Conformational analysis of sequence defined oligomers by molecular dynamics

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INTRODUCTION

- **Antibody-recruiting molecules** (ARM)[1] are a promising class of molecules in the field of immunotherapy.
- Combination of **anchoring groups** (for **target cell** binding) and **haptens** (for **antibody** binding) to trigger response of **immune effector cells**.
- Aim: increase of the binding affinity by using multivalent ARM[2].

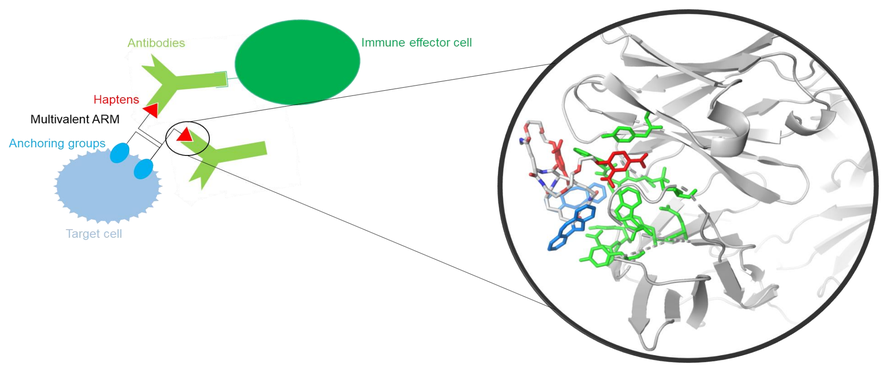
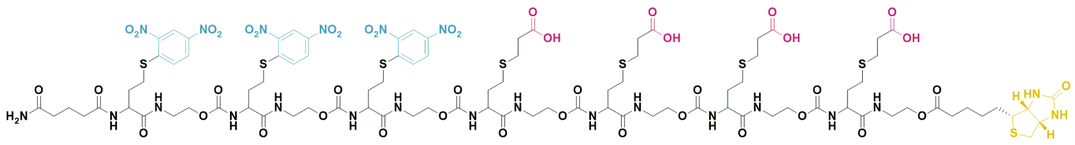
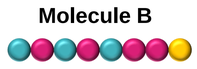
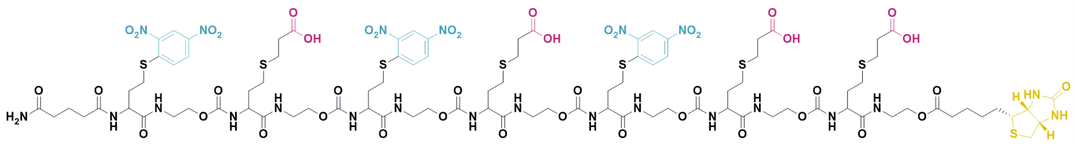


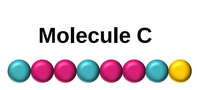
Figure 1: Sketch of the ARM-mediated immunotherapeutic approach.

- **DNP groups** used for antibody-recruitment.
- Modelling of 3 sequence defined antibody-recruiting oligomers with different spacing of DNPs.









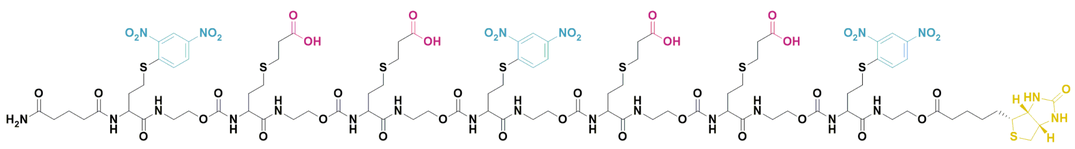


Figure 2: Primary structures of antibody-recruiting oligomers.

What is the influence of the position of DNPs on their accessibility ?

METHODOLOGY

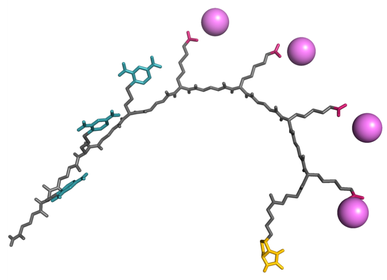


Figure 3a: Initial structure of molecule A.

Molecular dynamics parameters

- GAFF 2 force field/AMBER16[3] in a water box model (TIP3P)
- AM1-bcc charges[4]

- 375 ns production time with timestep of 2 fs
- Snapshots recorded every 0.5 ns (750 structures)
- **Deprotonated acids** : Total charge of the molecule -4
- **Sodium ions** used as counter ions.
- Positionnal restraints on **biotin**

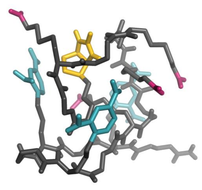
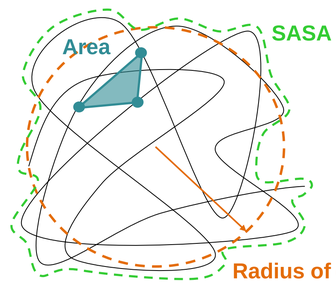


Figure 3b: Final structure of molecule A.

Conformational parameters



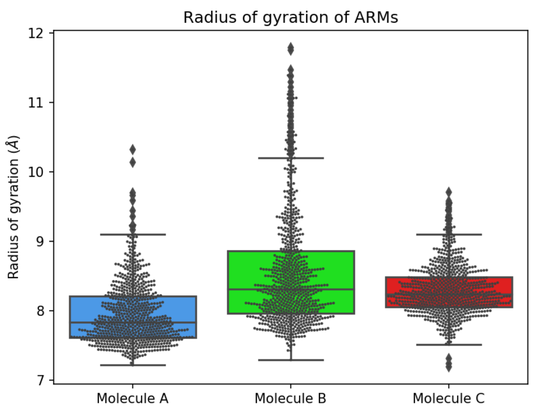
- Radius of gyration
- Solvent accessible surface area

DNPs accessibility

- Distance between DNPs (triangle area)
- Solvent accessible surface area

RESULTS

Global structure of ARM



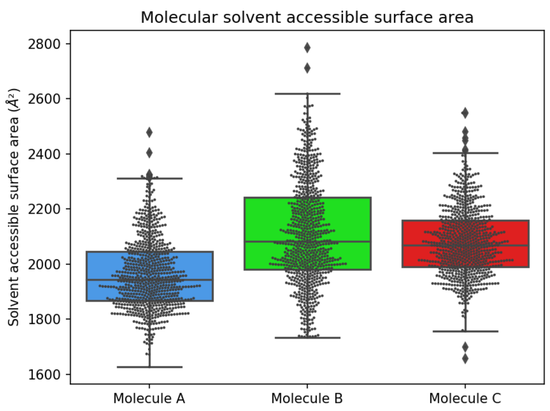
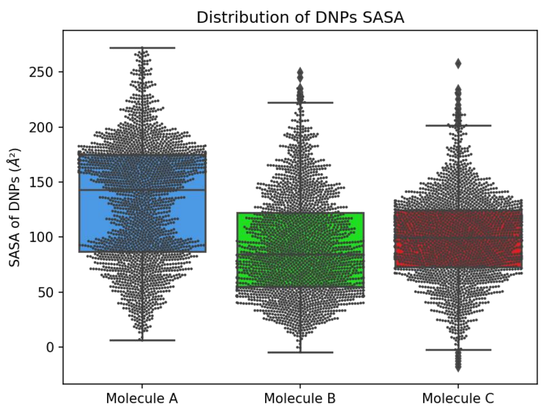


Figure 3a: Box-and-whisker plots of radius of gyration and SASA of oligomers.

DNP accessibility



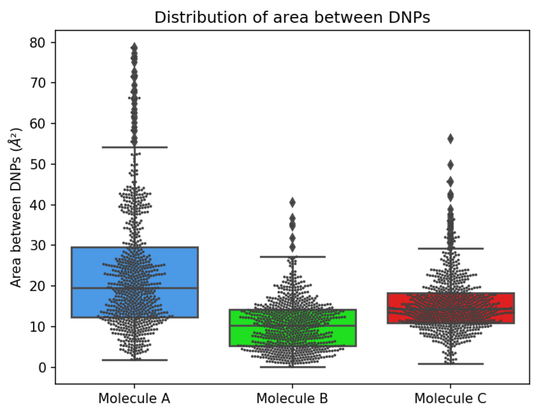


Figure 3b: Box-and-whisker plots of DNPs SASA and DNPs spacing.

	Median radius of gyration (Å)	Median SASA (Å²)
Molecule A	7.8	1943
Molecule B	8.3	2082
Molecule C	8.2	2069

The size of each molecule was assessed by looking at the radius of gyration and the molecular SASA.
The 3 molecules adopt a globular compact shape in solution (Figure 4).
Size of molecules does not significantly change but molecule A is slightly more compact.

	Median SASA (Å²)	Median area (Å²)
Molecule A	143	19.5
Molecule B	85	10.3
Molecule C	100	14.3

The SASA of each DNP group was measured to evaluate their accessibility. DNPs from oligomer A are in general more accessible than for B and C. This is illustrate by the last snapshots of each MD (Figure 4) where DNPs are located on the edge of the globular structure of oligomer A.

Despite proximity of DNPs in the primary structure of oligomer A (Figure 2), the DNPs are more separated during MD. This leads to a larger area of the triangle formed by the DNPs.

Those results suggest that DNPs (Figure 4, in blue) are more accessible for molecule A and could facilitate the binding of antibodies.

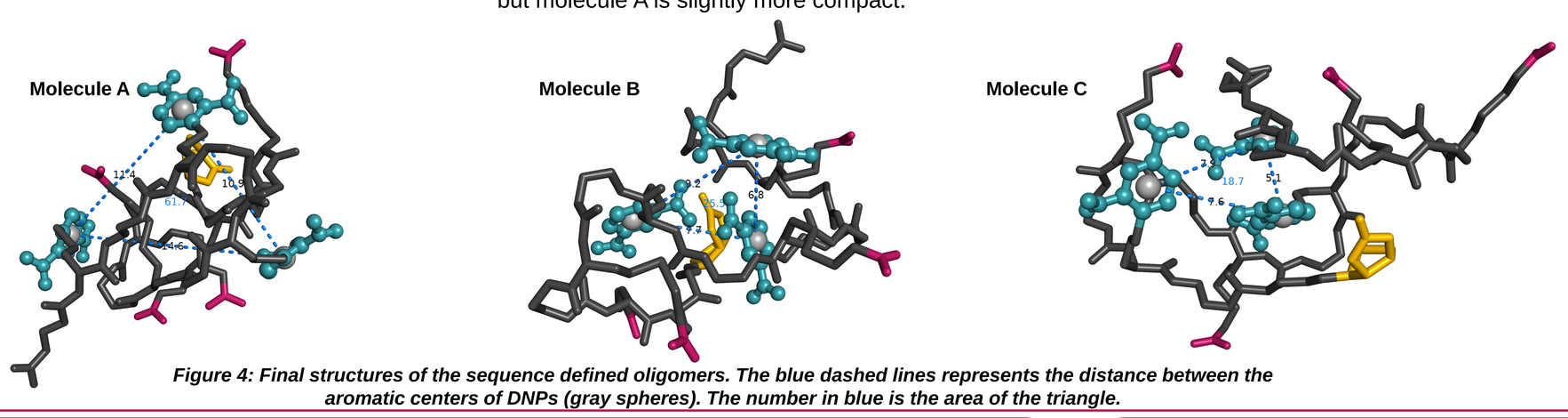


Figure 4: Final structures of the sequence defined oligomers. The blue dashed lines represents the distance between the aromatic centers of DNPs (gray spheres). The number in blue is the area of the triangle.

CONCLUSION AND PERSPECTIVES

- The molecular modelling approach allows us to get insight on the conformation of sequence defined antibody-recruiting oligomers.
- Those results highlights the importance of inspecting the 3D structure of molecules as the spacing in 2D does not necessarily reflect a good separation in a globular structure.
- Avidity measurements and antibody recruitments have been measured experimentally and showed better results for oligomer A.

ACKNOWLEDGMENTS

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