Subproject C5.1

Simulating Nanoscale Structure Formation

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Introduction and Summary

The use of DNA to foster a nanoscale structure formation, in particular for extended or even periodic three-dimensional assemblies remains a research field of intense current interest [1, 2],. In this funding period two prominent reports for DNA-mediated nanocrystal formation were published [3, 4], where nanoparticles coated with single-stranded DNA spontaneously assembled into marginally stable crystals. While these reports demonstrate progress in the 30-year quest to exploit DNA hybridization to stabilize periodic three-dimensional structures, they also illustrate current limitations and difficulties in their realization. To date, the crystals are only marginally stable, they cannot be removed from their growth-medium and there is no control of the crystal packing. As a result, the experimental data for their characterization is difficult to interpret and synthetic efforts still proceed through labour- and material-intensive trial and error. Simulation methods, such as those developed in this project, can help to elucidate the experimental findings, understand key parameters of crystal-design and thus aid and expedite the experimental process.

We have therefore developed methods, both on the atomistic and mesoscopic scale, to simulate DNA-mediated nanocrystal growth and stabilization to support the experimental efforts of this project. Crystallization was observed in several samples (see report Richert) in the approach pursued in this project, but much work remains to be done for crystal characterization and the optimization of the crystallization conditions.

To aid the experiment we have performed atomistic simulations to characterize the flexibility and stability of small representative fragments, typically comprising a few organic cores and the linking DNA double-strands. Such simulations yield insights into the local parameters of the material, but due to the constraints on the system size and time-scale that can be studied with fully atomistic models, cannot describe the process of large-scale structure formation. We have therefore extracted parameters for more coarse-grained models, where one organic core with its attached DNA is modelled as a single rigid object interacting with its environment through effective potentials. Using Brownian dynamics simulations [5-7] we are able to fully characterize the growth of crystallites comprising up to 1000 building blocks and analyze structural features as a function of their parameters (such as coordination number of the core, interaction strength and stiffness, temperature and concentration). These simulations have yielded information regarding the design of suitable organic cores (in particular coordination number and the degree of flexibility) and the crystal structures that may occur for specific building blocks.

The simulation protocols we have developed to model the comparatively slow process of the DNA-crystal formation could also be successfully applied, with little adaptation, to other challenging problems in nano structure formation:

- An adapted version of this approach could be used in cooperation with AG Schimmel (CFN 2.3) and AG Schön (CFN B2.4) to develop structural and functional models for the atomic transistor developed at the CFN[8, 9]. (see reports in CNF area B)
- Together with AG Bräse we investigated nanostructure formation of small molecules with potential applications as drug-carriers in biological membrane. (See details below)
- Together with AG Woell we investigate diffusion of small molecules in metal organic frameworks(MOF), a novel class of nanoscale at meta-materials with designed geometry and functionality. (See details below)
- We have pioneered a novel simulation of the deposition and function of amorphous thin organic films, used for organic light emitting diodes (OLED). The morphologies we have

generated were subsequently used to study functional properties (with J.Nelson, Imp. College, J. Luc Bredas, Georgia Tech, C. Lennartz, BASF), se.g. charge mobility, which were found to be in agreement with experiment[10].

- In the third application, we developed the method to further characterize protein-assisted nanoparticle synthesis[11, 12]. Our simulations generated structural models for the complex of nanoparticle and protein, which are presently not directly observable in experiment and helped to interpret the experimental data, in particular the CD spectra of the protein-nano particle complex (cooperation with: Behrens/ITC, Bürck/IBG and Dgany/Hebrew University).

These results demonstrate that we could develop a novel and widely applicable set of tools in this CFN project that can help understand the complex process of nanostructure formation on time scales that are beyond traditional simulation techniques. By incorporating sequence-specific coarse-grained models recently developed by the dePablo group [13, 14], we will increase the predictive power of these methods to quantify DNA association kinetics in the next funding period. In addition we will seek further cooperation, within the CFN and beyond, to apply our techniques to elucidate complex experiments in nanostructure formation and function.

Project: DNA based Nanocrystals

The unique structure of DNA molecule suggests a promising way of building various nanoscale structures [2], including possibly three-dimensional crystals [1]. A number of extended two-dimensional and references therein), several finite 3-dimensional assemblies [1, 15, 16] and two proof-of-principle experiments for DNA-assisted crystal formation of nanoparticles [3, 4] have been reported to date. However, to date there has been no report of successful synthesis of DNA-mediated nanoparticles based on organic cores, the approach pursued in this CFN project.

In this project we plan to attach complementary, “sticky”, ends of single-stranded DNA attached to different cores, which can self-assemble by DNA-hybridization to form extended structures. Specially designed (organic) cores can have several, possibly different sticky ends, which designs a predefined structure and possibly function into the assembly process. To succeed with this approach the molecules must bind sufficiently well to stabilize the crystal, i.e. to compensate for the loss of entropy, yet binding must remain reversible to permit healing of structural defects.

In this project we have chosen structural units comprising a rigid organic cores (AG Bräse) to which several flexible single-stranded DNA “arms” (AG Richert) are covalently attached. Even within this general framework many fundamental questions regarding feasibility and optimization of crystal-growth protocols remain to be answered: What is the optimal number of arms? What is their optimal length? What are the optimal complementary building blocks? i.e. should all the particles carry the same or different DNA-sequences? What are the optimal conditions for the efficient self-assembly in terms of temperature, concentration etc.?

In order to somewhat reduce the vast possible experimental parameter space, we have developed models to understand the impact of various important parameters using all-atom and coarse-grained models. The coarse-grained approach employs the Brownian dynamics method [5, 6, 17], where each particle was represented by a rigid geometrical object carrying an effective potential that models its interactions with the other building blocks. The degrees of freedom of such an object are translation and rotation, while internal degrees of freedom are neglected. The DNA-arms are taken into account by a special anisotropic potential between the particles. Each arm defines a direction

that is fixed in the local coordinate system of a building block and corresponds to the attachment point of the single-stranded DNA to the organic core. We considered the cases of 4 and 6 arms arranged in a symmetrical manner (tetrahedral and octahedral, respectively). Two arms belonging to different particles can be "complementary", resulting in attractive interactions when their directions are approximately antiparallel and the distance between the centres of the corresponding building blocks is close to an optimal value derived from microscopic parameters. The sequence-specific free-energy of interaction between two such arms can be extracted from known DNA hybridization data.

Using this model we are able to simulate the assembly of several hundred particles from the solution to one or several crystallites, depending on the parameterization and the environmental conditions. We carried out an extensive set of simulations, varying the rules of complementarity, the temperature, concentration and other system parameters to understand the propensity of the system to form a unique, periodic three-dimensional structure.

We obtained a number of key results that helped interpret the experimental data and guide the experiments:

1. We started with simulations that most closely approximated the experimental conditions pursued at the time, i.e. tetrahedral organic cores with short identical palindromic DNA attachments. We found that for a broad spectrum of parameters, the building blocks with this interaction pattern tend to assemble into objects comprised of 5-membered rings, as the interior angle of the regular pentagon (108°) is very close to the tetrahedral angle between the arms of a particle (109,5°). Because objects with five-fold symmetry cannot form extended periodic structures, aperiodic clusters of dodecahedra are generally observed in the simulations (Fig. 1.1, left panel).

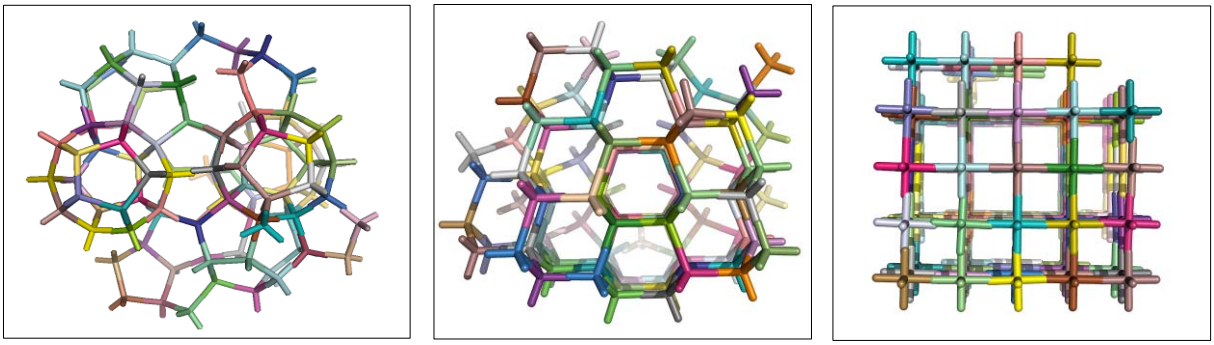

Figure 1.1. From left to right: structures obtained for complementarity rules 1, 2, and 3, respectively.

2. Rings with an odd number of edges can be avoided, even for tetrahedral cores, when we employ two sets of building blocks with complementary, but different DNA sequences, labelled "A" and "B". In this model each arm of the A-particle is complementary to each arm of the B-particle, but there is no binding between building blocks of the same type. In these simulations the particles aggregate into structures showing 6-membered rings, as in the diamond or ice Ih crystal lattices. However, we observe only short-range order because some regions of the material assemble into diamond-like and some into ice-like arrangements of rings, which never heal into a single crystal in our simulation (Fig. 1.1, middle panel). We thus concluded that tetrahedral cores should have severe fundamental difficulties to aggregate into the envisioned extended three-dimensional crystals and discussed alternate building blocks to realize this goal[18].

3. We thus tried different core coordinations, in particular octahedrally coordinated, sixfold substituted fullerenes. In these simulations we found perfect cubic crystals in our simulations, in which the fundamental building block is a 4-member ring (Fig. 1.1, right panel). AB Bräse proceeded to synthesize octahedrally coordinated cores, for which improved association behavior could be demonstrated experimentally[19].

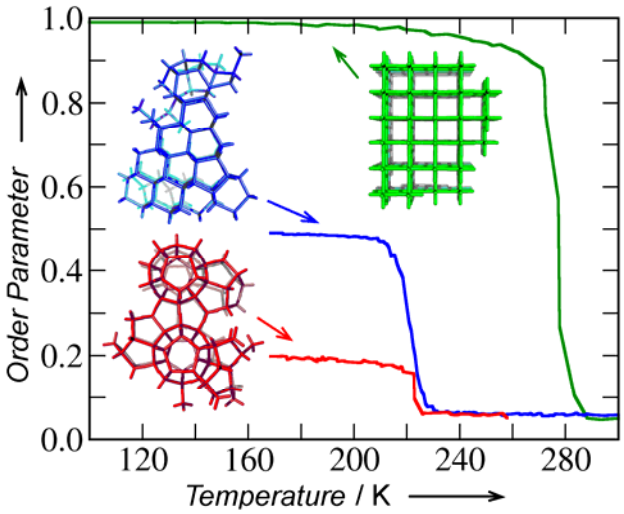

Figure 1.3. Order parameter as a function of temperature for adiabatically cooled simulations for tetrahedral cores with flexible (red) and rigid (blue) core-linker connection and an octahedral core with flexible bonding propensity (green).

For characterization of the structures we introduced an order parameter that characterises the degree of geometrical order (but not thermal stability). A theoretical analysis of our coarse-grained model shows that, in addition to the number of arms and the "complementarity rules", the most important parameter of the model that can affect the system structure is the rigidity of bonds between the particles in case of the model system of type 1 (tetrahedral cores with palindromic DNAs). One would expect that, with an increase of the rigidity, the 5-member rings become energetically unfavourable in comparison with the 6-member rings. Indeed, additional simulations with a more rigid energy potential demonstrated the propensity of the system for 6-member rings and, consequently, for more ordered structure. Figure 1.3 shows the dependence of the order parameter on the temperature for the system of type 1 with the increased rigidity of bonding (blue line) as compared with the previously investigated systems of the same type (red line) and of type 3 with octahedral cores (green line)[19]. Our results illustrate, how even coarse-grained models can help to understand the difficulties in crystallization experiments and guide experiment on the basis of these effective models.

Project: Interaction between small molecules and membranes

The interaction of different molecules and biological membranes are in many cases of great interest. Antimicrobial peptides, gold nanoparticles (AuNPs) and peptoids are interesting novel candidates for pharmaceutically active compounds. To understand and optimize their efficacy, the interactions of these systems with biological membranes need to be characterized. In cooperation with different groups (Tab. 1) we studied the interaction of these candidate molecules with biological membranes in black lipid membrane (BLM) experiments and in ongoing implicit membrane simulations.

AG Bräse (CFN)	Karlsruhe Institute of Technology	Peptoids
AG Ulrich (CFN)	Karlsruhe Institute of Technology	Antimicrobial peptides
AG Hilpert	Karlsruhe Institute of Technology	Peptides
AG Simon	RWTH Aachen University	Gold Nanoparticles

Table 1. Cooperation partners.

For the experiments, realized in cooperation with the Würzburg group (AG Benz), we used membranes composed of different phospholipids to examine the interaction of the candidate molecules with the different membranes by measuring a transmembranevoltage-driven transport of ions through the membrane. To gain further insight into the processes on the nanometer-scale we carry out simulations with a new implicit membrane model in POEM (**P**rotein **O**ptimization with **E**nergy **M**odels [26]).

We performed experiments for 20 different candidate molecules and we are now performing the corresponding simulations. First results, such as those for the antimicrobial peptide Gramicidin A, indicate a good agreement between experiment and simulation: In the experiments we observed pore formation (Fig. 1) and first simulation results show the formation of a helix in the implicitly modeled membrane (Fig. 2).

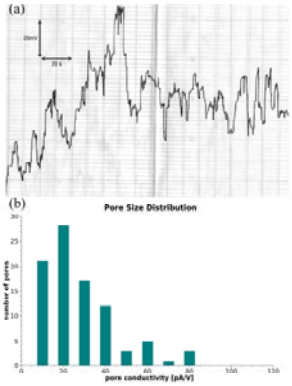

Figure 3.1. (a) experimental results of GramA ->pore formation (b) pore size distribution

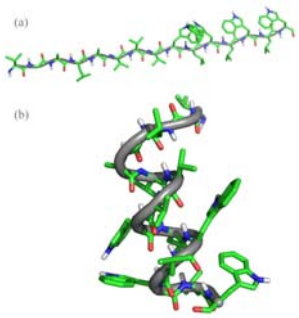

Figure 3.2. Simulation of GramA (a) starting structure: elongated peptide (b) simulation result: helix

In contrast, the related molecule Gramicidin S does not show pore formation in the experiment in the examined concentration range. First simulations of a Gramicidin S monomer suggest that it adsorbs to the membrane-water interface, supporting our experimental results.

In future simulations we want to extend the modeling of all the experimentally examined molecules, amongst others to dimers and tetramers of Gramicidin S and A to investigate if pore formation is possible at appropriately chosen concentrations and to AuNPs to understand why 1.4nm sized AuNPs showed no effects in the experiments whereas 15 nm sized AuNPs induced an increase in transmembrane conductivity. In upcoming experiments we will investigate the influence of the AuNP ligands and additional antimicrobial peptides.

Project: Metal-Organic Frameworks (with AG Woell, new funding period)

Metal-organic frameworks are crystalline compounds consisting of a periodic structure of metal ions or clusters coordinated to rigid organic molecules to form one-, two-, or three-dimensional structures that can be porous [21,22,23] (Fig. 3.1). In some cases, the pores are stable to elimination of the guest molecules (often solvents) and can be used for the storage of gases such as hydrogen and carbon dioxide. In addition MOFs have a high potential for promising application in gas purification, gas separation, catalysis and as molecular sensors [24,25].

We have studied the diffusive motion of ferrocene in two different metal-organic frameworks: MOF1 := $Cu(BDC)(DABCO)_{1/2}$ and MOF2 := $Cu(NDC)(DABCO)_{1/2}$ with a single ferrocene molecule embedded by means of forcefield based atomistic simulations. Figure 3.2 shows the fluctuations of the parameter *r* (defining the distance of the ferrocene center from the origin) during a molecular dynamics simulation of 500 ps. The corresponding histogram indicates that in MOF1 the ferrocene molecule resides with a higher probability at the center of the pore, than in MOF2. In

the second MOF the molecule is likely to be located near the "walls" of the pore, because of the stronger interaction with the larger linker building block (containing an additional benzene ring).

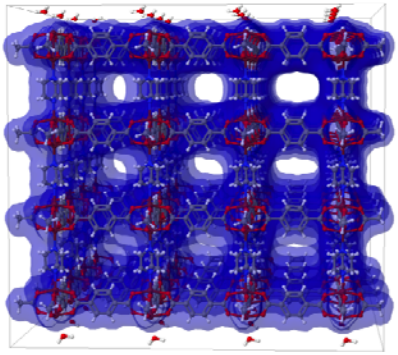

Figure 3.1. Structure of the studied metal-organic framework Cu(BDC)(DABCO)1/2. The blue colored surrounding of the molecular compounds shows the solvent accessible surface.

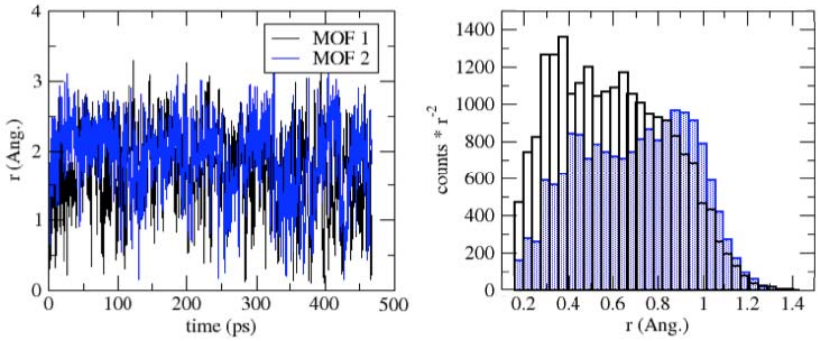

Figure 3.2. Statistical analysis of the ferrocene motion inside the pore of MOF1 (black) and MOF2 (blue). (*left*) Position of ferrocene during a 500 ps MD-simulation. (*right*) Corresponding histogram of the ferrocene distance *r* from the center of the pore.

To investigate diffusion of ferrocene on longer timescales we have performed Monte-Carlo simulations using the POEM simulation package [26]. Figure 3 shows a histogram for distances of the ferrocene center from the origin using 9 million simulation steps for each MOF structure. One can observe that the ferrocene is no longer restricted to the center pore. In agreement with experiment diffusion rate for the ferrocene in the first MOF is higher than in the second.

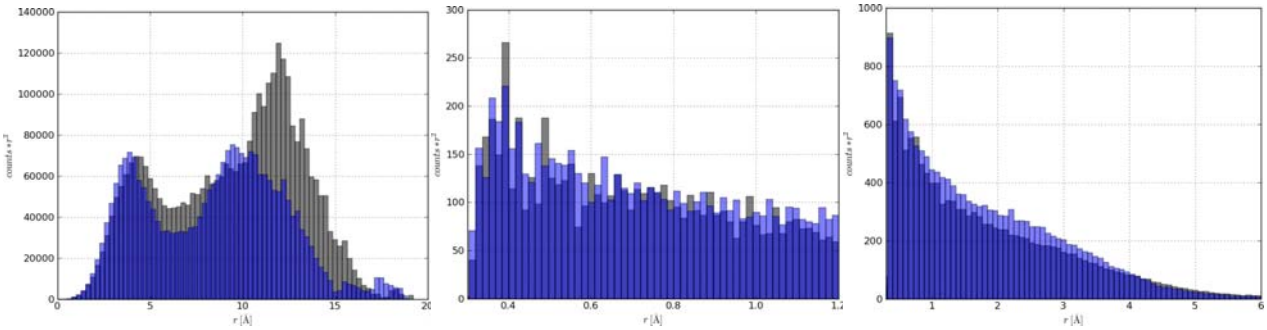

Figure 3.3. Statistical analysis of the ferrocene motion in MOF1 (black) and MOF2 (blue) using MC simulations. The histogram shows the distance *r* of the ferrocene from the center of the pore. The bimodal distribution in the left panel indicates diffusion of the molecule between different pores.

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