

## 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,<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> Thus, assembling

biopolymer blocks such as proteins and nucleic acids at the subcellular level, often with a precision of a single nanometre,<sup>3</sup> 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.<sup>4</sup> 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.<sup>3,4</sup> 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.

## References

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