Into the fold

In spite of its promise, nanotechnology has seen little uptake among biologists. DNA origami may be able to avoid this fate.

Most methodological development in the life sciences occurs through improvements, modifications or combinations of existing techniques punctuated by rare game-changing developments. There is hope that nanotechnology will provide such groundbreaking new methods, but despite considerable promise it has had minimal impact on practicing biologists.

Recently there has been a lot of excitement among nanotechnologists and others about DNA origami. This method of producing DNA nanostructures, first described in 2006, uses DNA oligonucleotides as 'staples' to fold the 6,407-base-long strand of M13 bacteriophage single-stranded DNA scaffold into a two- or three-dimensional structure, as opposed to assembling nanostructures out of oligonucleotides alone, as in previous methods. This greatly simplifies the synthesis of DNA nanostructures and improves their yield manyfold, thus making it possible to create structures that would otherwise be impractical to make. The high yields help ensure the structures are not just curiosities but can be used as research reagents.

The fact that DNA nanostructures use a biological molecule as a building block instead of inorganic materials may make biologists more amenable to using them. And the relative ease of their synthesis should eliminate the high barrier of entry that has hindered adoption of other technologies. But despite the excitement and advantages of the technology it is still unclear what exactly these structures are good for.

DNA origami has delivered some intriguing proof-of-principle applications such as alignment of membrane proteins for nuclear magnetic resonance–based structure determination and programmed synthesis using molecular walkers on a DNA track. Targeted functionalization of DNA nanostructures for attachment of proteins or peptides could be used to network proteins and enzymes, create novel enzymatic activities or serve as artificial extracellular matrices.

But the technology and applications are still immature. Some of the applications being proposed by people unfamiliar with the limits of the technology, such as artificial antibodies, are probably unrealistic. Some researchers though are starting to apply the technique in comparatively straightforward and practical ways. The single-molecule biophysics community, for one, is taking notice of this technology, which may prove well suited for controlling the patterning or assembly of proteins for single-molecule studies.

In two papers in this issue researchers provide practical advice and solutions to help bring this technology closer to potential users. Dietz and colleagues provide a primer on DNA origami that includes basic background information, step-by-step guidelines for creating DNA nanostructures and pointers to helpful software. In a similar vein, Shih and colleagues describe how to adapt agarose gel–based electroelution for purifying DNA nanostructures with improved yield of intact structures. We hope these papers help lower the barrier for people to try DNA origami themselves.

Despite the advantages DNA origami offers for creating nanostructures, there is room for improvement. First, only one good scaffold is available. Different and longer scaffolds are needed for creating the larger and more complex nanostructures necessary for numerous applications.

Second, conjugation of functional groups to specific locations on DNA structures is required for many potential applications. But existing conjugation strategies are tedious, and a good general robust method is lacking.

Finally, although existing design software for DNA origami represents a huge advance over manual methods, the software still uses a bottom-up design process. This is fine for developers of the technique, but those who just want to create a specific structure will demand a top-down design solution that allows a user to define the final desired structure using a good graphical user interface, after which the software will tell them how to get there. Such software should define the necessary DNA sequences and provide a workflow—including functionalization steps—that ensures a properly folded structure with the correct functionalization. This will become increasingly important as structures become more complex.

With further development and strategic collaborations between DNA nanotechnologists and biologists—to help ensure optimal syntheses of technology with high-impact applications—DNA origami may make a productive transition from idealized *in vitro* settings to messy biological applications. This is crucial for bringing DNA origami into the fold with other important biological research methods.