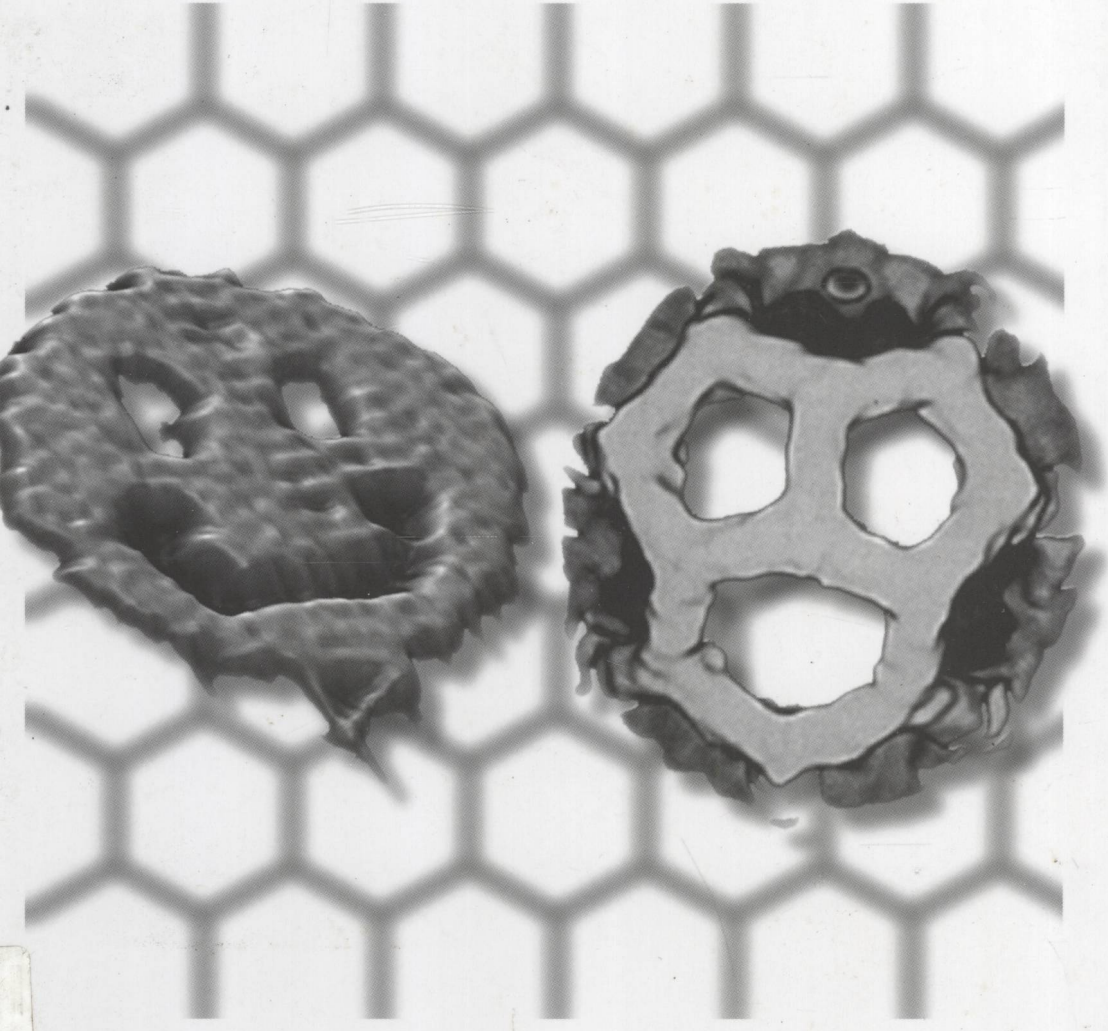
RSC Nanoscience & Nanotechnology

Maxim Ryadnov

Bionanodesign

Following Nature's Touch



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Maxim Ryadnov
Department of Chemistry, University of Leicester, Leicester, UK

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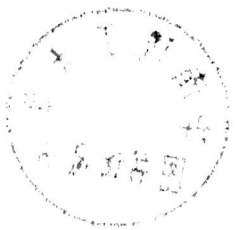

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Preface

The progress of today's science and technology encounters an increasing demand for finer and more efficiently performing materials with properties superior to those of current and hence ageing devices. Whether this concerns electronics or drug delivery, cancer diagnostics or alternative energy sources the search for means of miniaturising the existing materials or devising fundamentally new components with higher capacities appears to be relentless.

A saving solution to this is widely proposed as the design and fabrication of nanostructures, molecular architectures with dimensions featured below 100 nm.

By convention, and as originally formulated by Richard Feynman, the challenge of constructing macroscopic structures through the manipulation of individual molecules or even atoms prompted the emergence of a rapidly evolving field – nanotechnology. By definition, nanotechnology mirrors complex organisation at the nanoscale and is underpinned by a variety of related physical events that are combined into one universal process – molecular self-assembly.

The phenomenon of self-assembling molecules is attractive from both academic and application perspectives. However, preferential attention is being given to approaches whereby nanostructured materials or their components can be produced, moreover, produced at whim; that is, designed.

The pursuit for routes that can lead to rational or at least predictable design strategies invoked the main objective of this publication – to bring together contemporary approaches for designing nanostructures that employ naturally derived self-assembling motifs as synthetic platforms.

Entitled *bioinspired nanoscale design* or *bionanodesign* the book is written in the shape of a review, referenced as fully as permissible within the context of biomolecular recognition and self-assembly, which forms a general trend throughout.

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The volume is composed of three core chapters focusing on three prominent topics of applied nanotechnology where the role of nanodesign is predominant. Specific applications that arise from designed nanoscale assemblies as well as fabrication and characterisation techniques are of a much lesser focus and whenever they appear serve as progress and innovation highlights.

In this sense, the book takes a nonstandard approach in delivering the material of this kind. It does not lead straight to applications or methods as most nanotechnology titles tend to do, but instead it admits the initial and primary stress on "nano" rather than on "technology". The task is significantly eased by the cohort of brilliant bioinspired designs reported to date and complicated by the volume they create almost on a weekly basis. For this reason, the author apologises for the inevitable, but not necessarily deliberate, omission of examples, many of which may prove to be equally if not more influential in bionanodesign.

Maxim Ryadnov
November 2008

A designer knows he has achieved perfection not when there is nothing left to add, but when there is nothing left to take away.
Antoine de Saint-Exupery

There's plenty of room at the bottom
Richard Phillips Feynman

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CHAPTER 1

Introductory Notes

1.1 Inspiring Hierarchical

It is becoming widely accepted that the decisive role in building nanostructures belongs to the hierarchical nature of molecular self-assembly, which renders the process a "bottom-up" strategy in accessing architectures of various complexities. The approach is thus reverse to the notion of miniaturising materials,[1] which assumes a top-down direction. Indeed, historically "top-down" methods such as photolithography were the first to be introduced into the practice of nanofabrication and processing. Yet, otherwise fairly efficient in nanoscale patterning and shaping on solid surfaces, the methods soon proved to be limited by the very basis of the technology – the use of devices that are considerably larger than the target materials. In this respect, hierarchical self-assembly, which allows for the spontaneous building of a target composite from the bottom up, *i.e.* from individual molecules up to microscopic functionally specialised shapes and morphologies, offers a promising alternative with practically unlimited capacities.

In principle, this is what reserves the potential to define and manipulate the properties of desired structures and materials at the nanoscale.[2]

Notably, a strong dependence on this is exhibited by biopolymers whose precise functional expressions necessarily determine the morphological diversity of biological structures. Conversely however, additional constraints are required to provide the accurate reproducibility of a given assembly by a certain biopolymer type, to which a gratifying provision is made by another intrinsic property of self-assembly characteristic of biological systems.

This is autonomous control over supramolecular propagations of individual molecules. The main mechanism here involves molecularly encoded folding, which enables correlation of each level of architectural hierarchy with the structural assignment of specialised self-assembly patterns.[3] Thus, assembling

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biopolymer blocks such as proteins and nucleic acids at the subcellular level, often with a precision of a single nanometre,[3] becomes possible. However, one's ability to reproduce such a state of control and prediction remains to be demonstrated. Admittedly, this is due to incomplete understanding of molecular self-assembly *per se*, whilst gaining more insight into biomolecular hierarchies can lead to qualitatively new models and protocols in designing materials with otherwise unknown or unachievable properties.[4] Therefore, an explicit guidance to the fabrication of functional or specialist nanostructures is of paramount importance.

1.2 Encoding Instructive

Replicating Nature's designs faithfully reproduced over millions of years presents perhaps the most straightforward route to success. Nature shares examples of nanodefined self-assemblies in virtually all levels of biological organisation. These may include, but are not limited to, the repertoire of topologically infinite DNA structures, the wealth of viral forms, the functional elegance of enzyme machineries and protein cages, the architectural unification of extracellular matrices and biological membranes. Taken together these are soliciting for a robust design rationale that claims to be innate within the broadest possible spectrum of nanostructures.

But what are the ways of extracting or adapting this for engineering artificial systems?

Intriguingly, of different types as well as within every single type, natural designs are individually unique and especially in functions they carry or are assigned to. On the one hand, this creates precedents of conserved templates readily adaptable for synthetic designs. On the other, biopolymers universally obey the same assembly principle; they adopt three-dimensional secondary structures to build functional quaternary systems – natural nanoscale objects.

Synthetic designs reported to date take both routes. Protein or DNA structures based on preassembled native folds as well as systems designed from scratch, but unambiguously through the emulation of natural assembly elements, are peers. Therefore, a general approach to tackle the problem may focus on the assimilation of Nature's ways in creating macromolecular assemblies and specifically by employing and extending the structure–assembly relationship of existing examples. Eventually, this may constitute the sought essence of a structure-based strategy that specifically exploits biomolecular recognition for the generation of nanoscale composites. Steady progression in this direction revealed in the past decade states that systems shown as more advanced tend to result from better understood assembly elements. For instance, designs derived from DNA manifest precision and control to match, whereas unparalleled is also the representation of self-assembly elements in different biomolecular classes, with proteins and peptides giving the richest repertoire of self-assembling motifs.

1.3 Starting Lowest

Yet, irrespective of the chemical archetype or class of assembly, the synthesis of a discrete system that would span nano- to microscale dimensions is never a trivial task.[3,4] Monodispersity, an ability to maintain the internal order and morphology of resulting assemblies, reproducibility of prescribed assembly modes are amongst major hurdles to overcome towards functional nanostructures.

Naturally occurring systems are free of such obstacles. This is partly because there are no limitations in size and shape in choosing assembling components where complexity is not an issue and any is affordable, and partly because natural nanostructures are highly conserved sequential couplings of exquisitely fitted subunits that use spatially self-maintained molecular arrangements.

In principle, employing design assumptions offered by natural self-assembling motifs should be beneficial for engineering artificial systems or mimetics, which in this notation can be viewed as bioinspired. Logically, nanoscale objects generated in this way can lead to materials with predictable and tuneable properties that are frequently referred to as "smart" materials. However, this hardly proves to be the case and in particular for *de novo* nanoscale designs that, despite their impressive numbers, remain short of original examples.

Indeed, where the total number of particular designs may well have approached hundreds, rationally designed nanoscale morphologies are confined to a very few. Naturally, the latter is determined by applications, but possibly to a larger extent by the synthetic inaccessibility of large biomolecular subunits of natural assemblies.

As an inevitable consequence, the success of artificial designs is hampered by the need of finding efficient ways that would allow for control over assembly of smaller, simpler, albeit more entropy-dependent, self-assembling motifs. Therefore, very often identifying a suitable molecular candidate with high reproducibility and predictability in assembly, even with the admittance of more sophisticated chemistries, is critical.

1.4 Picturing Biological

Given Nature's preference for biopolymer precursors in constructing nanostructures a set of requirements can be identified for a potential self-assembling candidate as follows.

First, it must be synthetically accessible in a monodisperse form. This requirement is limiting and hence indispensable for any type of intended nanostructures. This also directly relates to the autonomous control of the nanoscale assembly.

Second, it has to adopt a recognition pattern ensuring minimised impact of entropy factors (*e.g.* inter- and intramolecular dynamics) on the assembly. This ensures the hierarchical order of the assembly and consequently presents a major morphology-specifying parameter.

Third, its assembly should obey the chosen mode of hierarchical ordering encoded and hence predetermined in primary sequences. This requirement is intrinsic for all biopolymers but can be waived for certain molecular mimetics that preferentially lean on bulk forces supporting self-assembly, *e.g.* the hydrophobic effect.

There are several biomolecular motifs that can meet such design criteria. With their encoding traits established empirically, all attest strong correlations between the chemistry and assembly. However, of notable advantage are those represented by two main classes. These are nucleic acids and proteins or rather their shortened versions, oligonucleotides and peptides, respectively. Other motifs developed and used over the course of the last several years can be seen as their derivatives or supplements.

Exemplified by just these two, the main factors underlying the functions of native nanostructures including monodispersity, consensus folding and environmental responsiveness provide inspirational impacts on artificial designs. The influence of such examples on scientific thought is immense and in conjunction with the growing body of synthetic develops and constantly improving analytical techniques is stimulative towards more systematic studies for elucidating main compatibility marks between structural principles behind native nanoscale designs and synthetic nanostructures.

All in all, this urges putting mainstream trends in nanofabrication, existing and probable, under the strong emphasis of design aspects. An attempt to address this or at least to touch some of the most design-responsive points in the prescriptive self-assembly is made in this volume.

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CHAPTER 2

Recycling Hereditary

It has been more than half a century since the year that defined the way biology is taught today. The big five – five research papers published in *Nature* within a span of three months in 1953[1–5] – hit the longstanding milestone in biology: the deciphering of the architectural code of DNA. The importance of the discovery has been stressed and recapped in numerous reviews and books that collectively put the matter into a dimension of the all-time scientific heritage of undisputable proof. Although it is difficult to identify a biologically relevant discipline that does not benefit from the knowledge of the DNA structure, none is likely more dependent in its essence on the accuracy with which the geometry and spatial organisation of DNA is predicted and described than biological nanotechnology. With the core characteristic of nanotechnology being the creation of diverse structures with nanoscale precision on the one hand and the refined specificity of binding interactions offered by Watson–Crick base pairing on the other, DNA has emerged as a leading instrument in nanodesign.[6,7]

In fact, according to various estimations, the human genome contains from thirty to hundred thousand genes, with all being based on the same molecular module, DNA. This clear statement for DNA as the central molecule of life has confirmed its central status in nanotechnology likewise within just a decade.[6–9]

Forged by Seeman[8] the notion of DNA nanotechnology – the term now widely accepted[10,11] – will be expanded in this chapter starting from the concepts of topological DNA variations pioneered by Seeman[8] to algorithmic DNA self-assembly conceived by Winfree[12] and applied to origami layouts of artificial DNA scaffolds developed by Rothemund.[13]

2.1 Coding Dual

DNA is termed by many as the language of genes, or, to put it another way, as a repository of the information genes carry and require passing to/over successive

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generations. Invariably, such a function, which rationalises the very notion of DNA, dictates the structural parameters and folding paths of the molecule. These, apart from having to be conserved and independently exquisite (by default), need to be able to accommodate a simple and faithfully reproducible mode of self-replication that can be translated into the material of life – proteins. A set of rules that ensures this happening over and over again is termed the genetic code, with its specialisation established as the assignment of a codon, a triplet of nucleotides, to one of twenty proteinogenic amino acids.[14] Strictly speaking, there is more than one genetic code[15,16] as well as more than one mode of DNA base paring.[17] However, those are particular cases and can be ignored within the context of DNA structural reproducibility.

More important in this regard is the fact that (1) only a part of genetic information is encoded by the code, and (2) each cell type (except stem cells of course) specialises in expressing only one set of genes despite having the full copy of the genome. Furthermore, the genome is believed to contain the so-called "pseudogenes",[18] inactive and nonexpressible parts of the genome that are often thought of as an evolutionary artefact or "junk" with no functional purpose.[19] The term is admittedly provisional and debatable as "noncoding" DNA accounts for about 90% of the human genome and, for one instance, can be a stored material with an unidentified function.[20,21] This may prove to be very important from the standpoint of nanodesign as the functional uncertainty of junk DNA as opposed to translated DNA can relate to structural alleviations observed for noncoding DNA structures; that is, the requirement for protein-coding DNA, which is read from one end to another, to be a linear molecule can be waived for noncoding DNA.

In turn, this implies that DNA architecture is intrinsically amenable to different topologies and shapes, the repertoire of which, as can be judged by the recent progress in DNA-based designs, seems to be inexhaustible.[22] Whether the latter is predisposed by Nature or is imaginatively artificial, designing novel DNA structures comes down, if not to the detailed understanding of DNA chemistry then to at least the visionary acceptance of its postulated architectural and hierarchical expressions. This is the departing point in any DNA nanodesign that once taken may be and is often overlooked in subsequent complexed and advanced examples.

2.1.1 Deoxyribonucleic

2.1.1.1 Building up in Two

DNA or deoxyribonucleic acid is a monodisperse polymer composed of three types of repeating units – carbohydrate (deoxyribose, pentose monosaccharide); heterocyclic base that can be one of four: adenine (A), cytosine (C), guanine (G) or thymine (T); and phosphate – that together make up one DNA monomer, nucleotide, Figure 2.1. Therefore, an alternative name for DNA commonly used as its chemical rather than biofunctional definition is polynucleotide. The sequence of phosphates and carbohydrates (sugars) coupled