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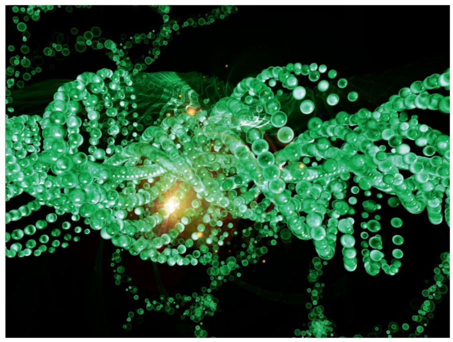
Unlocking biomolecular intelligence

Advances in DNA nanoengineering promise the development of new computing devices within biological systems, with applications in nanoscale sensing, diagnostics and therapeutics.

As nanotechnology emerged in the 1980s as a scientific field, researchers found inspiration in a bottom-up approach to designing machines, using molecules as building blocks[1]. After all, molecules and biomolecules can pack a large amount of functionality and processing power at the micro- or nanoscale. DNA has been a particularly promising candidate for designing molecular machines, as DNA molecules can be easily synthesized and modified to have specific functions and self-assembling properties. Logic circuits with DNA, based on sequence recognition and strand displacement, were demonstrated in 2006[2]. DNA origami, in which DNA units self-assemble into interesting nanomaterials with specific shapes and patterns, became a popular direction around the same time[3]. Recently, convolutional neural networks have been implemented in vitro using DNA strand-displacement circuits, which have been used to perform classification tasks[4]. As the field of DNA computing progresses, such classification capabilities might be deployed in the context of clinical diagnostics.

Various molecule-based smart devices have been proposed for applications in sensing, diagnosis and therapeutic delivery[5]. Inspiration can be found in nature, where biomolecular systems can sense dynamic environmental signals in complex environments, and, in response, activate regulatory



processes that are contingent on the timing of these signals. Implementing such functionality with artificially designed molecular machines is challenging, but one approach is to make use of the concept of a finite state machine (FSM), which is a model of computation used in fields such as mathematics, engineering and biology. An FSM is a device that can transition between a distinct number of states depending on the previous state and the present inputs. This enables FSMs to store and process information that depends on the sequence of events over time.

DNA lends itself well for building molecular FSMs, as it can be modified to take on various stable molecular shapes depending on specific interactions with the environment[6]. In a research Article in this issue of *Nature Machine Intelligence*, Zhao et al. present an innovative approach for a DNA-based FSM that is suitable for use within living cells. The authors' DNA FSM consists of two three-helix subunits that are connected to each other to form a six-helix nanotubular framework via four 'locks'. These locks can be opened, with a specific combination of signals, to produce five more possible different structural configurations. The FSM can reversibly switch between the six structural states in response to temporally ordered physiologically relevant inputs. Which configuration the DNA framework is in can be observed by fluorescence patterns.

As a proof of concept, Zhao et al. show that their DNA framework FSM can complete a task in the complex environment of a living cell, targeting a 'theranostic' application that integrates diagnosis and therapeutics. The authors show that their DNA machine can be used as a carrier for the controlled use of the gene-editing tool CRISPR–Cas9 to specifically attack tumour cells. With the multi-stage change in configuration after a specific sequence of several molecular cues, the DNA machine can release CRISPR–Cas9 with spatiotemporal precision.

The versatility of DNA nanoengineering offers the possibility to design smart devices with a range of structures and functionalities that can respond to signals at the cellular level. The area is already poised to have a considerable impact on healthcare and other industries[7]. Work at the interface between nanotechnology and machine learning, in combination with advances in molecular computing such as those proposed by Zhao et al., could tackle major scientific and technological challenges. Such interdisciplinary research could eventually unlock biomolecular machine intelligence, with the goal of addressing the complexity of nature at cell level with scientific ingenuity.

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