DNA as building block for self-assembly of micro-components

Ahlem Abbaci, D.Sinan Haliyo and Stéphane Régnier
Institut des Systèmes Intelligents et de Robotique (ISIR),
Univ. Paris 6 - CNRS, BP 61
92265 Fontenay aux Roses, France
Phone : +33 (0)1 46 54 78 12/86 15 - Fax : +33 (0)1 46 54 72 99
E-mail: abbaci@robot.jussieu.fr

***Abstract*— Biological processes, and in particular DNA hybridization, offer the potential to form the basis for the assembly of devices at micro- and nano-scales. Our aim is to imitate nature to self-assemble micro-scale parts (<100 microns) using DNA hybridization attachment process. In this paper, a new mechanical DNA hybridization modelling scheme is proposed in order to determine the feasibility of such processes. We expose here how and why DNA hybridization process can provide a good bound to self assemble components, and how molecular modelling methods allow to understand the physical mechanism of this process. Furthermore, the strength of DNA hybridization can be measured and optimised to corroborate and validate the modelling state using an experimental technology based on atomic force microscopy.**

I. INTRODUCTION

While techniques for synthesizing nanostructures at the molecular level and manufacturing complex form in microscale form bulk are progressing, assembling parts and components from different materials remain an important challenge in actual nanotechnology.

Increasingly, the self-assembly becomes an interesting approach and a primary need for the assembly of meso and micro-scale components. Many studies are found in the literature around this approach. Capillary forces seem to be a popular solution to guide the self-assembly process. Suath [1] explores 2D self assembly by capillarity between silicon and plastic parts. Xiong [2] proposes a new approach by changing the chemical nature of components to create specific interactions between the substrate and components. Concretely, the process is guided by electro-chemical hydrophobic alteration of specific assembly sites.

Alternatively, different self-assembly procedures based on other forces are investigated. In [3], small particles in 50 μm of diameter are transported and released on a substrate of silicon using an electric force field. Huang [4] uses magnetic forces in a solution to assemble nano-spheres. The result is a magnetized assembled system of components of some 4-5 micro in diameter and with strawberry shape. Finally, in [5] authors produce a semi-conductor microsystem of 200 μm in size . The process is based on the principle of geometrical recognition between components where the specific localization of adhesion sites guides the process.

In spite of the growing interest in this approach, the existing techniques of self-assembly lack maturity for inclusion into industrial development processes. Mainly, there are important constraints in material and geometry of the components which make the process more complicated than individual pick-and-place operations. Moreover, the study of the mechanical and (or) physical nature of the self-assembly process is disregarded in spite of the primary importance of this step in every assembly process. Hence, it is very difficult to establish the limits of the S.A process.

In general, works in the literature on S.A don't lean on any measurements or any mechanical and physical characterization of the process. It becomes evident and necessary to orientate the development of new technologies in the S.A field. In biology and life sciences, the S.A is a trifling and unavoidable process. S.A using biological inspiration appears to be an interesting development.

Our proposed approach is to investigate he bio-inspired bindings suitable for non-organic materials. This work is part of a European research initiative called GOLEM, whose objective is to characterize the assembly process at the micro-/nano-scale using dedicated tools (*http://www.golem-project.eu*).

II. SELF-ASSEMBLY USING BIOLOGICAL PROCESS IN MICRO AND NANO SCALES

Self-assembly is defined as "Spontaneously generating order in a system of components" [6]. It would allows to surpass some limitations appearing in traditional techniques of assembly. These limitations are mainly the complexity of the assembly process and the manipulation of too small component. In last ten years, many research laboratories started to explore this idea and today, self-assembly becomes an overall field of research. Its main idea is to place several components with some specific characteristics (electrostatic, photonic, geometric, etc.), in a particular environment, allowing and provoking specific interactions between components without human interaction.

The use of the biological assembly processes as they are found in the nature appears like an interesting solution. As Nature uses always the least of energy, mimicking or integrating existing biological processes in artificial self-assembly

0-7695-3085-0/08 $25.00 © 2008 IEEE
DOI 10.1109/ICQNM.2008.23

would be an efficient approach. The dimensions of the involved molecules being rather in nano-scale, the self-assembly approaches differs in micro and nano-scales.

At nano-scale, there are numerous studies focused on the construction of 3D structures using biological macromolecules like DNA. Up to date works are from Seeman [7], Shih [8] and Rothermund [9]. These works are centered on the molecules themselves and do not take in to account their interactions with inorganic materials. Proposed techniques explore the 3D conformational proprieties of DNA molecules by geometric, thermodynamic, and combinatorial manipulations, in order to create intracellular transport compartments. Those structures are used both in biological applications (diagnostic for example) and in nanotechnology [10]. The fabrication process of nano-structures of Wang [11] using DNA molecules and photonic waves is an other interesting example.

At micro-scale, the literature on self assembly is quite thin. McNally [12] propose to use existing biological processes (hybridization of DNA and protein docking) to stick biological molecules on silicon particles of 3x3 mm^2. Authors estimate that particles of $10^{-10}g$ require an interaction force of $\sim 10^{-10}N$. This estimation depends highly on experimental conditions. Valignat [13] presents self-assembling micro particles using DNA. Involved particles are spheres of polystyrene, about 1 micro-meter in diameter. This work is very interesting as it proves to practical feasibility of self-assembly using biological process.

The DNA hybridization process appears to be an appropriate tool for micro and meso-scale self-assembly. This choice can be justified first by the abundance of information about the DNA hybridization process. Indeed, the environmental parameters involved in this process are rather well known and moreover it is now possible to engineer specific DNA strands. Thus, it would be possible to control a hybridization process by adjusting these parameters. In this aim, it has been chosen to explore mechanical properties of DNA, in order to evaluate the possibility to integrate the hybridization into a controlled self-assembly process involving meso and micro-scale components.

III. DNA AS BUILDING BLOCK FOR SELF-ASSEMBLY

Different kinds of bio-bonds are available in nature and they can be split into 3 types:

- Protein/protein interaction: it is called docking. The attraction is specific because of the 3-D conformation compatibility of proteins.
- Protein/dsDNA interaction: many proteins are able to interact with double helix of DNA. One of those proteins is Polymerase that opens the double helix and allows the DNA replication.
- ssDNA/ssDNA interaction, which is also referred to as DNA hybridization.

Actually, the ssDNA/ssDNA interaction is the most appropriate for self-assembly purposes, mainly for the reasons stated at the precedent section. The details of this process are described below.

A. DNA molecule from a biological point of view

The DNA molecule is made of many nucleotides connected together. These elementary units are made of a phosphate group connected to a sugar, which is connected to a nitrogenous base. There are four nitrogenous bases found in DNA nucleotides: either adenine, guanine, cytosine, and thymine. There are two groups of bases: purines and pyrimidines. Purines have two ring structures: Adenine (A) and Guanine (G). Pyrimidines have single ring structures: Thymine(T) and Cytosine (C). The complimentary bases are: A-T and G-C. Note that the complimentary bases always include one purine and one pyrimidine. This is to ensure that the "rings" of the DNA helix are of equal width. Each nucleotide, A,C,T, or G can be regarded as a letter. This four-letter alphabet is used to write messages in a kind of code. So the number of possible sequences in an animal cell would fill several thousand books. In fact, a typical animal cell contains one meter of DNA. This genetic code was cracked in the early 1960's. A linear group of three nucleotides (triplets) was shown to code for an amino acid which is the elementary unit of proteins. There are 64 possible triplets corresponding to 20 existing amino acids. The genetic code is the same in all organisms. Thus, the DNA molecule appears as an intelligent material. While the computer science is based on a code of two letters 0,1, the DNA code is based on 4 letters A, T, C, G which can offer a great programming potential allowing geometrical conformations and specific recognitions between components to assemble.

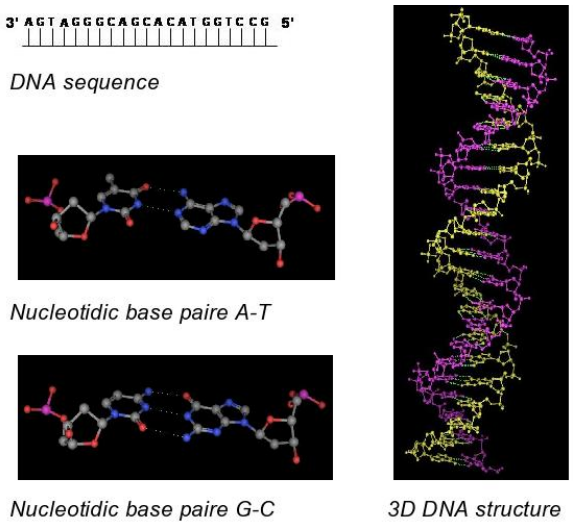

Fig. 1. Structure of a DNA molecule

B. The DNA hybridization for selective bounding

The advantages of using DNA as bounding material can be argued by the specific 3D structure of the molecule. Watson and Crick discovered the double-stranded structure of DNA in 1953, putting together pieces of the chemical puzzle that researchers had been collecting for more than

80 years. Because of the complementarity of the bases, the DNA molecule is composed of two strands: two nucleotidic chains (simple stranded DNA: ssDNA) which form the double helix (dsDNA). The nucleotides in each chain are always complementary. The diameter of the double helix is about 2 nm. The length between two bases on one chain is about 0.34 nm, and 10 bases approximately form one helix tour. The complementarity of the two chains is materialised by the hydrogen chemical connection which is more resistant than a Van der Waal interaction ($\sim$x10). Its length is about 2 Å. Since each DNA strand is precisely complementary to the nucleotide sequence of its partner strand, both contain the same genetic information. Strand A can serve as a mold or template for strand B, and vice versa.

DNA hybridization assemble two complementary DNA strands under particular conditions. This process has been used for a long time in DNA micro-arrays. These micro-arrays are designed for gene expression experiments, and can express thousands of genes with a single array [14], [15]. As stated above, DNA is a code made up of four bases (A, T, G, C) arranged in a complex order into long strands (Fig.1). Owing to its phosphate backbone, it is a highly negatively charged polymer. Thus, in DNA hybridization electrostatic forces play the major role; the method relies on strong Coulomb forces to bring complementary parts together. Short DNA strands (fewer than 100 base-pairs) are referred to as oligonucleotides. It was shown that this biological process is controlled by some key parameters. These controlling parameters define hybridization as a deterministic process. Each of these parameters have been studied and defined in the literature:

- **The temperature** is probably the most important controlling hybridization parameter [15], [16]. In fact, the most favourable temperature for hybridization can be estimated from the chemical proprieties of the solution and the DNA sequence [17] using the nearest neighbor model of Santa Lucia et al. [18].
- **The ionic composition** of the solution, especially salt concentration [15], [17], [19],
- **the DNA sequence** [17] and its complexity,
- its **length** and
- **the number of G-C pairs** present in the helix [15], [20].

The proposed principle for self-assembly is based on the DNA micro-arrays principle, as presented in Fig.2. Our approach involves complementary single DNA strands, each one attached on one of the to be assembled components, or to a component and its desired location on the substrate. The matching strands of DNA will find each other and bond when floating in proximity, thus attaching the nano particle to the substrate of to its counterpart. Moreover some environmental parameters described above, such as the temperature or ionic concentration can be used to control the process.

The success of proposed process, and ultimately, its feasibility requires the knowledge of the mechanical interaction between complimentary strands. In bio-chemistry, many models were proposed to optimise the hybridization results, specially on DNA micro arrays, but all have been purely based on thermodynamic and statistic approaches, thus they are described in terms of interaction energy. Moreover, the expression of this interaction energy differs greatly depending on the used approach and there aren't any trivial links to obtain the magnitude of the interaction force.

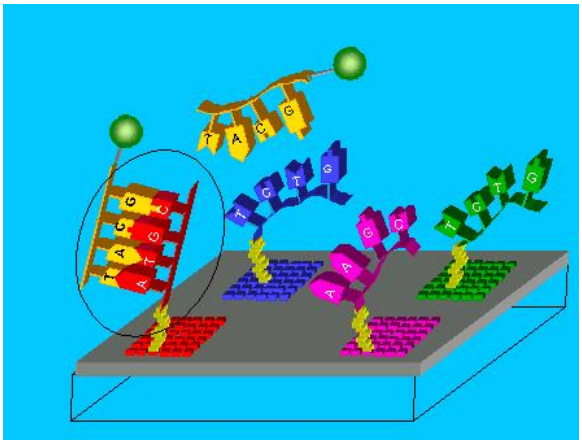

Fig. 2. Proposed self assembly process in DNA micro-arrays

In addition to the knowledge of the interaction force between DNA strands, it is also necessary to explore the attachment between an inorganic material and a DNA strand. Hopefully, there are existing techniques coming mainly from DNA micro array technologies which can be easily adapted to our approach. The attachment process is described briefly below.

C. *Attachment on a components surface*

Actually, there are commercial solutions in which the DNA can be rapidly and efficiently synthesized using methods like PCR (Polymerase Chain Reaction) and tailored to the needs of the user; its length can be selected in the range of 2 - 200 nucleotides (1 to 60nm) and its base-pair sequence can be designed. In order to tether DNA strands on surfaces, the chosen technique is to use the (strept)avidine/Biotin complex. This method has the advantage to be simple: by a chemical transformation of surfaces the avidin or streptavidin molecules can be deposited on surface. DNA strands to be tethered can be purchased directly with 3' or 5' end with a biotin molecule attachment. Then, based on the specific recognition of this complex, biotinylated strands will be attached to surfaces.

The biotin-avidin or biotin-streptavidin interaction has some unique characteristics that make it ideal as a general bridge system in our application [21]:

- The non covalent interaction of avidin or streptavidin with biotin is characterized by a high affinity ensures that, once formed, the complex is not disturbed by changes

in pH or manipulations such as multiple washings when the complex is immobilized.
- Avidin or streptavidin binding to biotin is specific enough to ensure that the binding is directed only to the target of interest.
- Both streptavidin and avidin possess four binding sites per molecule. This is a very useful property for more sensitive detection reagents in pertinent applications.
- Biotin is a small molecule (244.31 Da) that, when introduced into biologically active macromolecules, does not affect their biological activity.

Avidin is a glycoprotein of some 67 kDa composed of 4 subunits of 128 amino acids. Streptavidin is also composed of 4 subunits. The difference between the two proteins is on the fact that straptavidin does not contain carbohydrates and its mass is about 66-75kDa. Streptavidin is usually more employed than avidin because of here weak non-specific interaction. Biotin is also known as vitamin H. This protein is present in all cells and acts as a co-factor of carbonylation enzymes. The carboxyle group is the association site of the molecule.

Using atomic force microscopy (AFM), Piramowicz performed dynamic force measurements of the adhesive forces in (strept)avidine/biotin system [22]. They determined the rupture forces assigned as F_1, F_2 and F_3 correspond to the force needed to break one, three or two bonds in a streptavidine/biotin complex, assuming that the F_1 force is the unbinding force of a single streptavidine/biotin pair for the force loading rate of $3900pN/s$ and found that F_1 is about $255pN$, F_2 about $765pN$ and F_3 about $510pN$.

IV. Modelling of DNA hybridization

The mechanical properties of DNA are closely related to its molecular structure. The base-pair sequence of a DNA strand has been shown by Rief [23] to be extremely important for the mechanical properties of that strand.

In order to grasp the bio-bound functionality to its full extent and to be able to make predictions on the quantitative and qualitative nature of DNA strands interaction, we will investigate a modelling approach of the hybridization process. The aim of this approach is the DNA molecule programming in order to obtain the needed bound of a particularly specific self-assembly process. The proposed modeling consists in two phases: the first involves the design of the process, and the second allows the modelling of the dynamic aspects of the self-assembly, essentially by describing different interaction forces.

- **First modelling phase:** This module would allow to determine the ideal initial conditions of the self-assembly process by optimizing the environment (temperature, solvent concentration, ...etc) and conditions on component to assembly (density of bio-bond on surfaces, geometry, ...etc). Ion concentration, sequence composition and length of DNA strands will be optimised using DNA micro arrays optimisation algorithms to avoid "mismatches" (true-negative and false-positive of DNA strands hybridization), in particular by controlling the G-C content of sequences . Temperature would be determined using the nearest neighbor model of Santa Lucia et al. [18].

- **Second modelling phase:** Different interaction forces can be easily described at different levels: molecular (potential energy), between two strands or between two complementary strands population (Newtonian force). The objective is to construct a multilevel model allowing to make the link between these different ranges of description.

This approach requires to model interaction energies at the molecular level. Hence, it is necessary to describe isolated DNA strands and the explore their interactions in terms of energy. Then, the interaction force can be derived form energy.

A. Molecular models

The mechanical characterization at the molecular scale traditionally means to compute the difference of potential energy between two conformational states of the molecule called, δV. There are many methods to compute this energy. One of them is performed using an appropriate interaction force field (CHARMM, ...etc) following the scheme:

$$V(x) = E_{str}+E_{ang}+E_{stb}+E_{oop}+E_{tor}+E_{vdw}+E_{ele}+E_{sol}+E_{res}$$

where x is an atom at one position and each terms corresponds to a configuration energy (bond stretch, bond angle bend, stretch-bend, out-of-plane, torsion, van der Waals, electrostatic, solvation, and restraint energies. To obtain the potential energy of a molecule, it is necessary to sum of all the included atoms energies. In this purpose, we use a commercial software called MOE. MOE is the chemical computing group's Molecular Operating Environment: an interactive software allowing molecular static and dynamic modelling and simulation. MOE provides a comprehensive visualization interface that permits multiple views of a molecular system *http://www.chemcomp.com*.
Based on the supplied SVL language on the MOE software and on a mathematical approximation , Daunay [24] developed an algorithm allowing to appreciate the Newtonian force interaction between two biological entities. We applied this algorithm on two complementary DNA strands of different lengths to obtain a first result which allows us to compare our approach to the further experimental results. The principle is to approximate the energy profile of a molecule by a constructed analytic function, which allows the derivation and thus computation of the force value on x, y and z axis. This method has the advantage to be independent of the type force field.

Fig.3 shows an example of such a simulation in this case, for a given DNA sequence, the interaction force between the 2 strands are calculated. Results are plotted in Fig.4

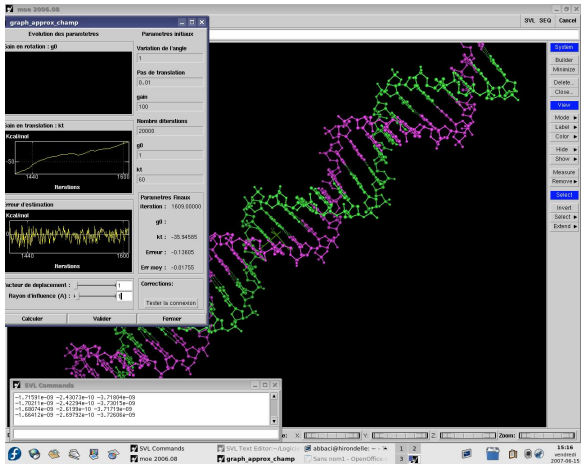

Fig. 3. Simulations on MOE

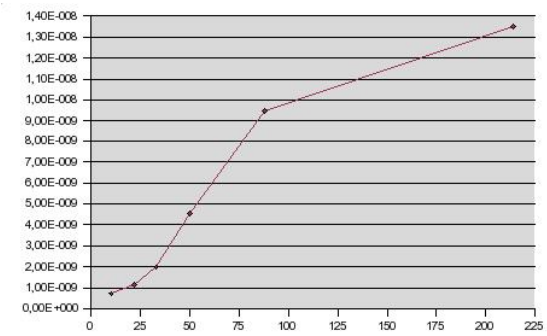

Fig. 4. Simulated results: interaction force (Newton) depending on the strand length (number of nucleotides)

B. A modelling scheme

Computing an approximate force interaction is a first quantitative characterisation of the hybridization process. Obtaining a kinetic information in addition could be more interesting. In this manner, the self-assembly system will be described entirely. Many works on the kinetic aspects of the hybridization are available in the literature. Having an idea on the velocity can allow us, by combining with a microfluidic description of the strands motion, to evaluate quantitatively the hybridization kinetics. Kinetic rules of the process are described by differential equations, where parameters define chemical interactions and are obtained in function of activation potential energy; as inspired by Erickson [25]. In this paper, authors base their approach on free floating DNA strands. This approach can be adapted to our case by including fixed position strands (tethered to a surface) in addition to the free floating ones.

Constructing a multilevel model based on the design sequence knowledge will allow self-assembly between two complementary strands population prediction. Thus, we have to simplify our molecular understanding of DNA hybridization mechanism. A footbridge between the microscopic and macroscopic scales of our process can be performed exploring the DNA persistent length notion. Jayaraman [26] showed that groups of 11 nucleotids can be considered as significant units to describe the overall strand behavior. This small fragment represents the persistent length which was proven to be the mechanical elementary unit in the molecular behavior of DNA.

Because of our deterministic approach, we make an attempt to develop our model surrounding this idea of fragmentation onto functional small units, but using another physical approach based on a model of two elastic rods coupled via forces that represent base pair interactions [27]. Knowing the interaction force value between two complementary elementary units of 11 nucleotides, we will be able to obtain the force interaction value between the two complementary strands. In this way, MOE will be used to construct a data base which will contain a big variety of units sequence with there interaction force estimated value. Hence, These results obtained at the molecular level can be included into a purely mechanical macroscopic model.

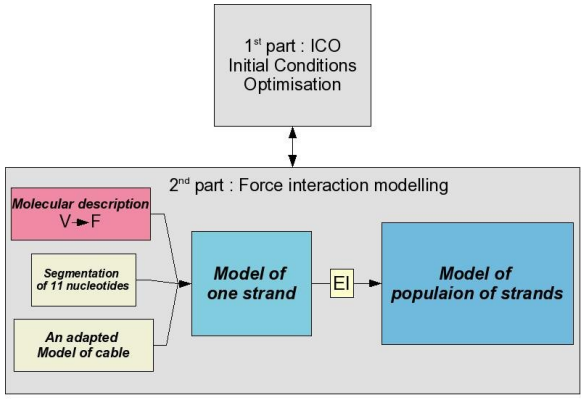

Fig. 5. The proposed modelling scheme

V. Experimental confrontation

In order to validate the proposed modelling, the strength of DNA hybridization can be experimentally measured and optimised using an experimental technology based on an atomic force microscopy.

In fact, experimental works were carried out on hybridised DNA, using atomic force microscopy (AFM) in the literature by fixing a DNA strand on the AFM point, its complementary on the substrate, and bringing them into contact, and then dissociate the formed double helix. This allows measuring the interaction force between the two strands. This experimentation was performed by some research teams [28]–[30].

To be able to compare those experimental data with the proposed model, and especially to provide the reference data for the modelling work, we have to estimate the interaction values of DNA hybridization dependent on some parameters

(e.g. Base-pair sequence, its length, etc). Afterwards, the correlation of real and experimental data would be carried out in order to affine the analytic functions describing the energy interactions in simulation.

VI. Conclusion

We propose an approach for self-assembly using DNA hybridization process. The approach is based on extensive modeling of the hybridization and aims to define both mechanical and chemical parameters involved in a given self-assembly operation. In this paper, first steps towards this modeling are presented. These works includes the construction of molecular level presentation of DNA strands in an simulation environment in order to obtain interaction energies, then forces between particles to assemble. An extensive analysis of existing bio-chemical data allowed us to propose such a molecular level model. Interactions forces are calculated using the energetically definitions obtained from this model, by approximating with analytical functions and their derivation. The future work is to create apply this method on several selected 11 nucleotide long strands as base mechanical blocks. These blocks will than be used to build rope-like mechanical models of DNA strands for automated calculation of desired parameters for a given self assembly. These parameters include environmental parameters like as well as DNA sequences or strand densities.

Acknowledgment

This work was supported in part by the European GOLEM project (http://www.golem-project.eu/index.htm). The GOLEM project is supported by the Nanotechnology program (NMP) of the European Commission under the sixth framework program (FP6).

References

[1] *Integration of Silicon Circuits Components Onto Plastic Substrates Using Fluidic Self-Assembly*. International Conference on MEMS, NANO and Smart Systems, 2005.

[2] X. Xiong, Y. Hanein, J. Fang, Y. Wang, W. Wang, D. T. Schwartzand, and K. F. Bringer, "Conrolled multibatch self-assembly of microdevices," *Journal of Microelectromechanical Systems*, vol. 12, no. 2, pp. 117–127, 2003.

[3] A. O'Riordan, P. Delaney, and G. Redmond, "Field configured assembly: Programmed manipulation and self-assembly at the mesoscale," *Nano Letters*, vol. 4, no. 5, pp. 761–765, 2004.

[4] H. Huang, J. N. Anker, K. Wang, and R. Kopelman, "Magnetically assisted and accelerated self-assembly of strawberry-like nano/microparticles," *J. Phys. Chem. B*, vol. 110, no. 40, pp. 19 929–19 934, 2006.

[5] W. Zheng, P. Buhlmann, and H. O. Jacobs, "Sequential shape-and-solder-directed self-assembly of functional microsystems," *PNAS*, vol. 101, no. 35, pp. 12 814–12 817, 2004.

[6] M. Boncheva and G. M. Whitesides, "Making things by self-assembly," *MRS Bulletin*, vol. 30, pp. 736–742, 2005.

[7] N. C. Seeman, "The design and engineering of nucleic acid nanoscla assembly," *Structural Biology*, vol. 6, pp. 519–526, 1996.

[8] W. M. Shih, J. D. Quispe, and G. F. Joyce, "1.7-kilobase single stranded dna that folds into a nanoscale octahedron," *Nature*, vol. 427, pp. 618–621, 2004.

[9] P. W. K. Rothermund, "Folding dna to create nanoscale shapes and patterns," *Nature*, vol. 440, pp. 297–302, 2006.

[10] R. Bashir, "Invited review, dna-mdiated artificial nanobiostructures: state of the art and future directions," *Superlattices and Microstructures*, vol. 29, no. 1, pp. 1–16, 2001.

[11] C. Wang, L. Lin, and B. A. Parviz, "Modeling and simulation for nano-photonic quantum dot waveguide fabricated by dna-directed self-assembly," *IEE Journal of Selected Topics In Quantum Electronics*, vol. 11, no. 2, pp. 500–509, 2005.

[12] H. McNally, M. Pingle, S. W. Lee, D. Guo, D. E. Bergstrom, and R. Bashir, "Self-assembly of micro- and nano-scla particles using bio-inspired events," *Applied Surface Science*, vol. 214, pp. 109–119, 2003.

[13] M. Valignat, O. Theodoly, J. C. Crocker, W. B. Russel, and P. M. Chaikin, "Reversible self-assembly and directed assembly of dna-linked micrometer-sized colloids," *PNAS*, vol. 102, no. 12, pp. 4225–4229, 2005.

[14] G. A. Held, G. Grinstein, and Y. Tu, "Modeling of dna microarray data by using physical properties of hybridization," *PNAS*, vol. 100, no. 13, pp. 7575–7580, 2003.

[15] Y. A. Chen, C.-C. Chou, X. Lu, E. H. Slate, K. Peck, W. Xu, E. O. Voit, and J. S. Almeida, "A multivariate prediction model for microarray cross-hybridization." *BMC Bioinformatics*, vol. 7, p. 101, 2006. [Online]. Available: http://dblp.uni-trier.de/db/journals/bmcbi/bmcbi7.html#ChenCLSPXVA06

[16] K. A. Peterlinz and R. M. Georgiadis, "Observation of hybridization and dehybridization of thiol-tethered dna using two-color surface plasmon resonance spectroscopy," *J. Am. Chem. Soc*, vol. 119, pp. 3401–3402, 1997.

[17] Y. Gao, L. K. Wolf, and R. M. Georgiadis, "Secondary structure effects on dna hybridization kinetics: a solution versus surface comparison," *Nucleic Acids Research*, vol. 34, no. 11, pp. 3370–3377, 2006.

[18] J. John SantaLucia, "A unified view of polymer, dumbbell, and oligonucleotide dna nearest-neighbor thermodynamics," *PNAS*, vol. 95, pp. 1460–1465, 1998.

[19] C. A. Mirkin, R. L. Letsinger, R. C. Mucic, and J. J. Storhoff, "A dna-based method for rationally assembling nanoparticles into macroscopic materials," *Nature*, vol. 382, pp. 607–609, 1996.

[20] E. Carlon and T. Heim, "Thermodynamics of rna/dna hybridization in high-density oligonucleotide microarrays," *Elevier - Physica A*, vol. 362, pp. 433–449, 2006.

[21] E. P. Diamandis and T. K. Christopoulos, "The biotin-(strept)avidin system: Principles and applicationsin biotechnology," *Clinical Chemistry*, vol. 37, no. 5, pp. 625–636, 1991.

[22] M. d. O. Piramowicz1, P. Czuba, M. Targosz, K. Burda, and M. Szymonski, "Sequence-dependent mechanics of single dna molecules," *Nature Struct. Biol*, vol. 53, no. 1, pp. 93–100, 2006.

[23] M. Rief, H. Clausen-Schaumann, and H. E. Gaub, "Sequence-dependent mechanics of single dna molecules," *Nature Struct. Biol*, vol. 6, pp. 346–349, 1999.

[24] *Energy-Field Reconstruction for Haptic-Based Molecular Docking Using Energy Minimization Processes*, RSJ International Conference on Intelligent Robots and Systems. IEEE, 2007.

[25] D. Erickson, D. Li, and U. J.Krull, "Modeling of dna hybridization kinetics for spatially resolved biochips," *Analytical Biochemistry*, vol. 317, pp. 186–200, 2003.

[26] A. Jayaraman, C. K. Hall, and J. Genzer, "Computer simulation study of molecular recognition in model dna microarrays," *Biophysical Journal*, vol. 91, pp. 2227–2236, Sept. 2006.

[27] S. M. Chitanvis and P. M. Welch, "Inuence of supercoiling on the disruption of dsdna," *The journal of chemical physics*, vol. 123, no. 12, pp. 124 901.1–124.901.5, 2005.

[28] L. T. Mazzola, C. W. Frank, S. P. A. Fodor, C. Mosher, R. Lartius, and E. Henderson, "Discrimination od dna hybridization using chemical force microscopy," *Biophysical Journal*, vol. 76, pp. 2922–2933, June 1999.

[29] O. H. Willemsen, M. M. E. Snel, A. Cambi, J. Greve, B. G. D. Grooth, and C. G. Figdor, "Biomolecular interactions measured by atomic force microscopy," *Biophysical Journal*, vol. 79, pp. 3267–3281, Dec. 2000.

[30] G. Lee, L. Chrisey, and R. Colton, "Sensing discrete streptavidin–biotin interactions with atomic force microscopy," *Science*, vol. 266, pp. 771–773, 1994.