

Programming Biomolecular Self-Assembly Pathways

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Nature knows how to make proteins and nucleic acids (DNA and RNA) dance to assemble and sustain life. Inspired by this proof of principle, researchers at the California Institute of Technology have demonstrated that it is possible to program the pathways by which DNA strands self-assemble and disassemble, and hence to control the dynamic function of the molecules as they traverse these pathways.

The team invented a versatile DNA motif with three modular domains that can be made to interact with complementary domains in other species of the same motif. Rewiring these relationships changes the dynamic function of the system. To make it easier to design such systems, the researchers developed a graphical abstraction of the motif that can be used to write "molecular programs."

As described in the January 17 issue of the journal *Nature*, the team experimentally demonstrated the execution of four such programs, each illustrating a different class of dynamic function.

The study was performed by a team of four at Caltech: Niles Pierce, associate professor of applied and computational mathematics and bioengineering; Peng Yin, senior postdoctoral scholar in bioengineering and computer science; Harry Choi, graduate student in bioengineering; and Colby Calvert, research technician.

Programming pathways is a bit like planning a road trip. The final destination might be important, but the true enjoyment is picking and

traveling the route. In the test tube, the goal is not solely to direct the molecules to assemble into a target structure, but to engage them in a sequence of maneuvers so as to implement a prescribed dynamic function before the system reaches equilibrium. The energy to power the reactions is stored in the molecules themselves. Each molecule is initially trapped in a high-energy state so that it can release this energy as it engages in handshakes with other molecules.

A molecular program is written and executed in four steps. First, the intended assembly and disassembly pathways are described using a graphical abstraction called a "reaction graph." This molecular program is then translated into molecular mechanisms described at the level of base pairing between individual complementary bases. Computational design algorithms developed in the group are then used to encode this mechanism into the DNA sequences. Finally, the program is executed by mixing the physical molecules.

To demonstrate this approach, the team experimentally demonstrated a variety of dynamic functions: catalytic formation of branched junctions, cross-catalytic circuitry with exponential system kinetics, triggered dendritic growth of molecular "trees," and autonomous locomotion of a molecular bipedal walker.

As Pierce describes it, these results take them closer to achieving a long-term goal of creating a "compiler for biomolecular function"--an automated design tool that takes as input a molecular program and provides as output a set of biomolecules that execute the desired function. He remarks, "It's about time for the stone age of molecular compilers to begin."

Source: Caltech

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