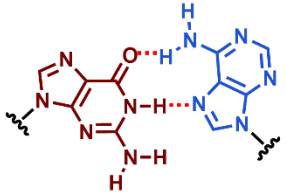


adénine (**A**) : thymine (**T**)

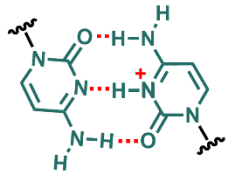


guanine (**G**) : cytosine (**C**)

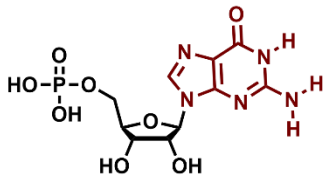
Paires canoniques de Watson-Crick

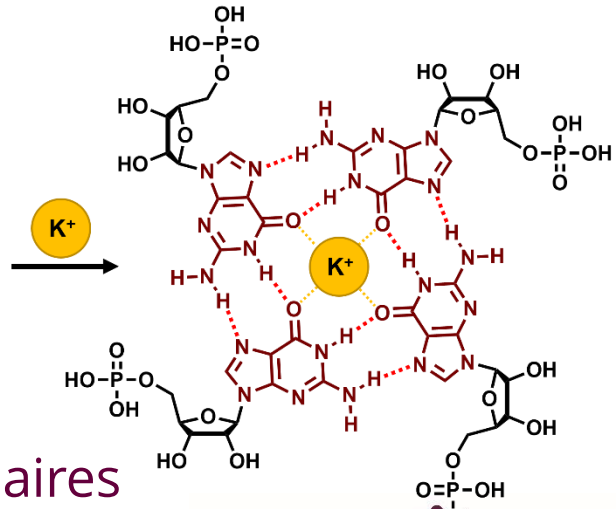


guanine (**G**) : adénine (**A**)



cytosine (**C**) : cytosine (C^+)

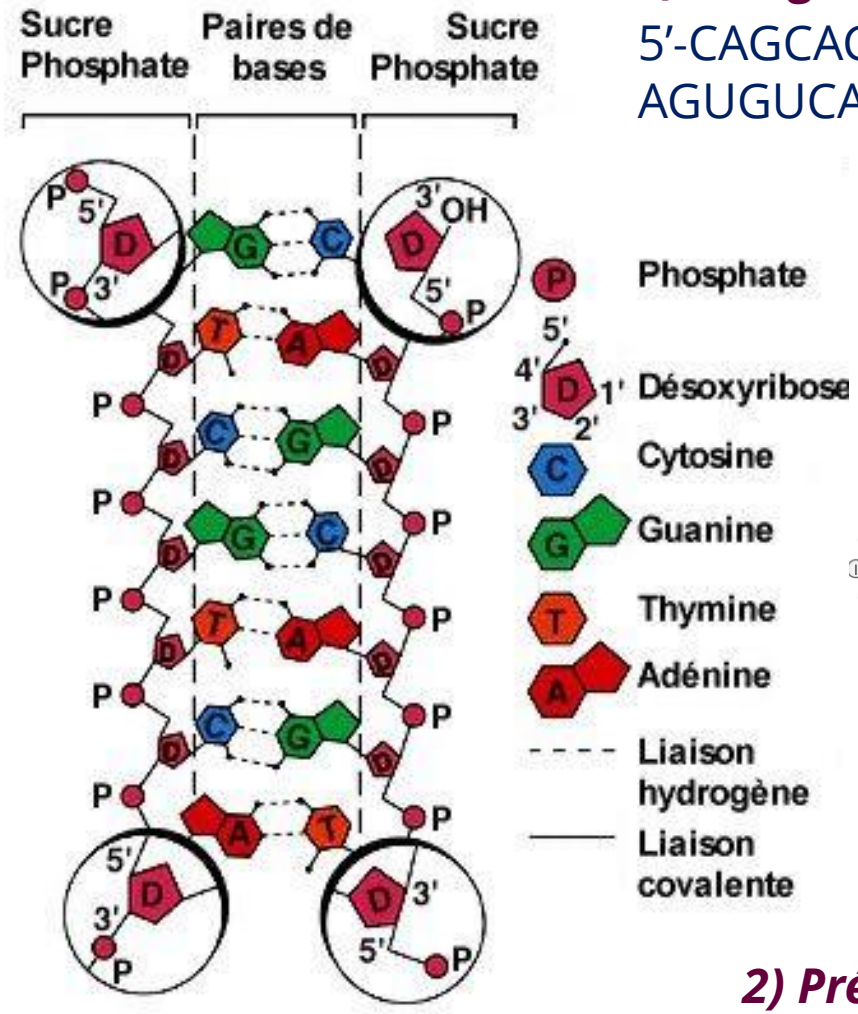




- Existence d'interactions complémentaires spécifiques
- Capacité d'interactions supramoléculaires et structures supramoléculaires complexes

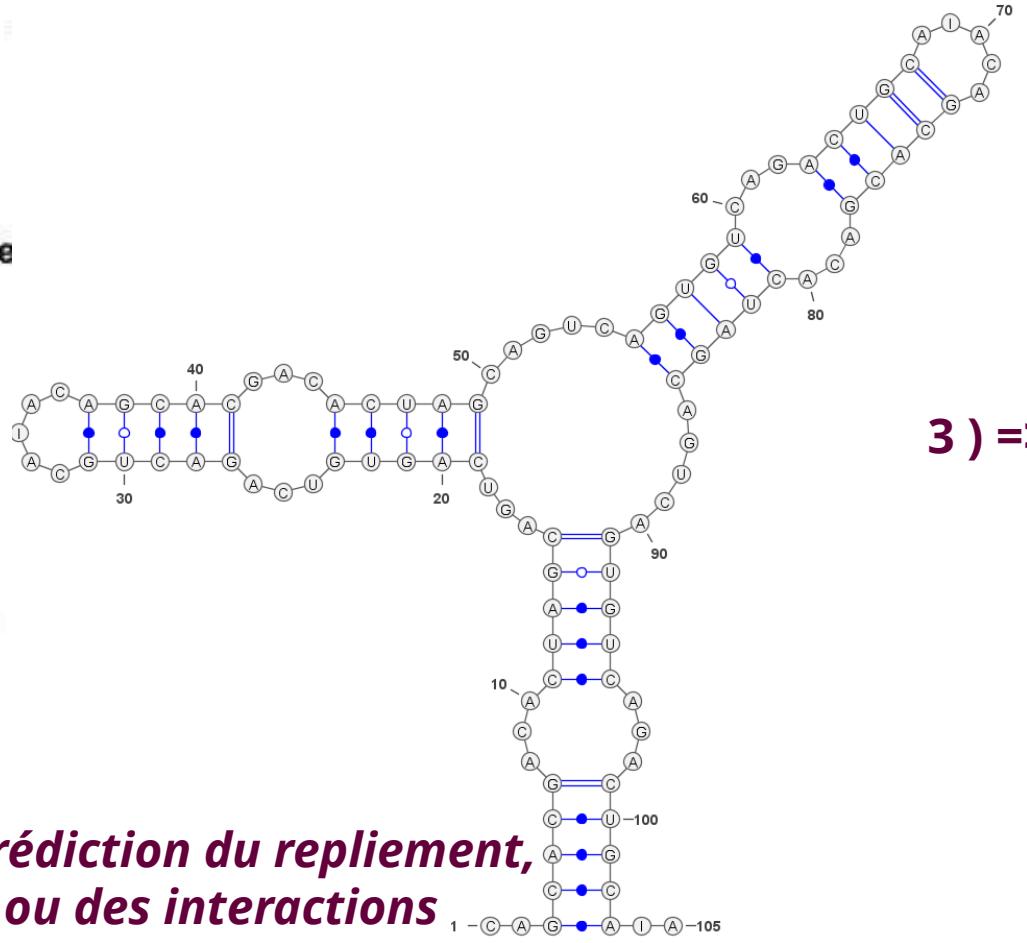
II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques



1) Design de séquence

5'-CAGCACGACACUAGCAGUCAGUGUCAGACUGCAIACAGCACGACACUAGCAGUC
AGUGUCAGACUGCAIACAGCACGACACUAGCAGUCAGUGUCAGACUGCAIA-3'



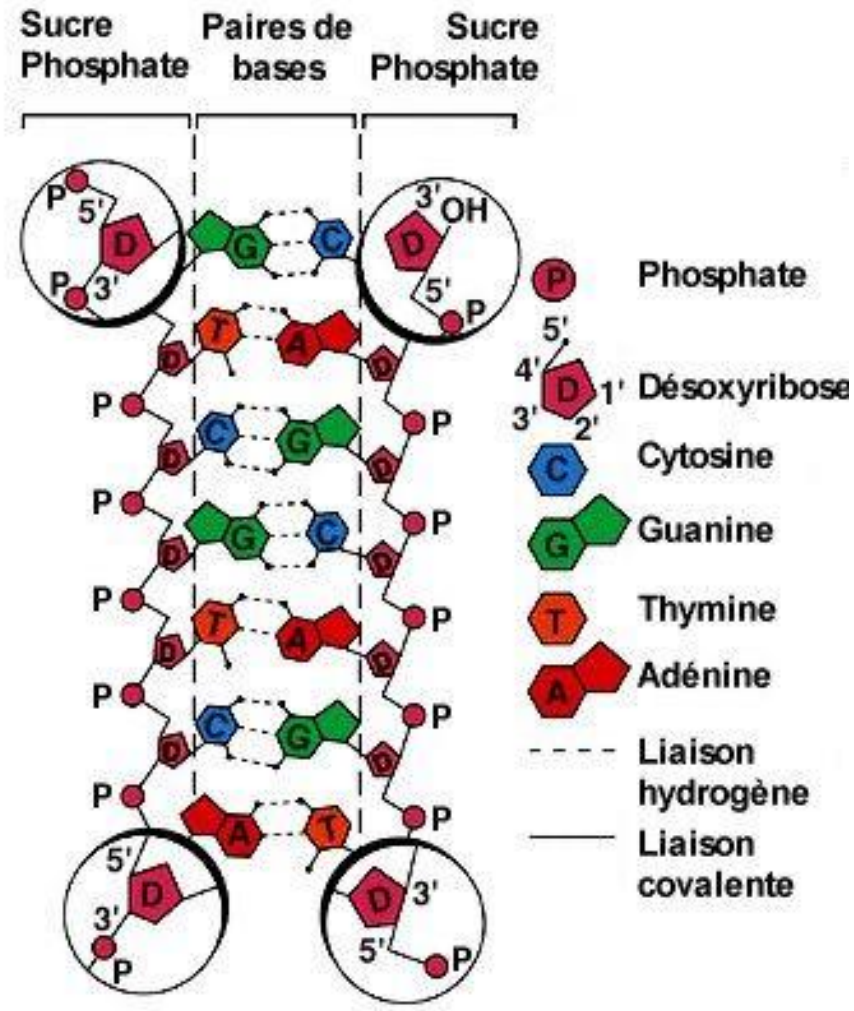
2) Prédiction du repliement, ou des interactions

3) => Structure spécifique

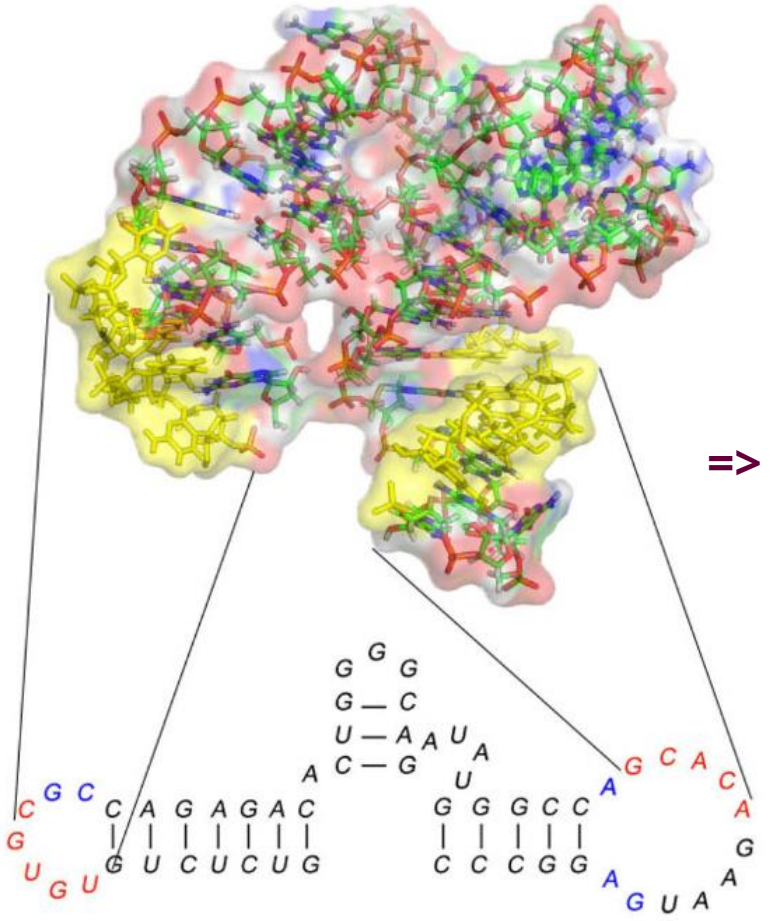
(un peu plus dure à prévoir)

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques



5'-CAGCACGACACUAGCAGUCAGUGUCAGACUGCAIACAGCACGACACUAGCAGU
CAGUGUCAGACUGCAIACAGCACGACACUAGCAGUCAGUGUCAGACUGCAIA-3'



=> Structure spécifique

(un peu plus dure à prévoir)

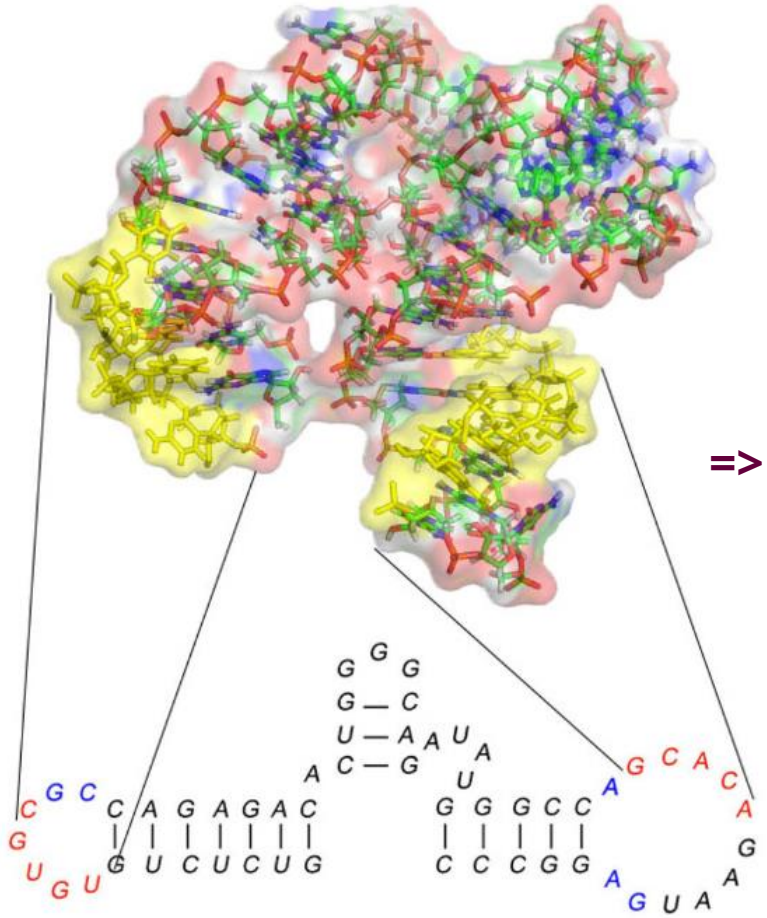
Structure secondaire proposée et structure tertiaire générée par modélisation moléculaire

Walsh *et al.*, *Biochem. Biophys. Res. Commun.*, 2009, **388** (4), 732-735

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques

5'-CAGCACGACACUAGCAGUCAGUGUCAGACUGCAIACAGCACGACACUAGCAGU
CAGUGUCAGACUGCAIACAGCACGACACUAGCAGUCAGUGUCAGACUGCAIA-3'



=> Structure spécifique

(un peu plus dure à prévoir)

=> Assemblage supramoléculaire précis

=> Interaction possible avec les acides nucléiques du vivant (thérapie génique, siRNA, interférons)

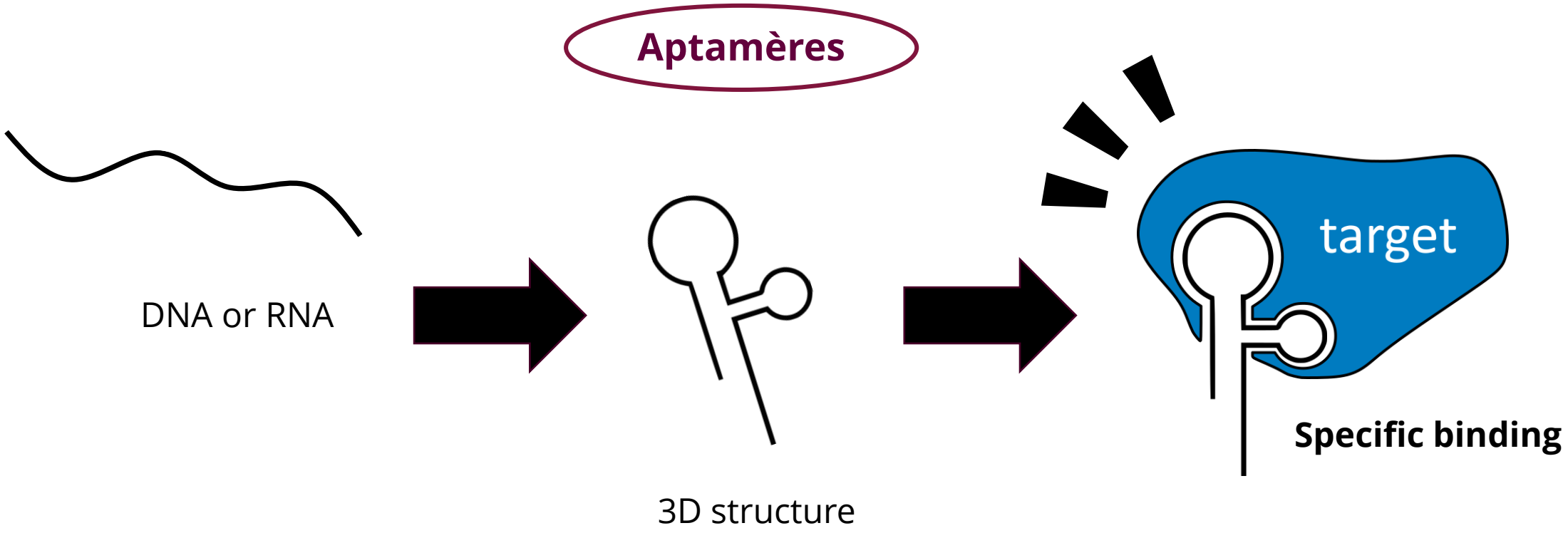
=> Systèmes aptamères

Walsh *et al.*, *Soft Matter*, 2009, *Biochem. Biophys. Res. Commun.*, **388** (4), 732-735

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques

=> Systèmes aptamères

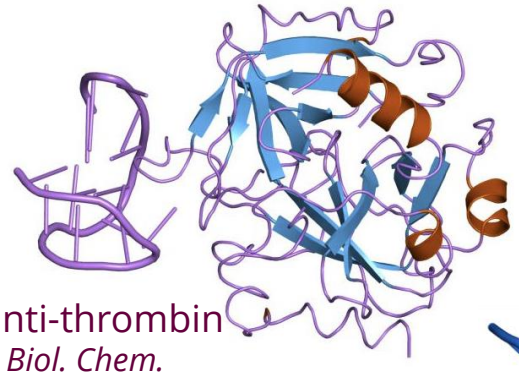


Xiong *et al.*, *Small*, **2022**
Nutiu *et al.*, *Chem. Eur. J.*, **2004**
Nakatsuka *et al.*, *Anal. Chem.*, **2021**

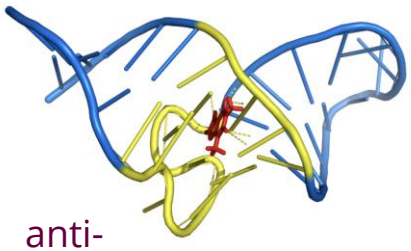
II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques

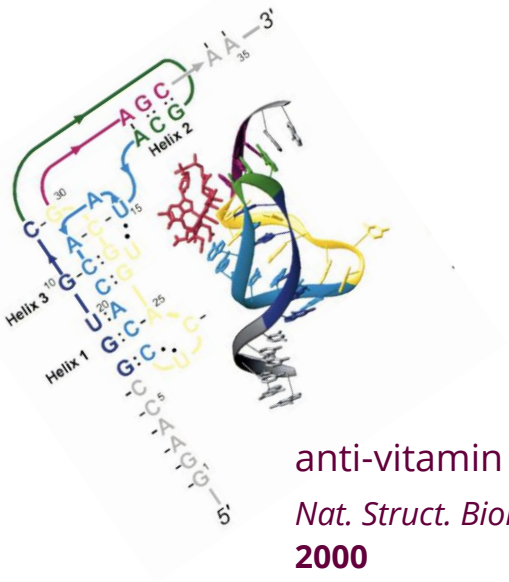
=> Systèmes aptamères



anti-thrombin
J. Biol. Chem.
1993



anti-theophylline
Science **1994**



anti-vitamin B12
Nat. Struct. Biol.
2000

- Proteins and peptides
- Sugars
- Ions
- Small molecules

> Spécificité

> Affinité (K_D)

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques

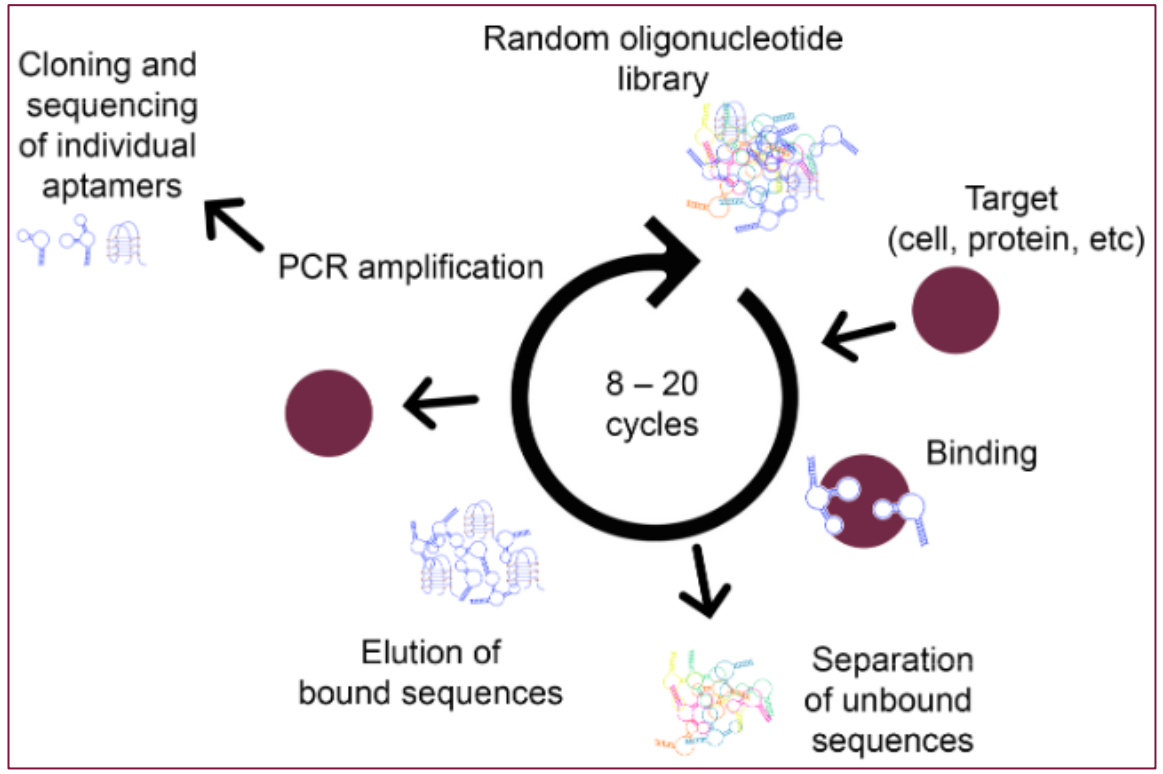
=> Systèmes aptamères

Processus de génération :

Bottom-up **vs** Top-down

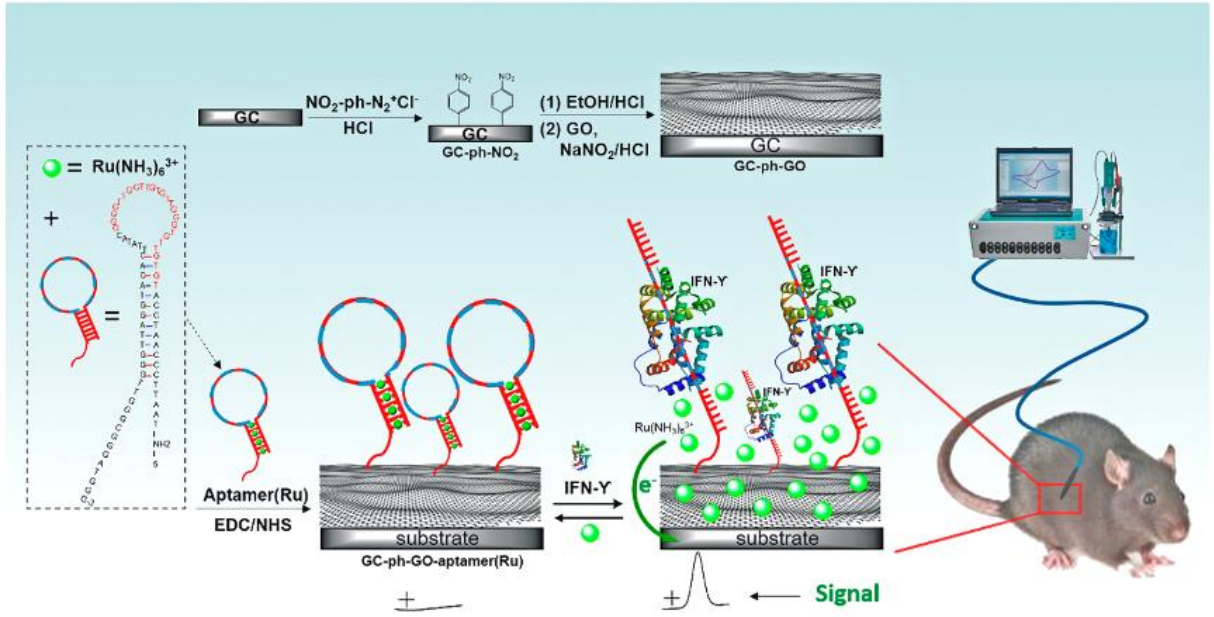
SELEX

Systematic Evolution of Ligands by Exponential Enrichment



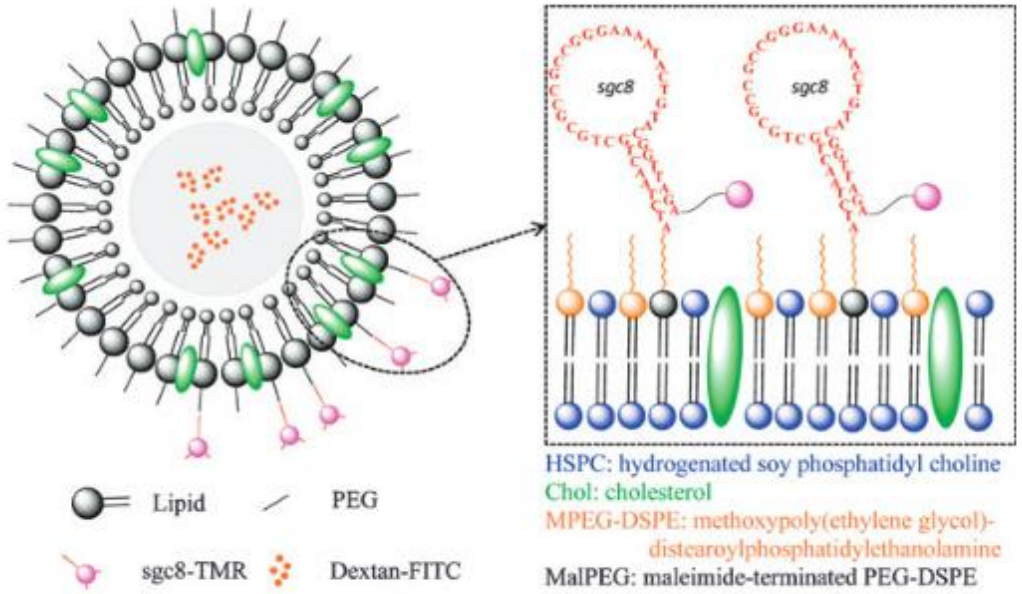
II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: acides nucléiques



Cao *et al. ACS Appl. Mater. Interfaces* **2018**, 10, 33078−33087

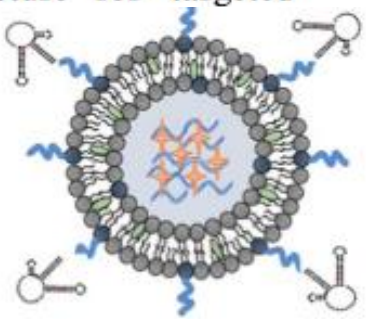
Détection



Scheme 1 Multifunctional liposome nanostructure for targeted delivery.

Kang *et al.*, *Chem. Commun.* **2010**, 46, 249–251

Alshaer *et al.*, *J. Control. Release* **2018**, 271, 98–106



Ciblage

siRNA/prot ⊂ lip-Apt1

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: systèmes hybrides

Systèmes hybrides = association covalente de molécules de classes diverses

Peptide

Polymères

Acides nucléiques

Lipides

Sucres

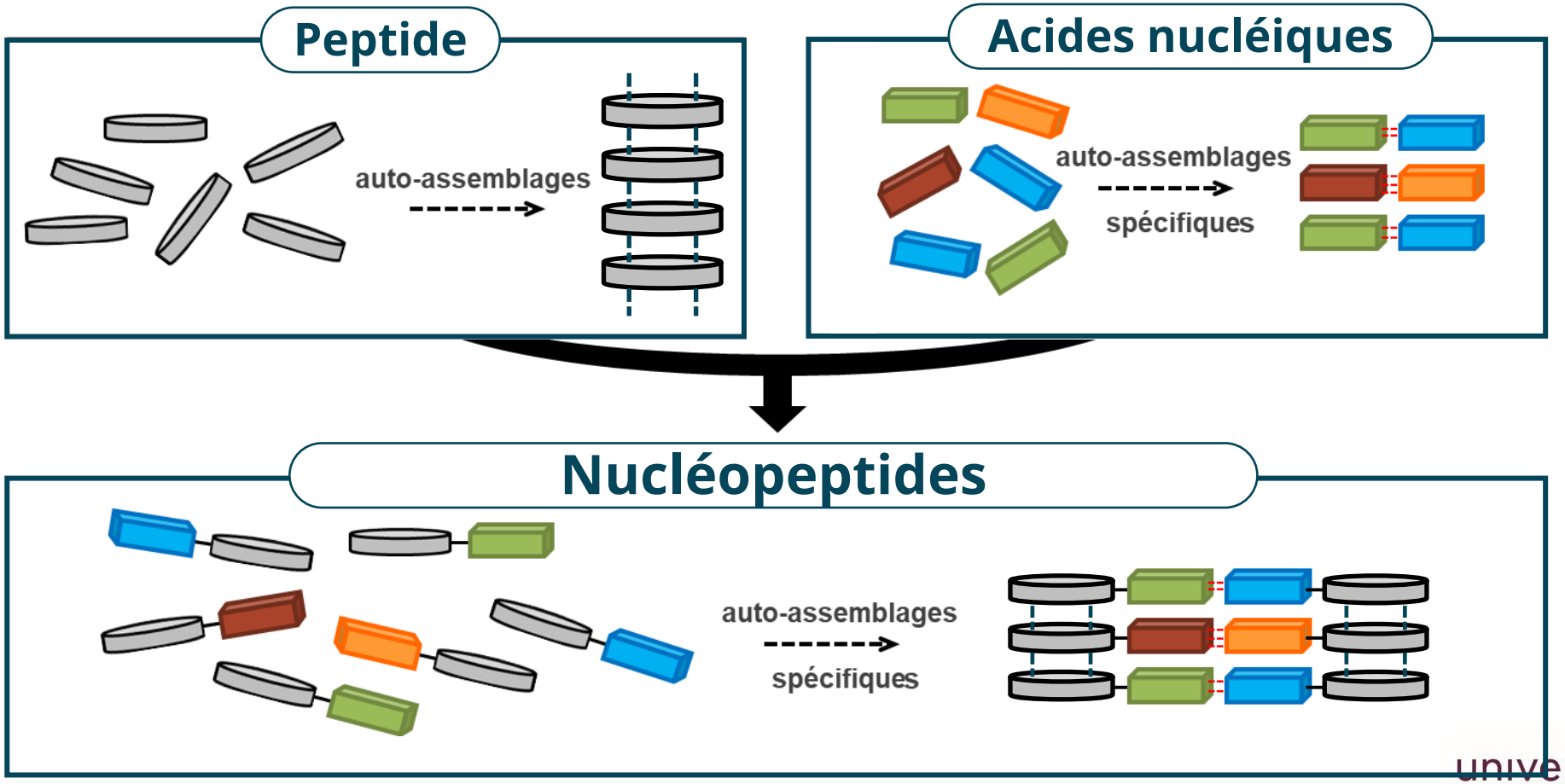
Systèmes Host-Guest

II] Systèmes supramoléculaires: *an overview*

II.6b) Programmer l'assemblage: systèmes hybrides

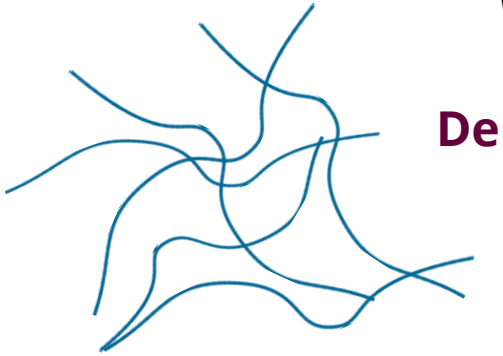
Systèmes hybrides = association covalente de molécules de classes diverses

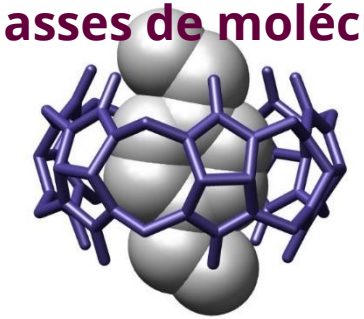
Exemple : Nucléo-peptides

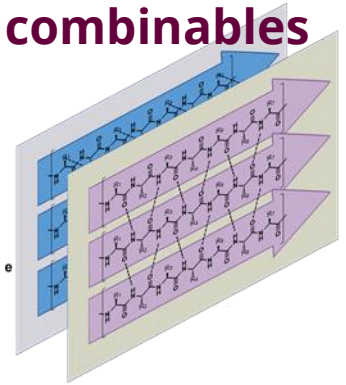


II] Systèmes supramoléculaires: *an overview*

II.7) **Conclusion**







De nombreuses classes de molécules disponibles et combinables

Différentes propriétés, possibilité de les moduler en modifiant la structure primaire

Affinité intermoléculaires

Equilibre hydrophile/hydrophobe

Stabilité interfaciale

Répartition des charges

Programmation spécifique

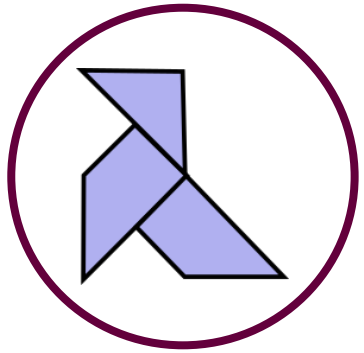
et avantages pour des applications différentes

III] Vers les applications

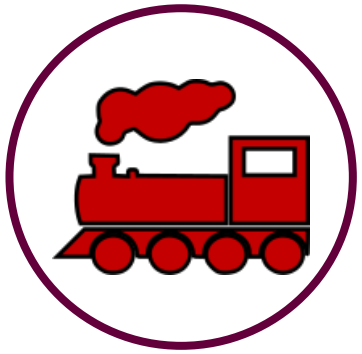
III] Vers les applications

III.1) Exemples particuliers

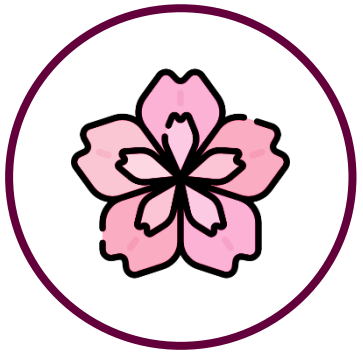
ADN origami



ADN Nanotrains et aptamère

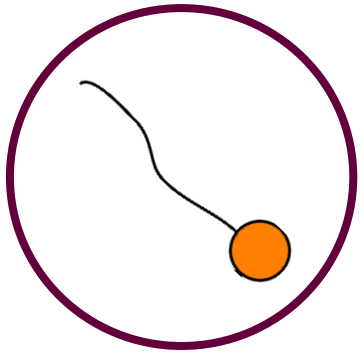


ADN Nanoflowers

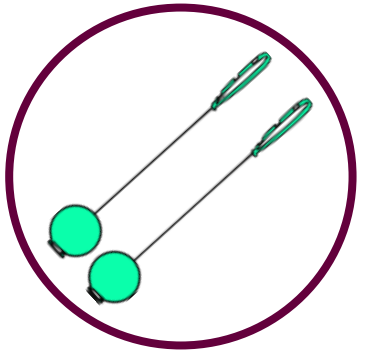


Responsive peptides

Peptides amphiphiles



Bola-amphiphiles



III] Vers les applications

III.1) Exemples particuliers

1-5 slides = 5–10 minutes

Définir le sujet en identifiant les classes de molécules impliquées, les interactions supramoléculaires impliquées

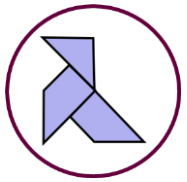
Présenter l'exemple en particulier décrit dans l'article

Imaginer ou décrire une application possible dans le domaine biomédical

Objectif : Présenter à vos camarades des exemples particuliers d'assemblages supramoléculaires

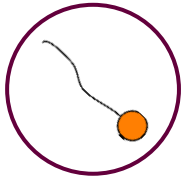
III] Vers les applications

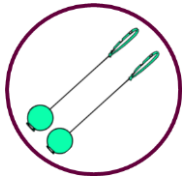
III.1) Exemples particuliers


ADN origami


ADN Nanotrains


ADN Nanoflowers


Peptides amphiphiles


Bola-amphiphiles

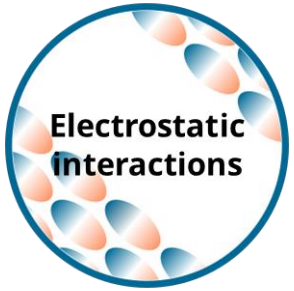

Responsive peptides

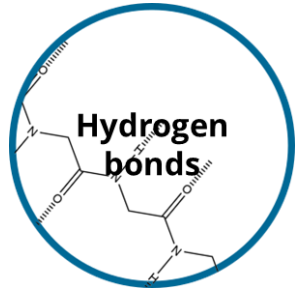
Définir le sujet

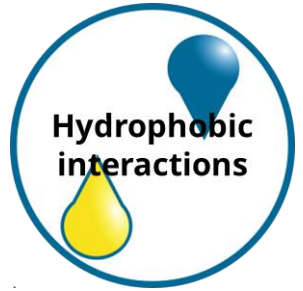
Identifier les classes de molécules impliquées, les interactions supramoléculaires impliquées

Présenter l'exemple en particulier décrit dans l'article

Imaginer ou décrire une application possible dans le domaine biomédical







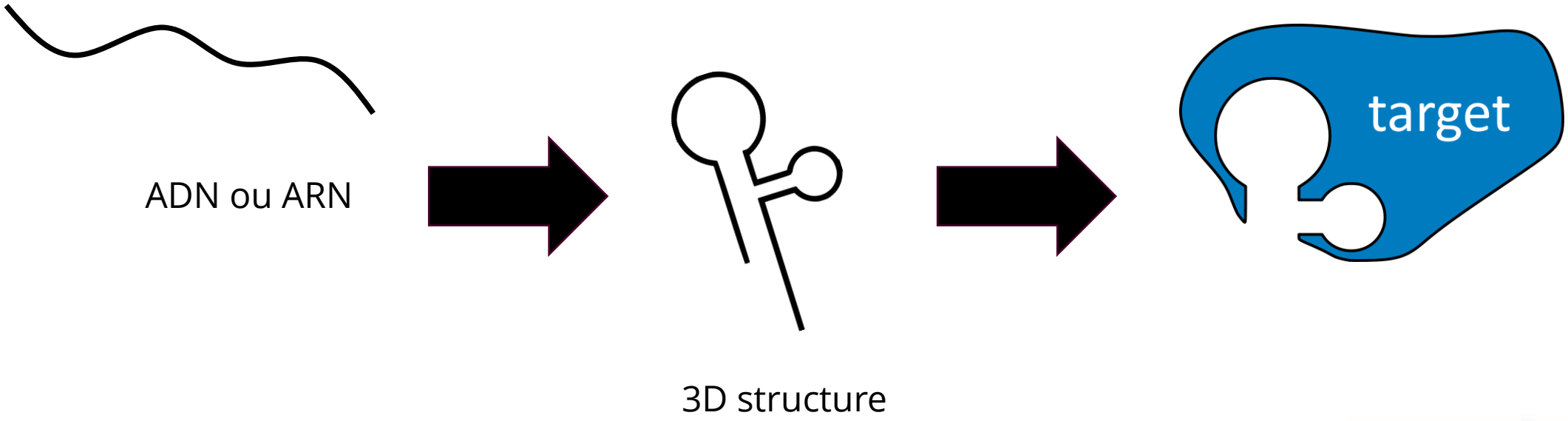
Images issues d'articles scientifiques avec leur source, svp

III] Vers les applications

ADN Nanotrains et aptamère

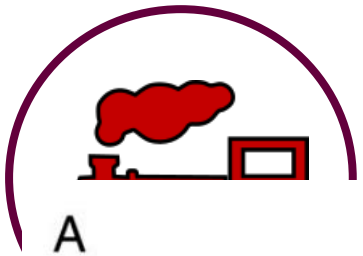
Self-assembled, aptamer-tethered DNA nanotrains for targeted transport of molecular drugs in cancer theranostics

Zhu *et al*., *Proc. Natl. Acad. Sci.*, 2013, **110** (20), 7998–8003



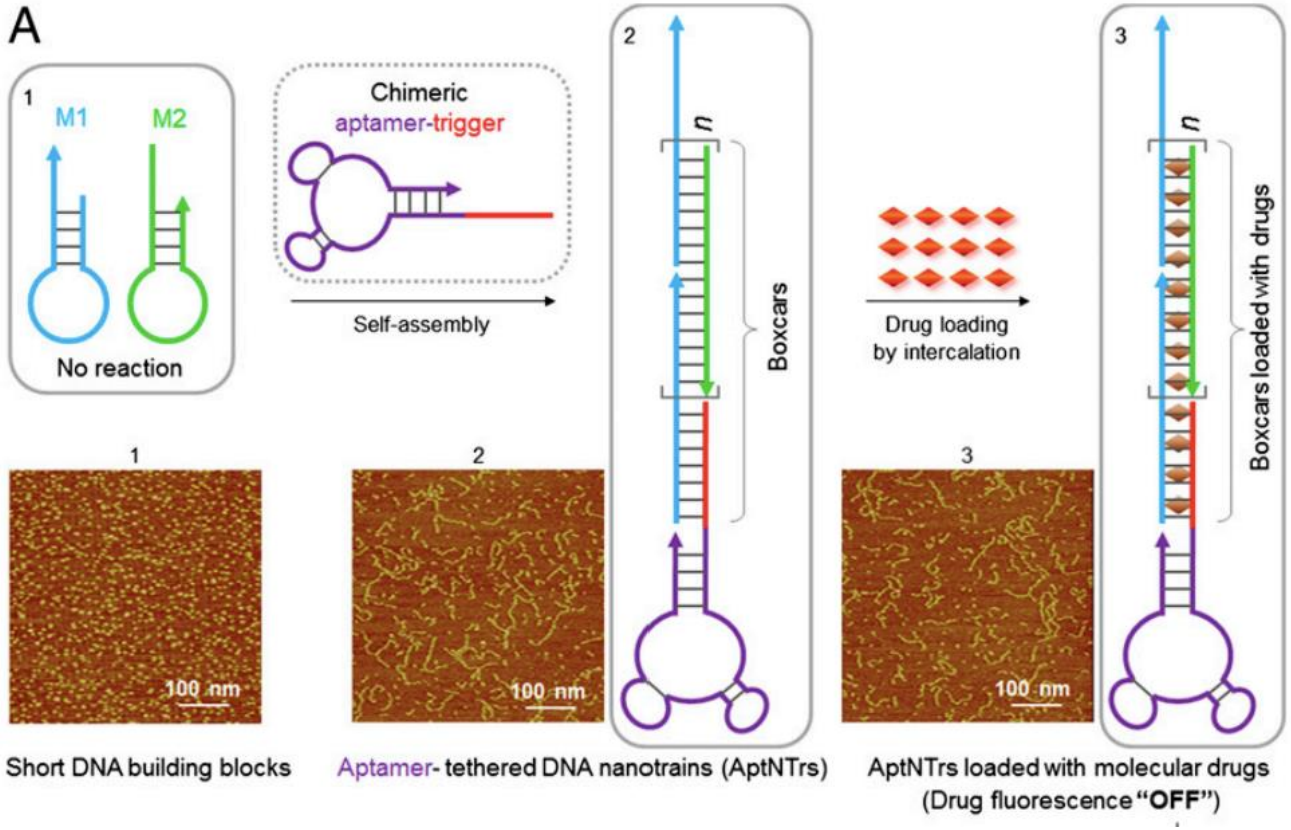
III] Vers les applications

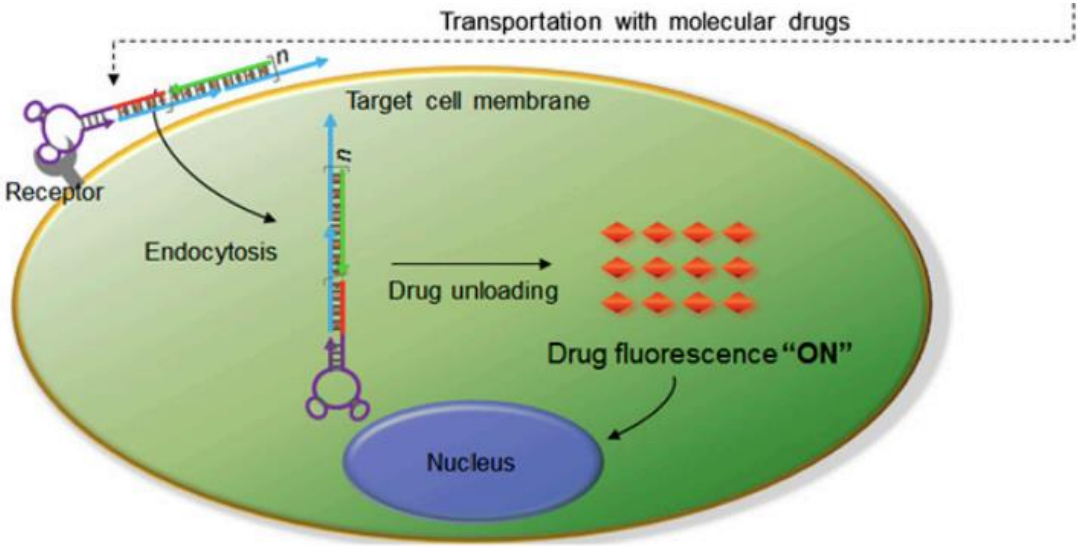
ADN Nanotrains et aptamère



Self-assembled, aptamer-tethered DNA nanotrains for targeted transport of molecular drugs in cancer theranostics

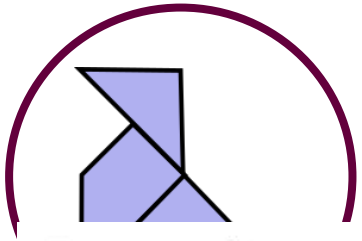
Zhu *et al.*, *Proc. Natl. Acad. Sci.*, 2013, **110** (20), 7998–8003





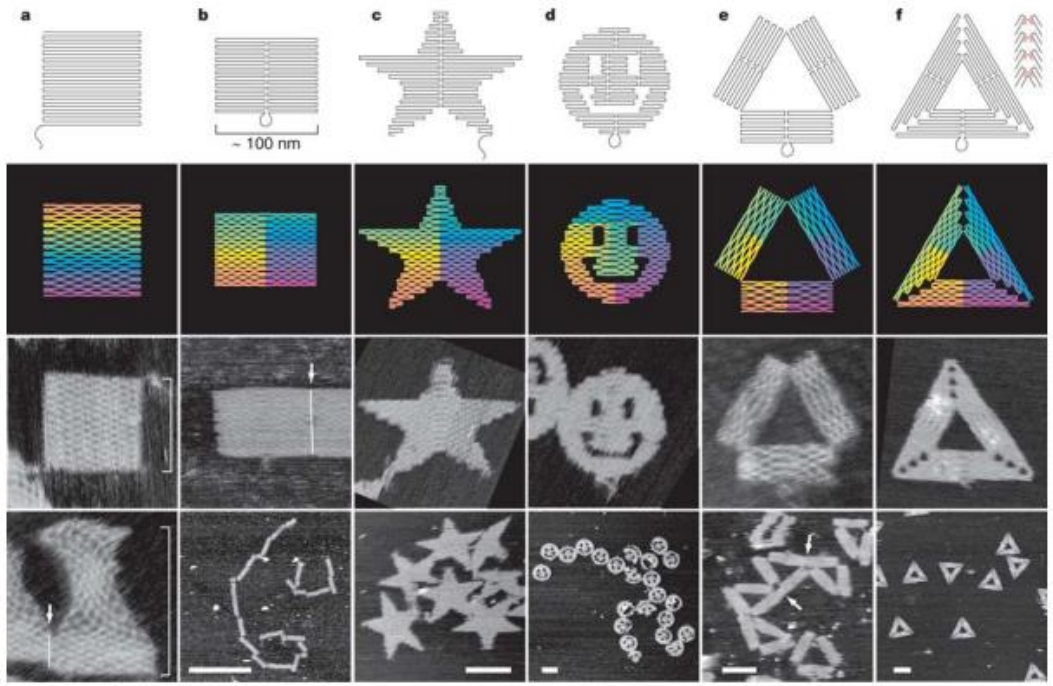
III] Vers les applications

ADN origami

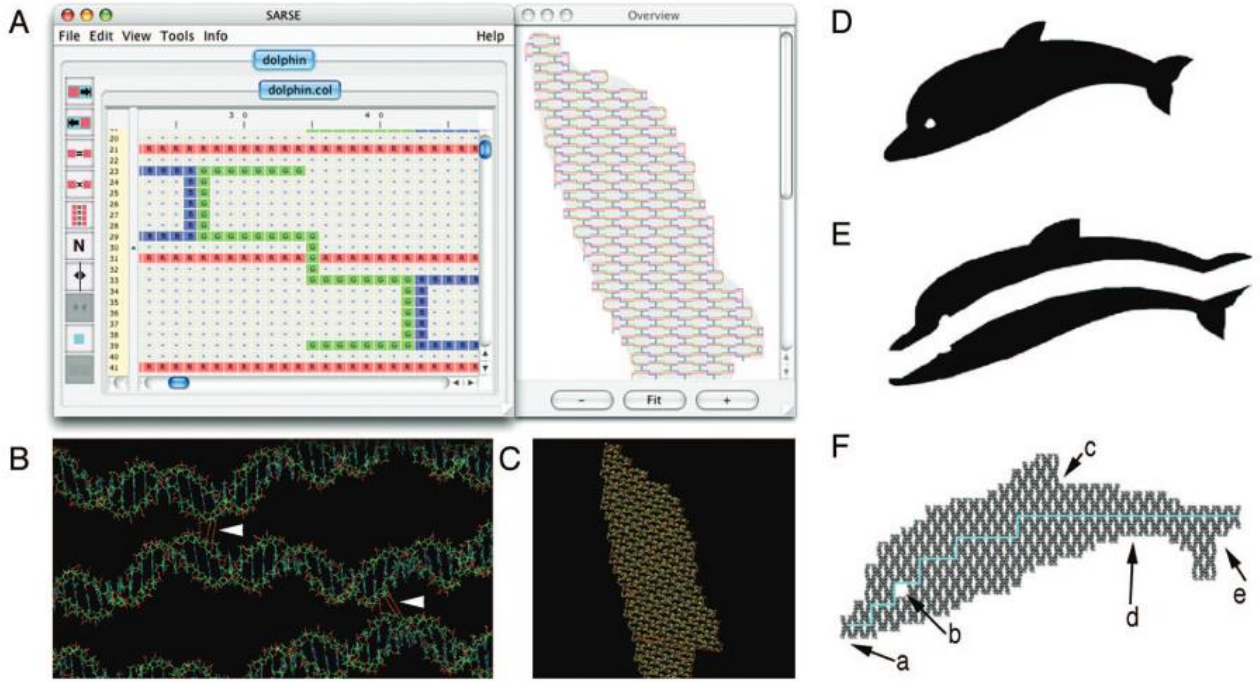


Self-assembly of a nanoscale DNA box with a controllable lid

Andersen *et al*., *Nature*, 2009, **459**, 73-76



Rothmund *et al*., *Nature*, 2006, **440**, 297-302

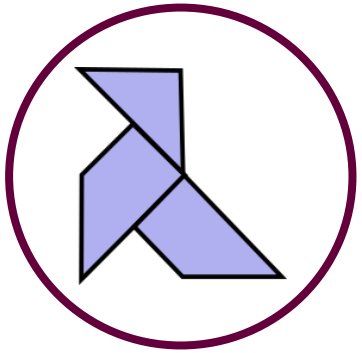


Andersen *et al*., *ACS Nano*, 2008, **2** (6), 1213-1218

Precise assembly conditions

III] Vers les applications

ADN origami

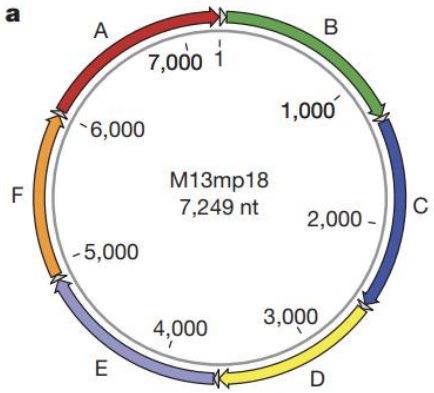


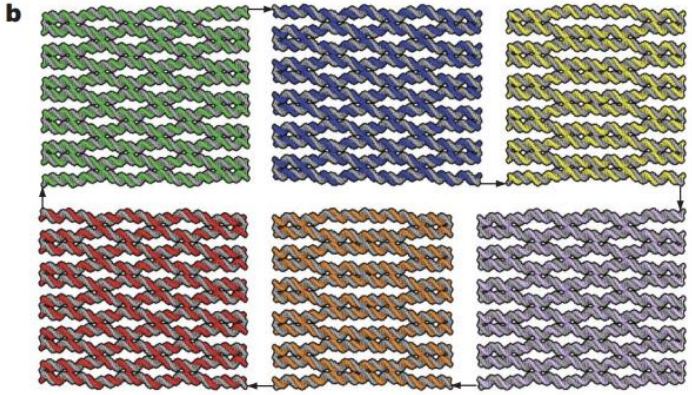
Self-assembly of a nanoscale DNA box with a controllable lid

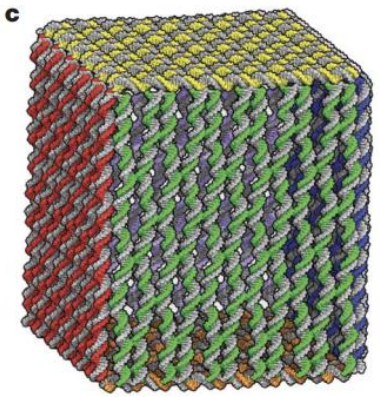
Andersen *et al.*, *Nature*, 2009, **459**, 73-76

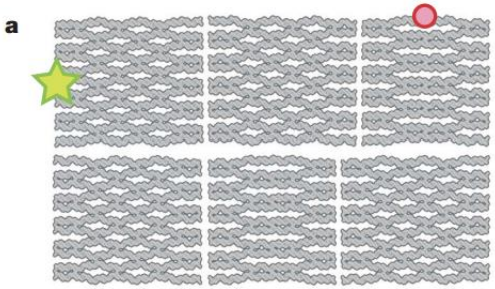
Face A

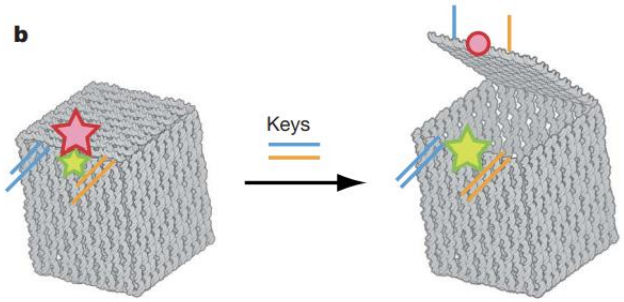
A-13,118	ATACAGTAACAGTACCTTAACGTCAGATGAATTTTTTTGAGTAA
A-17,14	ATTACCTGTTTTGGATTATACTTCTGAAATAATCCT
A-17,46	CAAAATCGACCTACCATATCAAAATCCTGATT
A-17,78	GGATTCGCCAGAAATAAAGAAATTAACCACCA
A-23,31	GGGTTAGACGCAGAGGCGAATTATTCATTTCA
A-23,63	ACGTAAAACTGATTGCTTTGAATACCAAGTTA
A-23,95	TTTCAGGTTTTTACATCGGGAGAAACAATAAC
A-37,14	GATTGTTTTTTTGATTAGAGCCGTCAATGCACTAAC
A-37,46	ATCAGATGGATTTAGAAGTATTAGATTGAGGA
A-37,78	GAAGGAGCGACAACTCGTATTAAACTGGTCAG
A-37,110	CATTATCATATTAATTTTAAAAGTTTTTTGAACCTC
A-43,31	CATTTGAGATGGCAATTCATCAATTAATGGAA
A-43,63	AACAATTCGGAATTATCATCATATTTATTTGC
A-43,95	CCGAACGTTTTTGCGGAACAAAGAGCGTAGAT
A-57,14	AACTAATATTTTTCGAACCACCAGCAGAACATTAAAA
A-57,46	AGGTTATCGGCGGTCAGTATTAACTAATGCGC
A-57,78	TTGGCAAACCACGCTGAGAGCCAGACAGACAA
A-57,110	AAATATCATAAAGCATCACCTTGCTTTTCCTTCTGA
A-63,31	AGAGGTGATAAAATATCTTTAGGAAGATAATA
A-63,63	CAACAGTGTCAACAGTTGAAAGGAACTTTACA







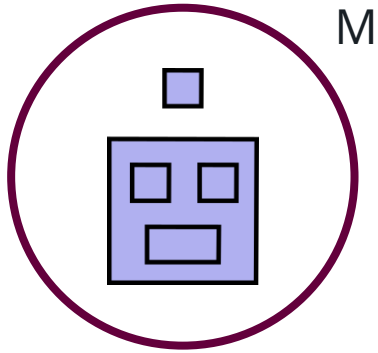




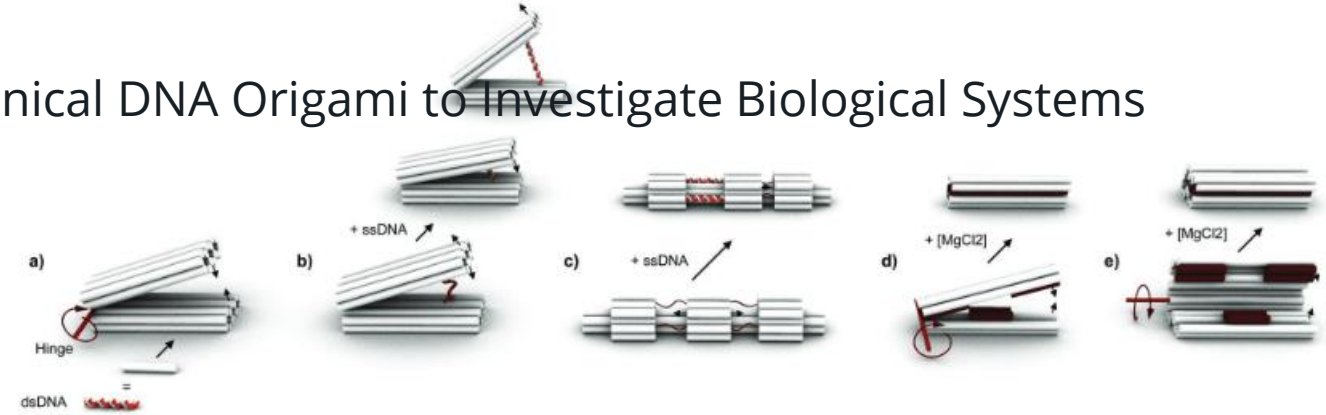
III] Vers les applications

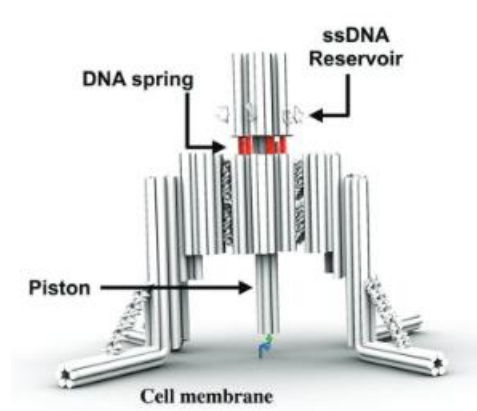
Pour aller plus loin…

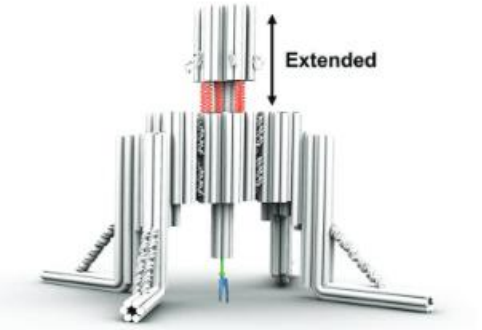
Robot ADN origami



Mechanical DNA Origami to Investigate Biological Systems

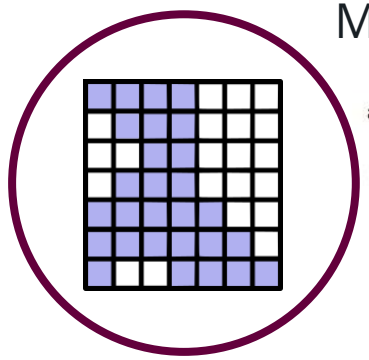




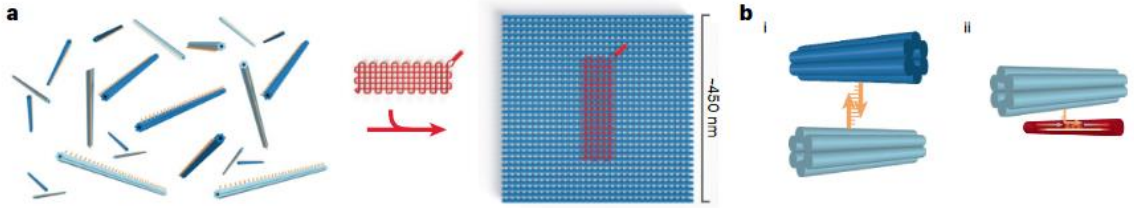


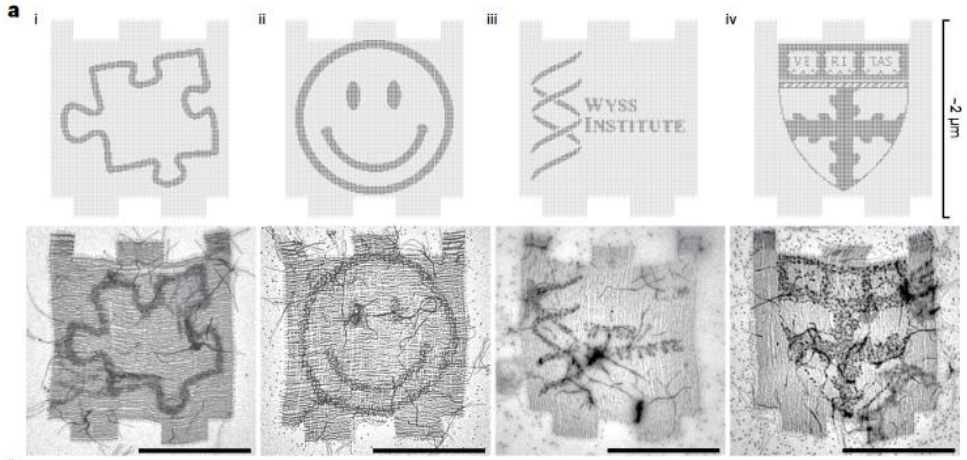
Mills *et al.*, *Adv. Biology* **2023**, 7, 2200224

Broderie ADN



Multi-micron crisscross structures grown from DNA-origami slats

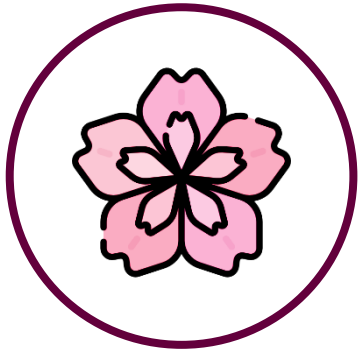




Wintersinger *et al., Nat. Nanotechnol.* **2023**, 18, 281, 2892023

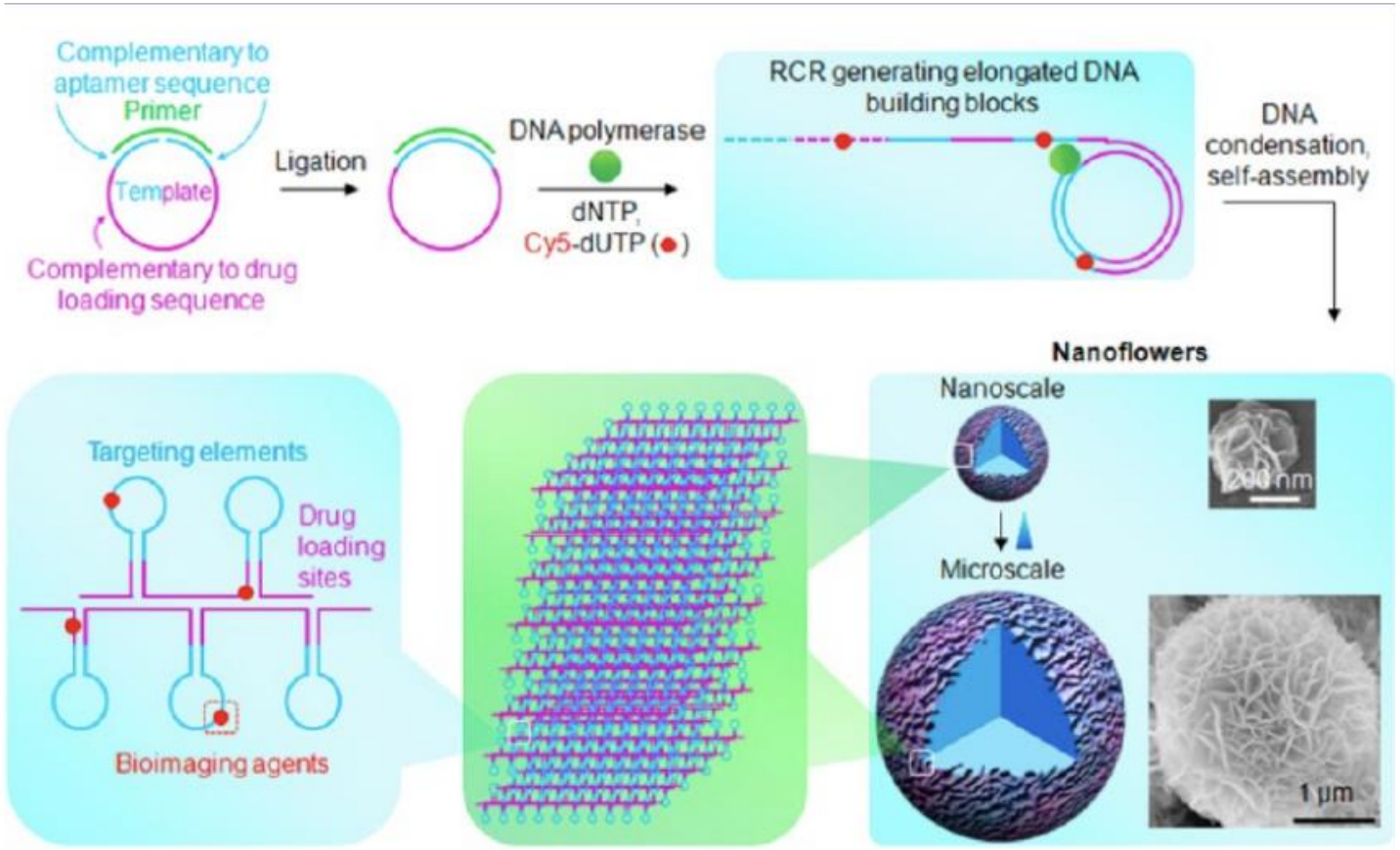
III] Vers les applications

ADN Nanoflowers



Noncanonical Self-Assembly of Multifunctional DNA Nanoflowers for Biomedical Applications

Zhu *et al.*, *J. Am. Chem. Soc.*, 2013, **135**, 16438-16445

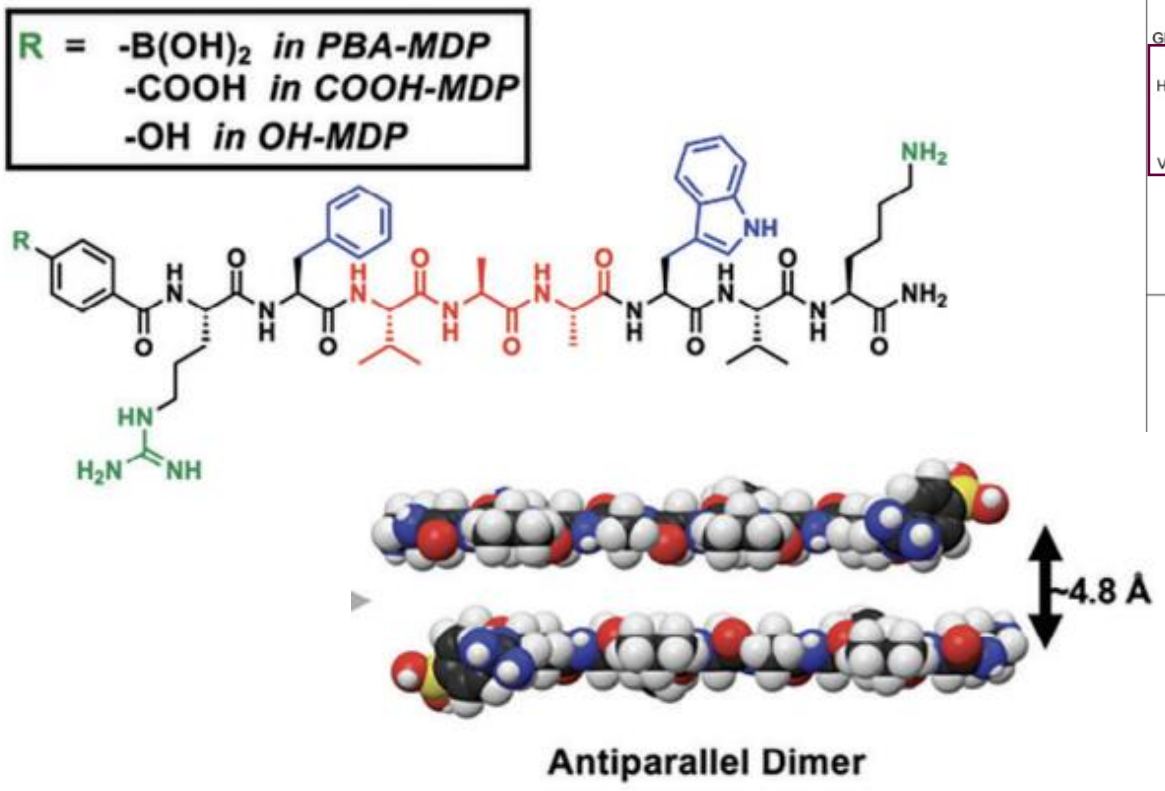


III] Vers les applications

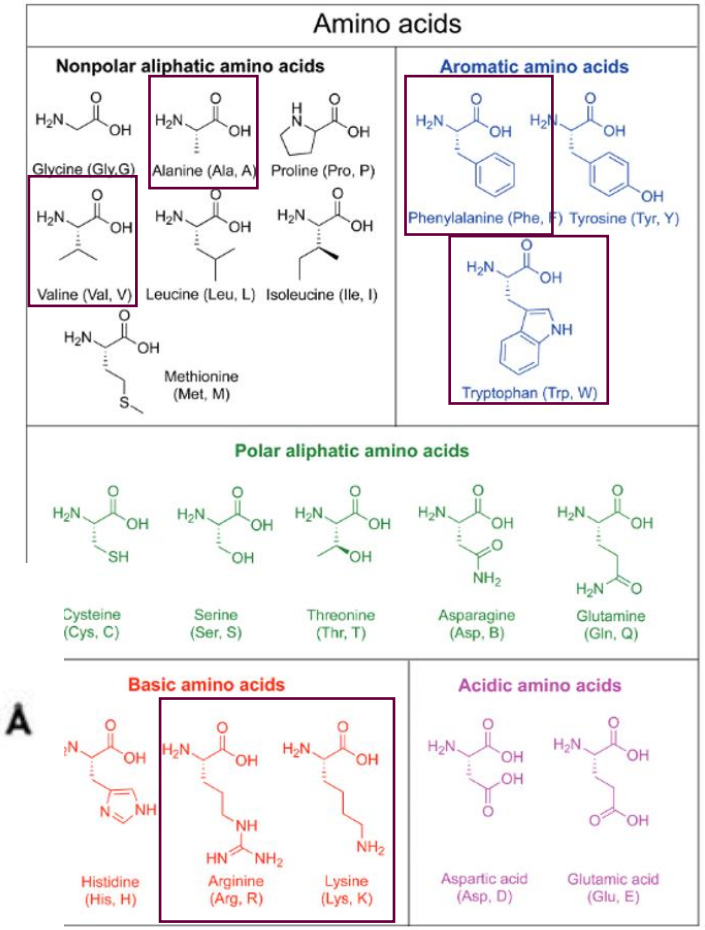
Responsive peptides

Glucose-Triggered Gelation of Supramolecular Peptide Nanocoils with Glucose-Binding Motifs

Yu *et al.*, *Adv. Mater.* 2023, 2311498



Jorsh *et al.*, *J. Sens. Sens. Syst.* **2016**, 5, 229–235



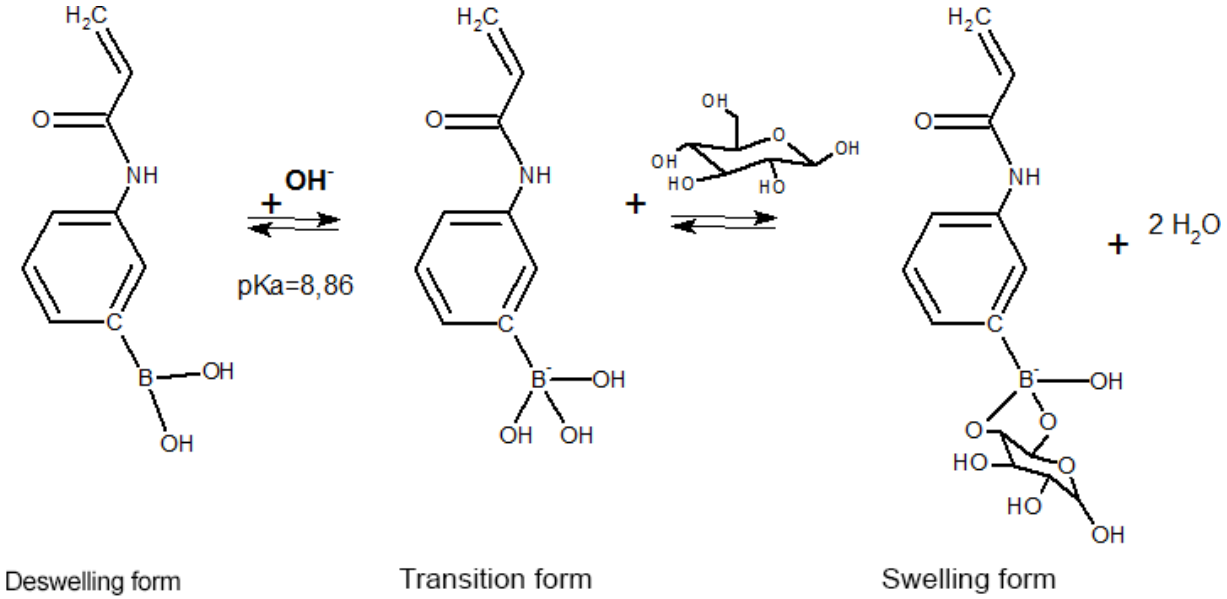
Structure et classification des acides aminés protéinogènes

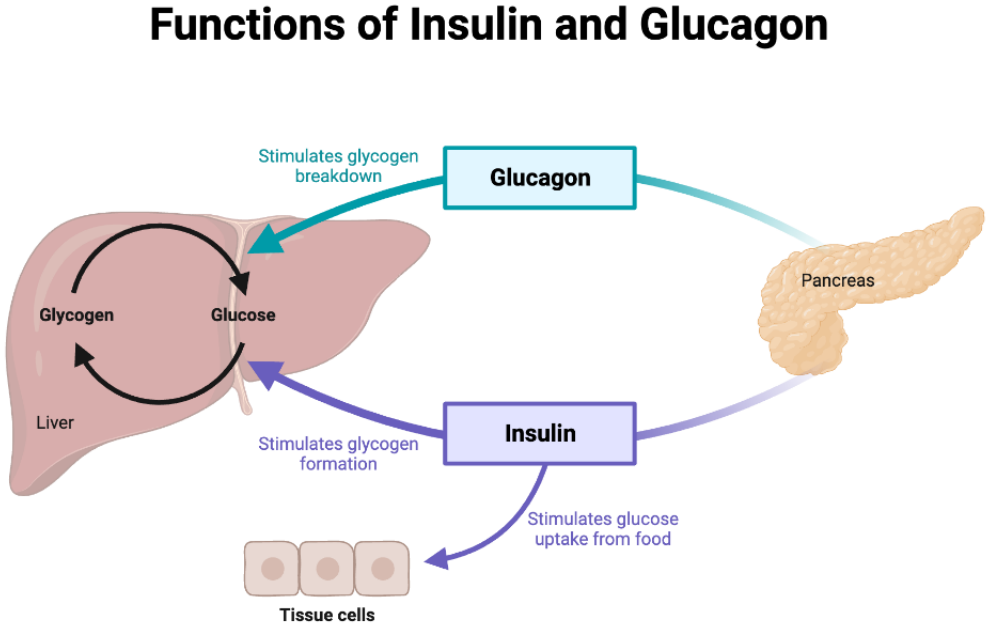
III] Vers les applications

Responsive peptides

Glucose-Triggered Gelation of Supramolecular Peptide Nanocoils with Glucose-Binding Motifs

Yu *et al.*, *Adv. Mater.* 2023, 2311498





Jorsh *et al.*, *J. Sens. Sens. Syst.* **2016**, 5, 229–235

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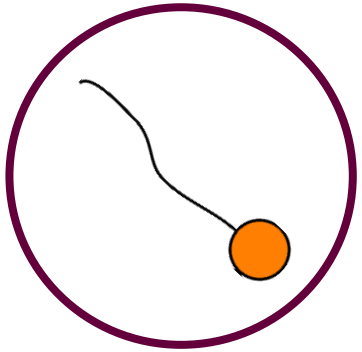
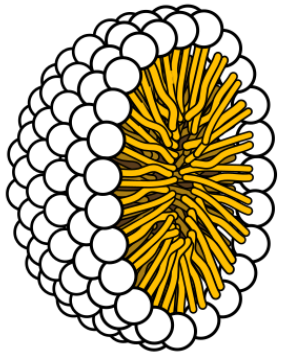
III] Vers les applications

Peptides amphiphiles

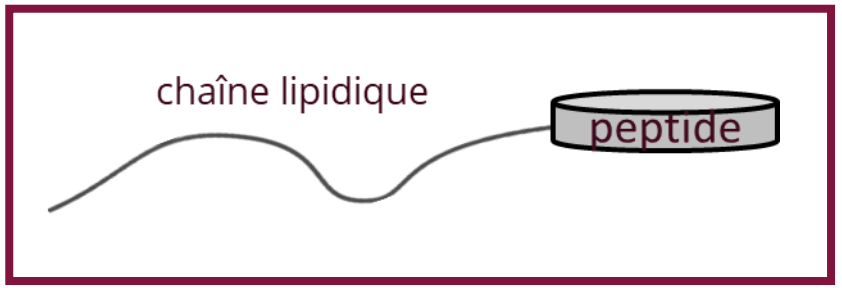


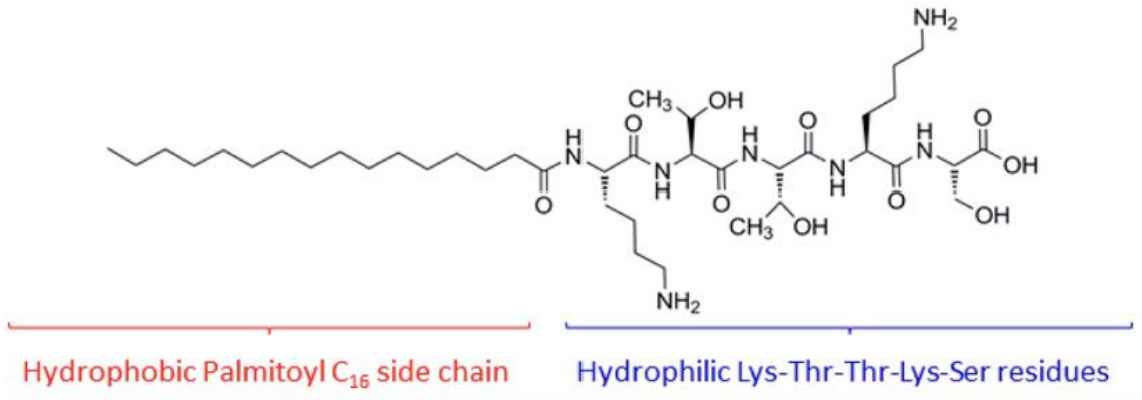
Micelle

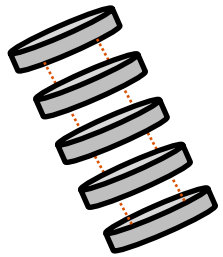


Collagen Stimulating Effect of Peptide Amphiphile C16−KTTKS on Human Fibroblasts

Jones *et al.*, *Mol. Pharmaceutics*, 2013, **10**, 1063-1069

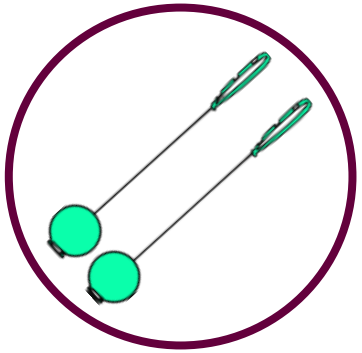






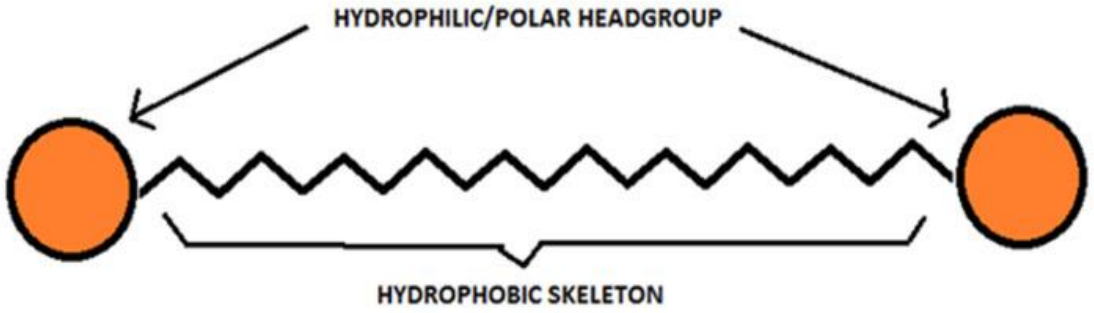
III] Vers les applications

Bola-amphiphiles

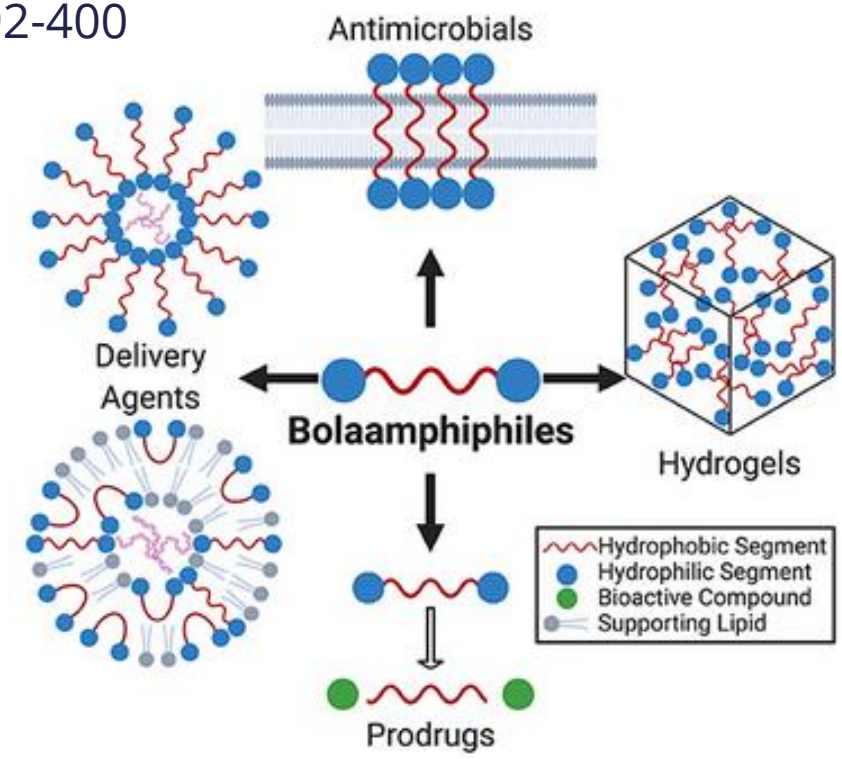


Lactose-ornithine bolaamphiphiles for efficient gene delivery in vitro

Jain *et al.*, *Int. J. Pharm.*, 2012, **423**, 392-400



Structure générale des bola-amphiphiles



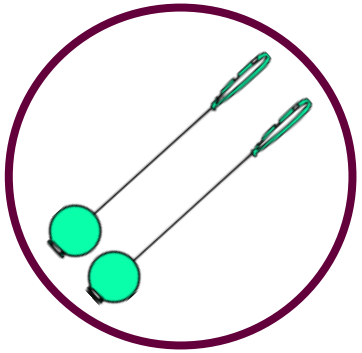
Applications possibles pour les bola-amphiphiles

Hughes *et al.*, *Front. Chem.*, 2021, **Vol 8** - 2020

Fariya *et al.*, *Adv. Pharm. Bull.*, 2014, **4** (Suppl 2), 483-491

III] Vers les applications

Bola-amphiphiles



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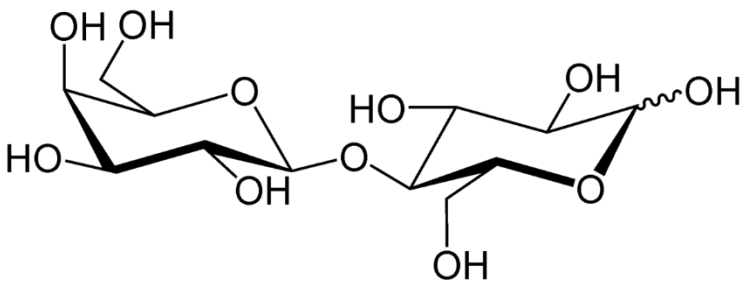
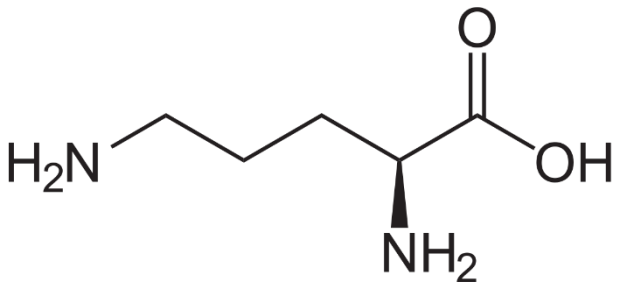
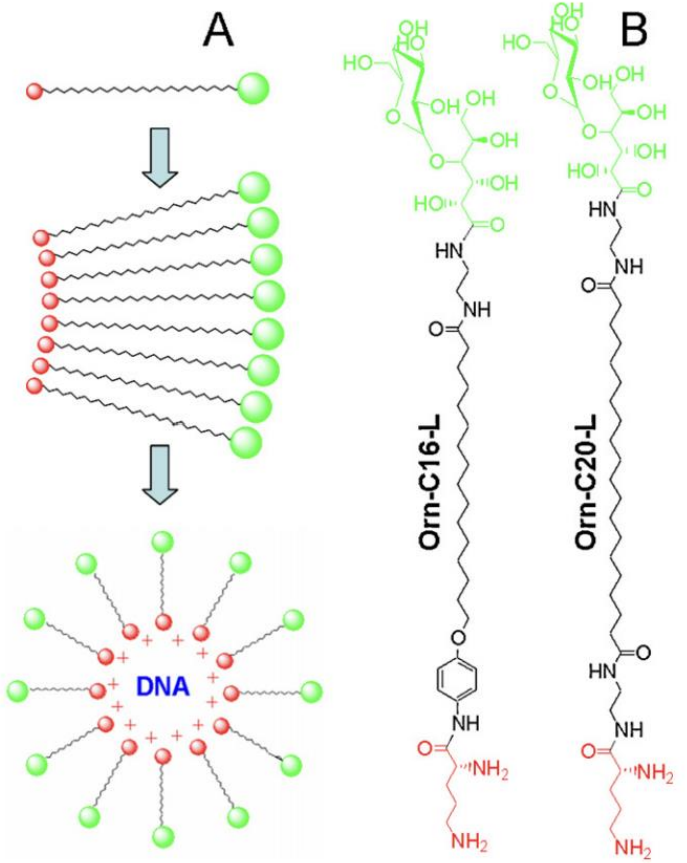


Structure moléculaire du lactose



Structure moléculaire de l'ornithine



III] Vers les applications

III.2) Propriétés et critères pour des applications biomédicales

Biosourcé

Bio-inspiré

Biocompatible

III] Vers les applications

III.2) Propriétés et critères pour des applications biomédicales

Biocompatible

Toxicité

Immunogénéicité

Dégradabilité/Métabolisation

III] Vers les applications

III.2) Propriétés et critères pour des applications biomédicales

Biocompatible

Toxicité

Immunogénéicité

Dégradabilité/Métabolisation

Matériaux

Auto-réparation (self healing)

Seringabilité/Thixotropie

Thermorégénération

Responsiveness

Nanotechnologies

Furtivité

Ciblage

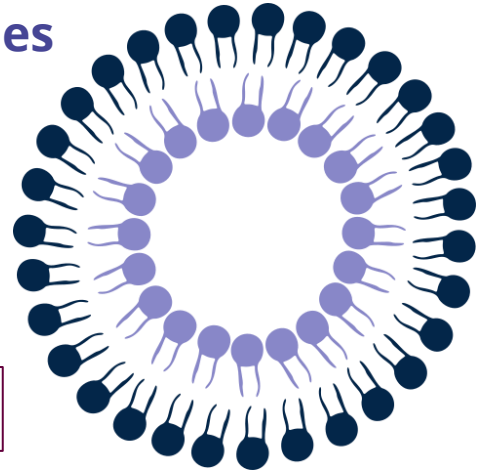
Pharmacocinétique

Avantages inhérents aux systèmes supramoléculaires

III] Vers les applications

Gels, nanogels, émulsions

Nanoparticules



Ingénierie tissulaire

Régénération osseuse, organes ou tissus

Délivrance d'agents thérapeutiques

Transport, stockage, libération contrôlée

Culture cellulaire

Substrat, matrice 3D, culture, différenciation

Biocapteurs

Gels antibactériens

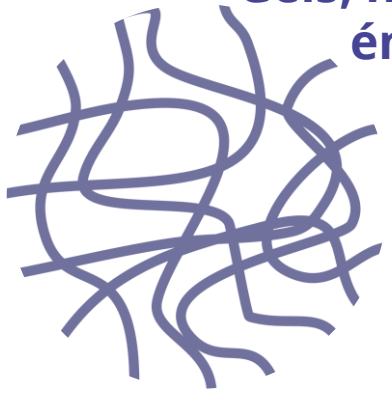
Diagnostic et théranostique

Pansements actifs

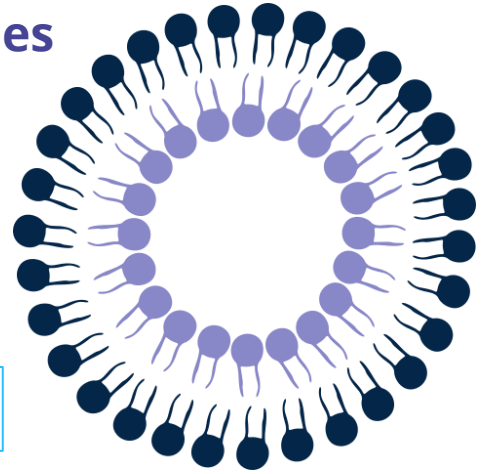
Webber *et al.*, *Nature Mater.*, 2016, **15** (1), 13-26

III] Vers les applications

Gels, nanogels, émulsions



Nanoparticules



Ingénierie tissulaire

Régénération osseuse, organes ou tissus

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Transport, stockage, libération contrôlée

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Substrat, matrice 3D, culture, différenciation

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Gels antibactériens

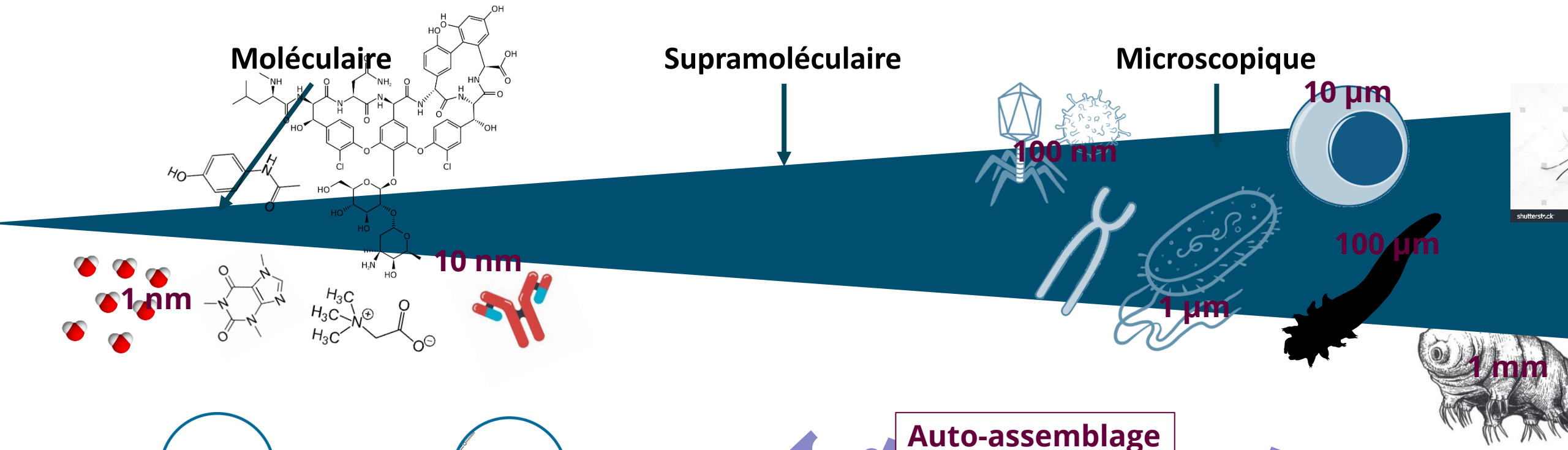
Diagnostic et théranostique

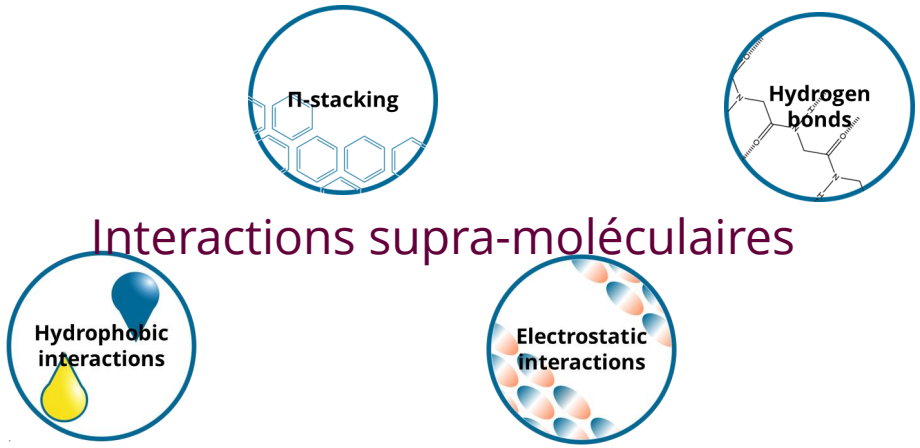
Pansements actifs

« Smart materials »

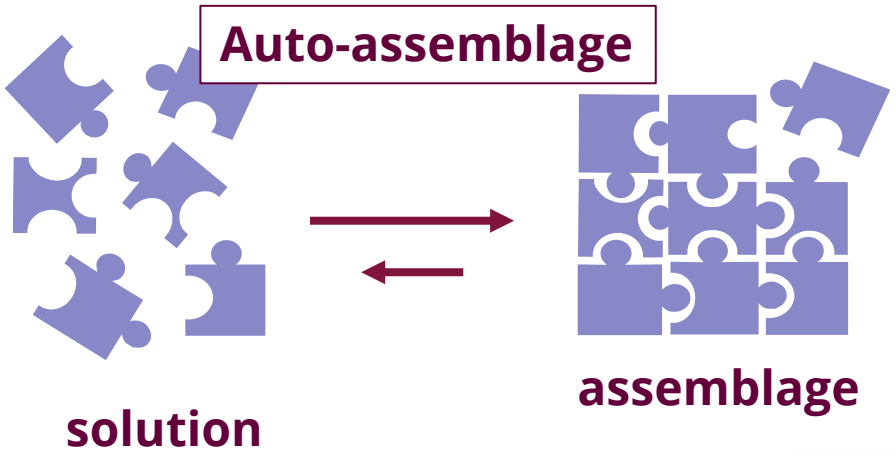
Webber *et al.*, *Nature Mater.*, 2016, **15** (1), 13-26

Conclusion

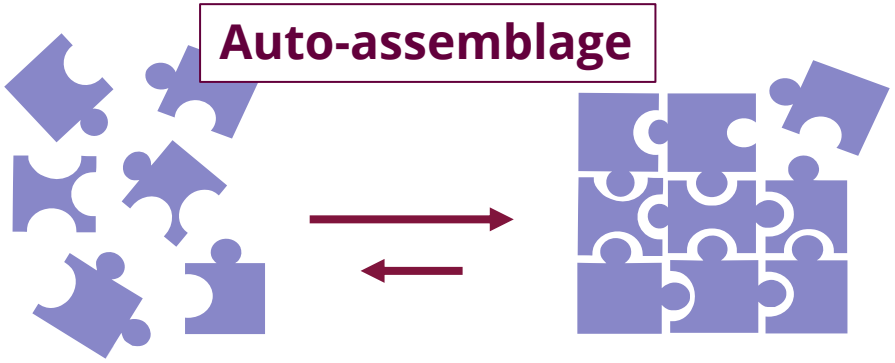




Interactions supra-moléculaires



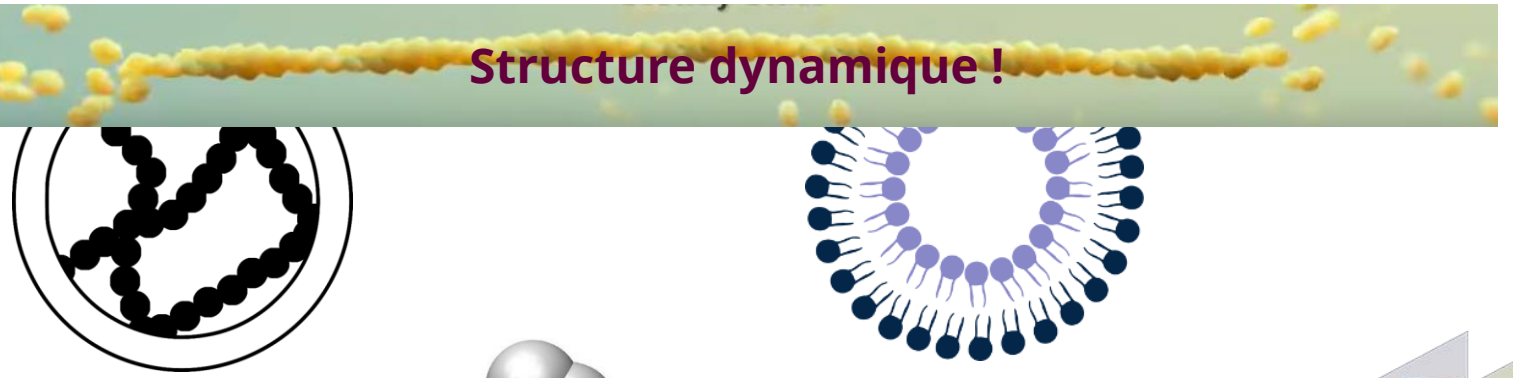
Conclusion

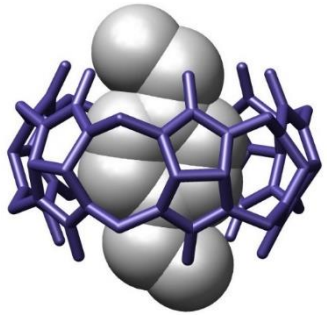


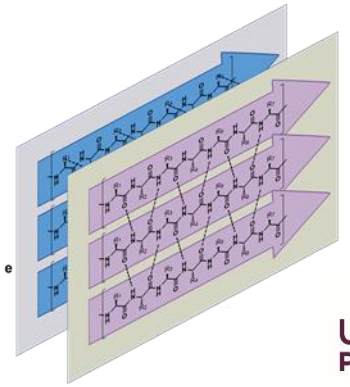
Métastable
(thermodynamiquement)

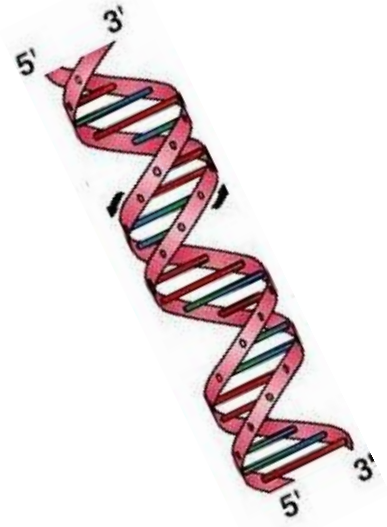
Cinétiquement piégée

Structure dynamique !

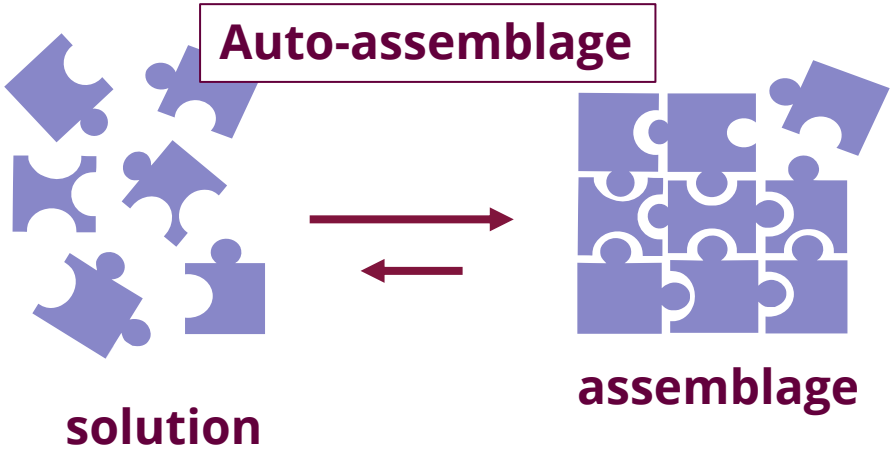








Conclusion



Métastable
(thermodynamiquement)

Cinétiquement piégée

S'inspirer du vivant…

Mais créer des systèmes synthétiques au **design rationnel**
aux **propriétés sur-mesure**

adaptées aux applications recherchée

Bibliographie

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Jean-Marie Lehn Nobel prize
https://www.nobelprize.org/prizes/chemistry/1987/lehn/speech/