Sequence-defined stereocontrolled oligomers bearing nucleobases: targeting specificity in supramolecular assembly

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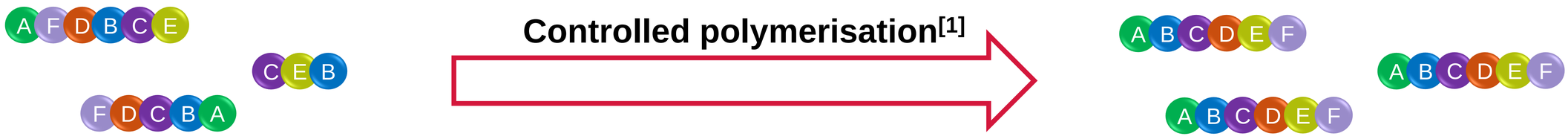
From disperse, heterogeneous polymers… …To uniform, monodisperse chains

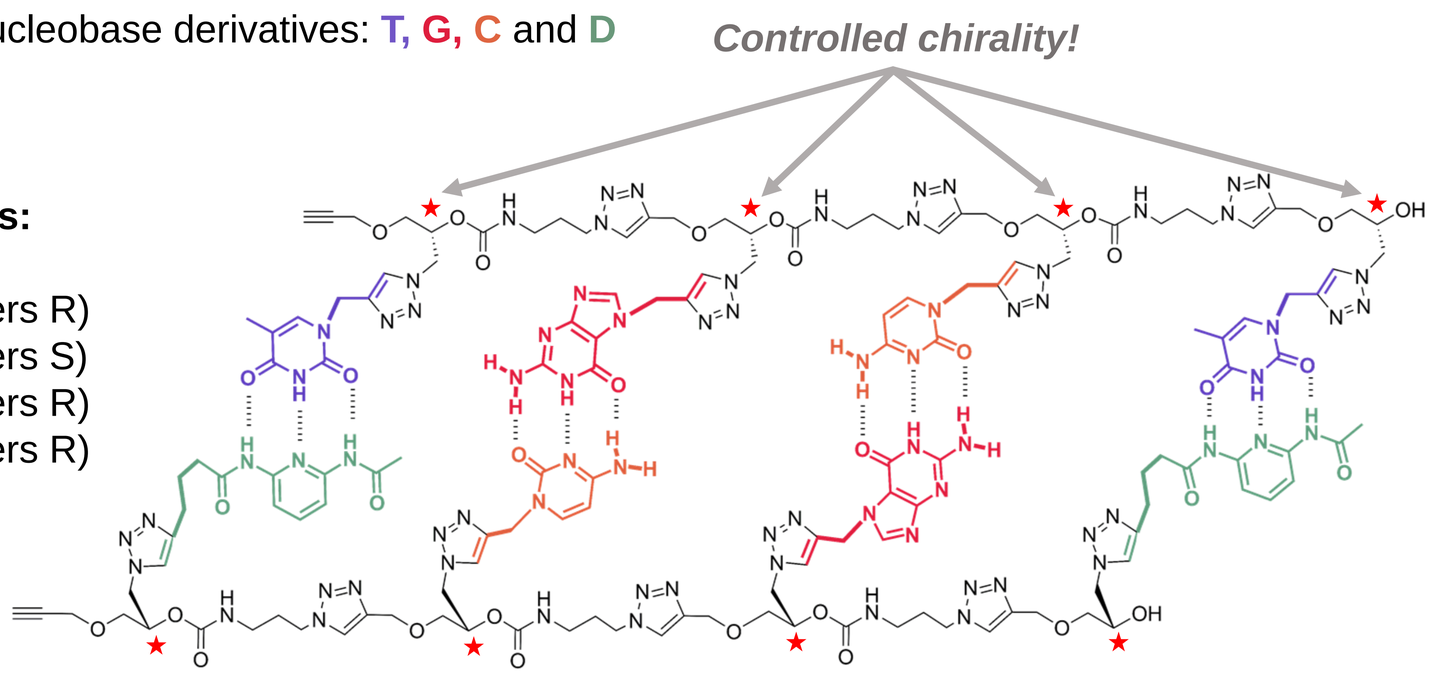


Controlling the **sequence** and **chirality** of macromolecular chains allows to precisely tune their **3D structures** and thus their **functions**, as is observed for biopolymers such as DNA or proteins

➔ Can we use this level of control to drive the **specific supramolecular assembly** of sequence-complementary partners ?

Introduction

- Recognition units = 4 nucleobase derivatives: **T, G, C** and **D**
- **Probe chain** = **TGCT**
- **4 different target chains:**
  - ➢ **DCGD** (all stereocenters R)
  - ➢ **DCGD** (all stereocenters S)
  - ➢ **DGCD** (all stereocenters R)
  - ➢ **GDDC** (all stereocenters R)
- Supramolecular assemblies studied by molecular dynamics **(MD)** simulations



Simulation methodology

- **AMBER** suite of programs[2]
- **GAFF 2** force-field[3]
- Implicit solvation **(acetonitrile)**
- Simulation length = 1 µs, timestep = 1 fs
- Snapshot saved each ns

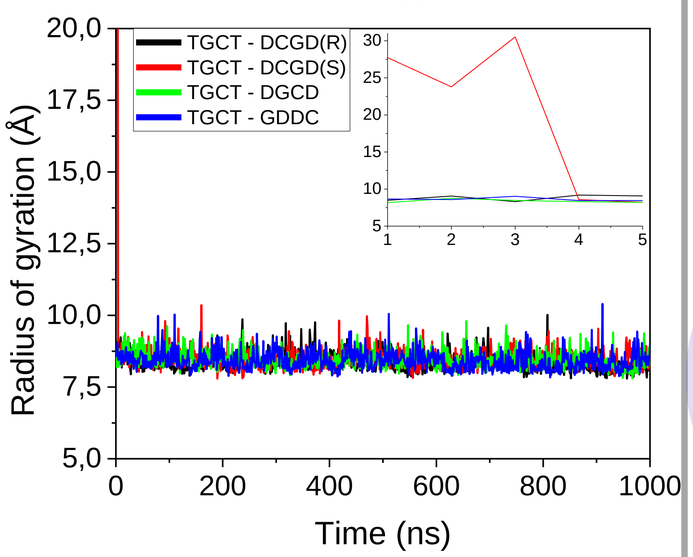
➔ **1,000 conformations**

- 4 replicas for each pair

➔ **Total of 4,000 conformations / assembly**

Results

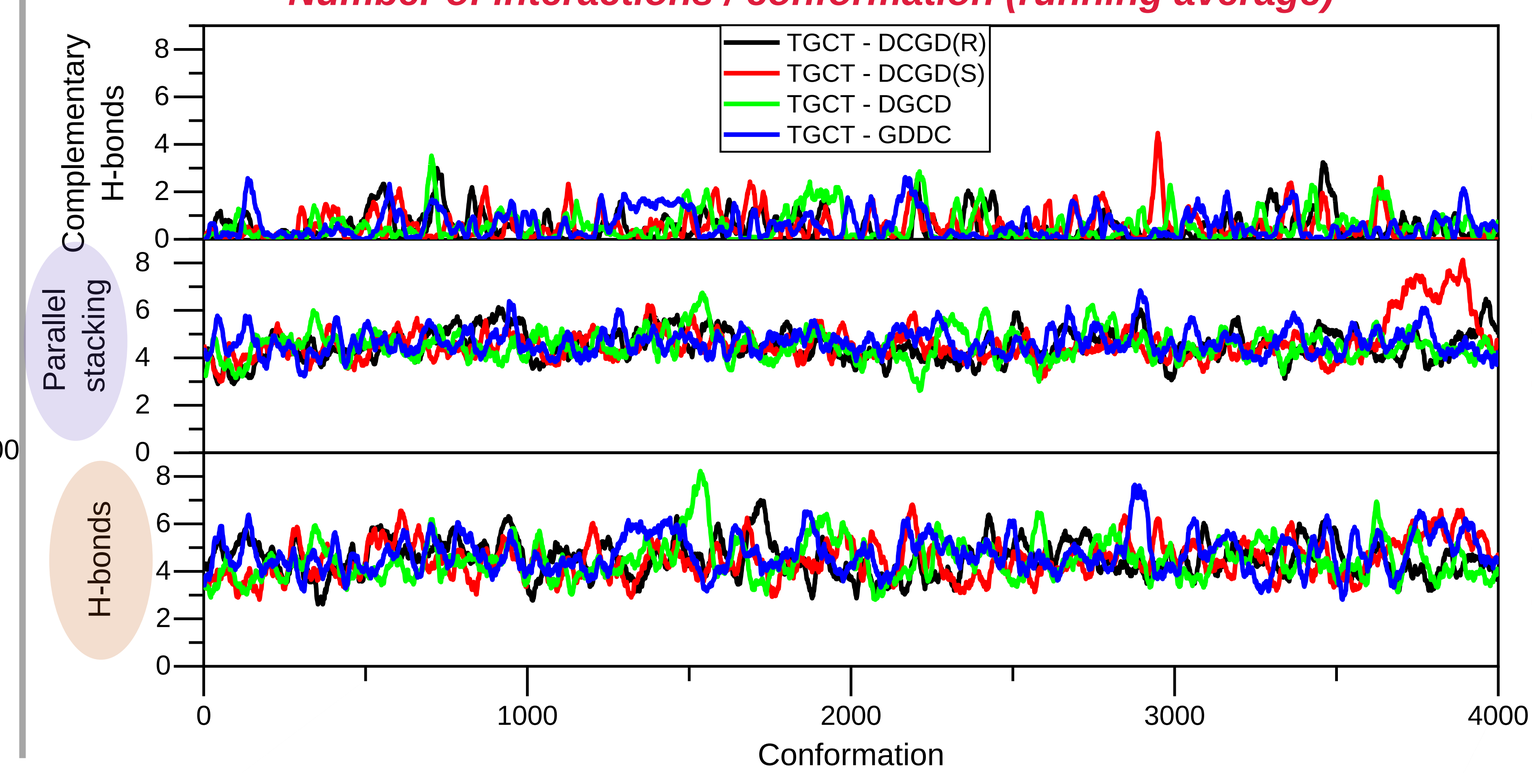
Radius of gyration



- Fast decrease of the R_G and stabilisation around 8.5 Å

➔ **Compact complex** with the 4 target chains

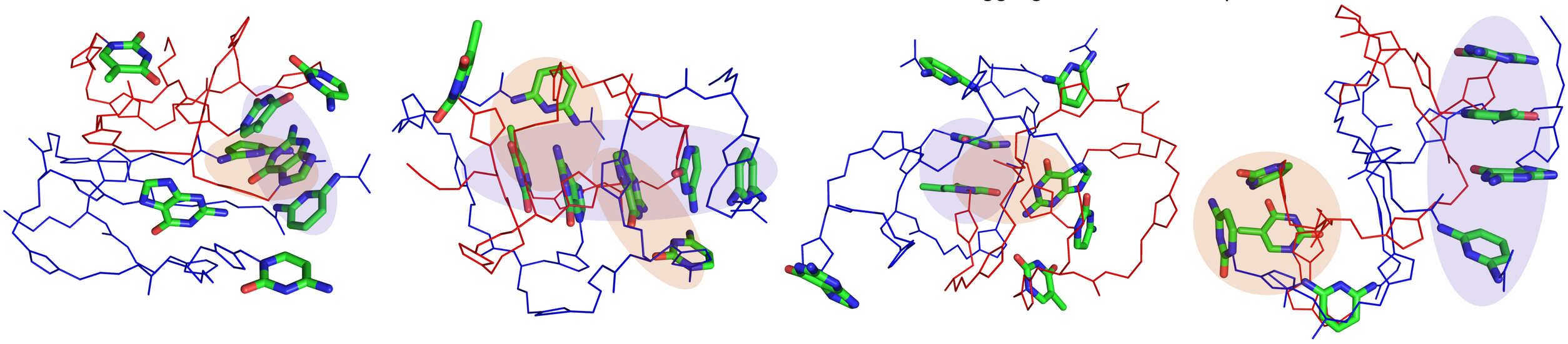
Number of interactions / conformation (running average)



Average number / conformation

Complementary H-bonds	0.5	0.6	
	0.6	0.6	
Parallel stacking	4.5	4.5	
	4.6	4.7	
H-bonds	4.5	4.5	
	4.5	4.8	

Last conformation of the simulation ➔ **Globular, disordered** aggregate for each complex



TGCT - DCGD(R) **TGCT - DCGD(S)** **TGCT - DGCD** **TGCT - GDDC**

Conclusion

- **TGCT** forms **disordered, globular and stable duplexes** with the four target chains
- **Lack of specificity** due to the flexibility of the chains and the competitive interaction network
- **Dense grafting of TGCT on a surface** is currently under investigation: this could reduce the folding and thus the conformational space in order to achieve more specificity.

References

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[2] R. Salomon-Ferrer, D. A. Case, R. C. Walker, *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2013**, *3*, 198.
[3] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, D. A. Case, *J. Comput. Chem*. **2004**, *25*, 1157.

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