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ACKNOWLEDGMENTS

We thank S. Scheres and X. Bai for cryo-EM advice; G. McMullen, C. Savva, J. Grimmert, and T. Darling for technical support; S. Leech for fresh pig brains; V. Bélissent-Edmands for assistance with proteomic analysis; S. Bullock, J. McKee, and J. Perillo for comments on the manuscript; and Y. Toshima for sharing her unpublished negative-stain EM model of the p60kD projection, which helped us to interpret our observations. This work was funded by the Medical Research Council, UK (MC_UP_4025_011), and a Welcome Trust New Investigator Award (WT100387). Cryo-EM maps are deposited with the Electron Microscopy Data Bank (EMD-2854, EMD-2855, EMD-2856, EMD-2857, EMD-2860, EMD-2861, and EMD-2862), and coordinates are deposited with the Protein Data Bank (5AF1, 5AFU, and 5AFL4). Author contributions: L.U. prepared dynactin and determined the TDB structure; M.G. and S.H. performed the cryo-EM data collection; L.U. developed the multidomain model; and D.W. performed the X-ray crystallography data collection.

SUPPLEMENTARY MATERIALS

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SCIENCE

Dynamic DNA devices and assemblies formed by shape-complementary, non-base-pairing 3D components

Thomas Gerling, Klaus F. Wagenbauer, Andrea M. Neuner, Hendrik Dietz

We demonstrate that discrete three-dimensional (3D) DNA components can specifically self-assemble in solution on the basis of shape-complementary and without base pairing. Using this principle, we produced homo- and heteromultimeric objects, including micrometer-scale one- and two-stranded filaments and lattices, as well as reconfigurable devices, including an actuator, a switchable gear, an unfoldable nanoblock, and a nanorobot. These multidomain assemblies were stabilized via short-ranged nucleobase stacking bonds that compete against electrostatic repulsion that impede the components’ interfaces. Using imaging by electron microscopy, ensemble and single-molecule fluorescence resonance energy transfer spectroscopy, and electrotophoretic mobility analysis, we show how the balance between attractive and repulsive interactions, and thus the conformation of the assemblies, may be finely controlled by global parameters such as cation concentration and temperature and by an allosteric mechanism based on strand-displacement reactions.

T o form complexes with other molecules, proteins often interact via shape-complementary interfaces to select and constrain the position of binding partners (1, 2). Proteins also tend to form only fragile contact interac-

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programming the structure and dynamics of higher-order complexes via weak interactions in shape space. More rarely, nucleic acid molecules can bind through weaker interactions than base pairing. Such recognition occurs between ribonuclease P (RNase P), an RNA-based enzyme, and its substrate, pre-transfer RNA (tRNA), which undergoes cleavage of its 5′ leader strand to yield mature tRNA (27). Here, we imitate the principle by which RNase P recognizes tRNA using programmable self-assembly with DNA (4–12) to produce discrete, shape-complementary three-dimensional (3D) components that interact via short-ranged, nucleobase stacking bonds. We present three means for actively influencing the conformation of objects once assembled: (i) changing cation concentration; (ii) changing solution temperature; and (iii) a site-directed allosteric mechanism based on toehold-mediated strand displacement reactions (13–20). With our method, a designer can encode a diversity of readily reconfigurable DNA devices and assemblies based on simple geometrical considerations and without having to program detailed strand sequences for connecting components.

In the system that inspired our assembly strategy, RNase P forms a particular tertiary fold that contains two structurally separated regions: one that scaffolds the active site and another that binds and orients the tRNA substrate (21) (Fig. 1A). Specifically, the acceptor stem and the T loop of tRNA appear to “click” precisely into a correspondingly shaped binding pocket in RNase P where they are held in place by a few nucleobase stacking interactions with the S domain of RNase P (Fig. 1A) (21). Together with the finding that edge-complementary single-layer DNA objects can interact specifically via DNA blunt-end stacking interactions on 2D substrates (22–24), we hypothesized that stacking interactions might suffice to stabilize 3D higher-order complexes made from multilayer DNA objects in solution.

**Motif design**

We thus abstracted and translated the type of shape recognition RNase P shows for tRNA to the

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**Fig. 1. Translating nonhybridization-based shape recognition principles from natural RNA to synthetic DNA objects.** (A) Illustration of the mechanism by which RNase P (blue and gray) recognizes tRNA (red and gray). Red: T-loop and the acceptor stem of tRNA. Blue: the shape-complementary binding pocket in RNase P. Yellow: interfacial nucleobases that interact through stacking interactions when tRNA binds to RNase P. The images were prepared with UCSF Chimera (28) based on the atomic coordinates listed in 3Q1R.pdb (29). (B) Schematic representation of RNase P–inspired shape recognition between complementary DNA components. Cylinder elements indicate double-helical DNA domains that are one helical turn long. (C) Schematic representation of four shape-complementary, orthogonal multilayer DNA origami bricks. Double-helical DNA domain protrusions are highlighted in red; recessions are shown in blue. Asymmetrical features are indicated in dark gray. Arrowheads indicate asymmetrical features along the helical and along the honeycomb pattern, respectively. Models are tilted such that the shape-complementary patterns for forming dimers AB and CD, and tetramer ABCD, are visible. AB and CD dimers thus show the faces of bricks B and C, respectively, that are not visible in the monomer models above. (D) Average negative-stain TEM micrographs of the self-assembled DNA tetrameric object ABCD in the presence of 25 mM MgCl$_2$. Black and gray arrowheads highlight the density from the designed asymmetrical features, as indicated above in (C). Scale bar, 20 nm. (E) Schematics of a switch object with one rotational degree of freedom in the open and closed conformations. Shape-complementary DNA double-helical domain protrusions and recessions are highlighted in red and blue, respectively. (F) Average negative-stain TEM micrographs of switch particles. Left: open state as populated in the presence of 5 mM MgCl$_2$. Right: two orthogonal transmission projections of the closed state, which is adopted in the presence of 25 mM MgCl$_2$. Scale bars, 20 nm.
Fig. 2. Reversible reconfiguration of shape-complementary DNA objects by changes in cation concentration or temperature and with a site-specific allosteric control mechanism. (A) Schematics of the switch object in the open and closed conformations, as in Fig. 1E. Arrows indicate positions of the organic dyes Atto550 and Atto647n, respectively, that were installed to enable a FRET-based readout of the conformation of switch ensembles in solution. (B) Ensemble FRET measured via donor quenching when titrating the concentration of MgCl$_2$ in solutions containing switch variants. Triangles: a variant with three-base-long hybridization bonds instead of stacking bonds at 16 sites. Circles and diamonds: variants with 16 or 12 possible stacking bonds in the closed state, respectively. Hexagon: a variant that cannot form stacking bonds to stabilize the closed state. The titrations were performed each in triplicate; error bars are the SD from the mean value. Solid lines: fit using a two-state model with a free-energy term that depends linearly on the cation concentration. The free energy changes by $-0.36$ and $-0.42$ kcal/mol per 1 mM MgCl$_2$ added for the versions with 12 and 16 designed stacking contacts, respectively. See fig. S35 for data obtained when titrating NaCl. (C) Temperature-dependent ensemble FRET measurements in solution, acquired for three switch variants. Triangles indicate the variant with hybridization bonds as in (B); squares indicate a static switch variant that is locked in the open state (see fig. S34); circles denote a gel-purified dynamic switch version with 16 stacking interactions. Solid line: two-state model fit with parameters $\Delta H = 46.2$ kcal/mol and $\Delta S = 0.146$ kcal/(mol·K). (D) Absolute intensity (in units “counts”) of the acceptor dye emission upon donor dye excitation (no normalization) as measured during 1020 cycles of temperature jumping with 3-min-long dwells at 25° and 50°C for the switch version with 16 stacking interactions [circles in (B)]. High-intensity levels at 25°C correspond to >90% of closed switches, and low-intensity levels at 50°C to <10% closed switches, as observed by TEM imaging. The experiment was performed in the presence of 11 mM MgCl$_2$ in solution. (Inset) Negative-stain TEM images acquired from samples fixated at 25°C and fixated at 50°C. See methods section. Scale bars, 50 nm. (E) Schematics of allosterically active switch objects. Insets highlight single-stranded DNA loops that were installed in the vicinity of the shape-complementary beam interfaces. A*$_t$ and A$_t$ denote DNA single strands. A*$_t$ is complementary to the single-stranded loops on the switch and features an additional nine-bases-long toehold motif. A$_t$ is fully complementary to A*$_t$ and can be used to displace A*$_t$ again from the switch. (F) Time-resolved ensemble FRET measurements with allosterically active switch objects. Absolute acceptor emission intensity upon donor excitation was normalized to the acceptor emission upon direct excitation to compensate dilution effects. Phase I: switch particles were equilibrated in 45 mM MgCl$_2$. The high FRET level corresponds to switch particles in the closed state, as corroborated by direct TEM imaging. Phase II: A*$_t$ was added to the solution. The FRET signal drops to levels consistent with switch opening. Phase III: A$_t$ was added to the solution. The FRET signal increases again to the original high FRET levels. Light gray: experiment performed with A*$_t$ and A$_t$ at 50 and 100 nM effective concentration, respectively. Dark gray: A*$_t$ and A$_t$ at 0.4 and 0.8 μM effective concentration. Solid lines: fit according to a bimolecular reaction model with zero off-rate and equimolar reactant concentrations. Phase II: on-rate = $3.1 \times 10^4$ 1/(M·s); phase III: on-rate = $0.7 \times 10^4$ 1/(M·s). (Insets) Average TEM micrographs acquired from samples in the respective phases. Scale bars, 20 nm.
arena of DNA molecules. Blunt-ended double-helical DNA protrusions on one domain assume the role of the tRNA acceptor stem, and corresponding recessions on another domain mimic the RNase P binding pocket (Fig. 1B). Nucleobase stacking interactions engage at the double-helical inter-
faces of the shape-complementary protrusions and recessions when the two domains are brought into contact, but only upon correct fit of the helices and given correct helical orientation of the interfacial nucleobase pairs. We used these building blocks in a combinatorial fashion (Fig. 1C) to create libraries of shape-complementary motifs. Shape-complementary partners will be accepted and precisely oriented, but noncomplementary binding partners will be sterically rejected.

To illustrate the shape selectivity and the ability of our recognition scheme to constrain the

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**Fig. 3. Self-assembly of higher-order non–base pairing shape-complementary DNA objects, demonstrating long-range order, ability to template multimerization geometries by shape, and reconfigurability.** (A) Schematic representation of filaments formed by cation-dependent reversible multimerization of a self-complementary multilayer DNA origami brick. (B) Negative-stain TEM micrographs showing typical filaments that grow in the presence of 25 mM MgCl$_2$. When the cation concentration is reduced to 5 mM MgCl$_2$, the filaments fall apart (top right). Increasing the cation concentration to 25 mM MgCl$_2$ gives filaments again (bottom right). Scale bar, 50 nm. (C) Schematic representation of a multilayer DNA origami hexagon with shape-complementary patterns of protrusions and recessions. Averaged single-particle negative-stain TEM micrographs of the hexagon in different views were acquired at 10 mM MgCl$_2$. Scale bar, 50 nm. (D) Schematic representation of a reconfigurable lattice formed by 2D polymerization of the hexagon and a typical negative-stain TEM micrograph acquired in the presence of 38 mM MgCl$_2$. Scale bar, 50 nm. (E) Schematic representation of a two-stranded filament that is formed from a modified hexagon (see fig. S82) and negative-stain TEM micrographs acquired at 35 mM MgCl$_2$. Scale bar, 50 nm. (F) Left: schematic representation of reconfigurable lattices formed by 2D polymerization of dynamic switch particles with 16 stacking interactions (see fig. S87). Negative-stain TEM micrographs of switch lattices taken at 25 mM MgCl$_2$ in the closed state (left; scale bar, 50 nm), at 5 mM MgCl$_2$ in the open state (middle; scale bar, 50 nm), and after raising the cation concentration again to 25 mM in the closed state (right image; scale bar, 50 nm) (see figs. S88 to S90 for lower-magnification images).
position and orientation of individual DNA objects within larger complexes, we designed four multilayer DNA origami bricks (Fig. 1C and figs. S1 to S7) that form the subunits of a tetrameric complex. The embossed surface of brick A fits precisely into the recessed surface of brick B and likewise for combinations of B with C and C with D. Bricks B, C, and D exhibit characteristic asymmetric features that helped identify their orientation when the bricks were imaged with transmission electron microscopy (TEM). Negative-stain TEM image data and an electrophoretic mobility analysis confirmed the successful assembly of the designed overall bricklike objects (fig. S7, A and B), as well as the self-assembly into all possible multimeric complexes as they are prescribed by the designed shape complementarity, including dimers, trimers, and a tetramer (Fig. 1D; fig. S7, B to F; and figs. S8 to S21).

To illustrate the ability of the click-in shape recognition scheme for precisely defining conformational states within a multidomain DNA object, we designed a switchlike DNA object consisting of two rigid beams connected by a pivot (Fig. 1E and fig. S22). The switch can dwell either in an ensemble of open states or in a closed state. The structure of the closed state is prescribed by shape-complementary patterns of double-helical DNA domains that can click into each other when the two beams draw together (Fig. 1E, right).

Direct imaging by negative-stain TEM confirms that the switch adopts open and closed conformations, where the closed conformation is structurally well defined (Fig. 1F).

**Structural switching**

Our RNase P–inspired shape recognition scheme creates a layered hierarchy between intradomain stability and interdomain interaction because it is based on few nucleobase stacking interactions, rather than the many nucleobase pairing interactions that stabilize entire DNA objects. As in RNase P (25, 26), the conformational equilibrium of objects that utilize such shape-complementary interactions is sensitive to the concentration of counterions in solution because of repulsions between the negatively charged surfaces of the DNA binding partners. These two properties, the tiered interaction hierarchy and the repulsive interfaces, create rich opportunities for adjusting the conformational equilibrium, and changing it reversibly and rapidly, by global parameters such as cation concentration and solution temperature.

We test these options in detail using ensemble- and single-molecule fluorescence resonance energy transfer (FRET) experiments, as well as TEM imaging and electrophoretic mobility analysis performed as a function of cation concentration and temperature with the switch object and for a dimeric brick complex. For both the switch and the dimeric bricks, increasing the cation concentration shifted the conformational equilibrium from the open or monomeric states to the closed or dimeric states, respectively (Fig. 2, A and B, and figs. S12 to S14, S23 to S25, S29 to S30, and S30, A and B). This process occurred in the presence of both monovalent and divalent cations, but only when attractive stacking bonds or even stronger hybridization-based interactions were included (Fig. 2B, supplementary text S1, and figs. S23, B to C, and S31 to S41), thus pointing against unspecific counterion-induced condensation effects. The transitions were reversible upon cyclic changes in the concentration of cations (fig. S23E).

The isotherms generated by cation titration agreed well with the predictions of a two-state model with a free-energy term that depends linearly on the concentration of cations (Fig. 2B and fig. S30B). Single switch particles sample the designed open and closed states on the time scale of fractions of seconds (supplementary text S2 and figs. S23, F to I, and S41 to S49). Increasing the concentration of cations shifts the equilibrium toward the closed state by predominantly reducing the average time that the switch dwell in the open state (fig. S23I).

The greater the strength of the designed interaction between the shape-complementary interfaces of the switch, the lower the cation concentration necessary for stabilizing the closed state (Fig. 2B and fig. S23, B and C). In the switch version with 16 stacking bonds, the transition occurred over a narrow concentration interval ranging from 6 to 12 mM MgCl₂. For stronger hybridization-based interactions at all complementary sites instead of the minimal stacking

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**Fig. 4. Reversibly reconfigurable non–base pairing multistate DNA devices with arbitrary shapes.** (A) Top row: schematic representations of a reconfigurable gear in a fully open state (left), in a partially compacted intermediate state (center), and in a fully closed state (right). The states can be cyclically prepared by adjusting, e.g., the cation concentration. Bottom row: average negative-stain TEM micrographs of the gear, acquired at 100 mM MgCl₂ (left) and at 20 mM MgCl₂ (center and right). The cation-dependent operation principle opening or closing is reversed with respect to, e.g., the switch (Figs. 1 and 2) due to additional cation-dependent attractive surface interactions with the TEM support grid that “pull” the gear open. (B) Top row: schematic representation of a nanoblock in three states. Bottom row: averaged negative-stain TEM micrographs acquired at 5 mM (left) and at 50 mM (center and right) MgCl₂. (C) Schematic representation of a heterotrimeric reconfigurable nanorobot (15 MD) that can be reversibly reconfigured in three different conformational states: disassembled, and assembled with open or closed arms, respectively, by calibrating the concentration of cations in solutions. Average negative-stain TEM micrographs of the nanorobot were acquired in the presence of the indicated MgCl₂ concentrations. MgCl₂ concentration increase was achieved by adding MgCl₂ stock solution; concentration reduction was achieved by diluting with Mg-free buffer. (See figs. S99 and S100 for TEM images from a complete assembly, opening, closing, disassembly cycle.) (D) Top row: schematic representation of two shape-complementary multilayer DNA origami objects in square-lattice packing (all other objects in this work were honeycomb-lattice packing). Bottom row: average negative-stain TEM micrographs in two distinct views of the heterodimeric complex at 50 mM MgCl₂. Scale bars, 25 nm.
interactions, the transition shifted to the low cation concentrations where the open state could not be prepared without compromising the overall structural integrity of the switch (Fig. 2B and figs. S23, B and C, and S31 to S34). When we used hybridization-based interactions distributed over fewer sites across the beam interfaces, the possibility for shifting the equilibrium could be restored, but at the expense of a structurally less-well-defined closed state (figs. S59 to S69). Analogous observations were made for the brick system (figs. S59 to S67). Changing the temperature of solutions containing switch variants or the dimeric bricks could also reversibly shift the equilibrium from closed or dimeric states to open or monomeric states, respectively (Fig. 2C and figs. S23J, S30C, and S69). The ability to shift the equilibrium by temperature changes depended on the concentration of cations in solution (figs. S23K and S90C).

Temperature-jump experiments (Fig. 2D) highlighted the robust reversibility of our shape recognition scheme and the absence of structural or functional degradation. During the course of 4.25 days, a solution containing the dynamic switch with 16 stacking interactions was cycled 1020 times between 25°C (closed state) and 50°C (open state; Fig. 2D and figs. S69 and S70). Ensemble FRET signals were collected in 18-s intervals (total illumination time = 13 min). Upon heating and cooling, the FRET signals decreased and increased in a steplike fashion to levels corresponding to the open and closed states of the switch ensemble, respectively (Fig. 2D). These results imply rapid equilibration with a time constant of <4 s, which is consistent with the average lifetimes of the open and closed states determined at room temperature with single-particle FRET experiments (fig. S23I). The shape-complementary brick monomer-dimer equilibrium showed rapid dissociation upon temperature jumps to 50°C (figs. S30D and S71) but slower association upon jumping back to 25°C. The data were consistent with the equilibration dynamics of a dimerization reaction starting from monomeric states (fig. S30D, inset, and supplementary text S7).

Methods that rely on toehold-mediated DNA strand displacement can directly influence the conformation of DNA objects by creating or resolving double-helical DNA domains (8–15) that stabilize those conformations. Because our RNAase P–inspired recognition scheme relies on shape complementarity on the one hand, and because RNA origami objects are elastic macromolecular structures on the other hand, binding equilibria can now also be affected allosterically—that is, through deformations that follow from molecular binding events at distal sites. To show this possibility, we installed single-stranded DNA loops in the vicinity of the shape-complementary interfaces in the switch and in the dimeric brick objects (fig 2E and fig S30E, left). The hybridization of loop-complementary DNA “signal” strands deforms the shape-complementary interfacial patterns (Fig. 2E and fig S30E, right) and thus can inhibit the attractive interaction. By separating the “signal” strand from the loops via toehold-mediated strand displacement, the deformation was reversed, and the attractive interaction between the shape-complementary interfaces was restored. We demonstrated this mechanism using ensemble FRET experiments performed with the switch and the brick dimers (Fig. 2F and figs. S30F and S72 to S79). The transition kinetics that we observed is consistent with those found for toehold-mediated strand displacement reactions (27). Hence, our shape recognition scheme can also be coupled to the well-established strand displacement methods in DNA nanotechnology.

Applications

Several attractive opportunities are created by the possibility to self-assemble higher-order DNA objects using our shape recognition scheme. First, the position of binding partners may be constrained with sufficient rigidity to template long-range orientation, as seen in experiments with a self-complementary brick that self-assembled into homomultimeric filaments with apparently seamless integration of up to hundreds of monomers and absence of bending deformations up to the micrometer length scale (Fig. 3, A and B, left, and fig. S80).

Second, simply decreasing or increasing the concentration allows recovering of the constituent monomers or restoring the growth of filaments, respectively (Fig. 3B, right, and fig. S81). The ability to reversibly shrink and grow filaments is of interest for creating active materials and in polymerization-based propulsion applications.

Third, different higher-order objects may be created from a family of similar building blocks by using simple shape alterations and without having to design interfaces with specific DNA sequences. To show this possibility, we have designed a hexagonal multilayer DNA origami brick where the six faces feature recession and protrusion patterns such that opposing faces are pairwise complementary but noncomplementary to the other faces of the hexagon (Fig. 3C and figs. S82 and S83). The hexagon can be prepared as a monomer (Fig. 3C) and self-assembled into 2D hexagonal lattices by raising the cation concentration (Fig. 3D and fig. S84). We also altered the hexagon brick such that only four out of its six faces could participate in shape-complementary stacking interactions, where two opposing hexagon faces may interact with each other and also two neighboring faces may interact, but only when rotating one binding partner around its short axis by 180° (Fig. 3E and fig. S85). This design modification caused the hexagon bricks to self-assemble specifically into two-stranded filaments (Fig. 3E and fig. S86). Natural two-stranded filaments such as actin also self-assemble from a single monomer and offer interesting properties such as nucleated growth and a superior length-to-monomer concentration ratio as compared to single-stranded filaments.

Fourth, nanoscopic changes in the geometry of individual building blocks may also be amplified up to the micrometer scale, which is an important step in creating synthetic assemblies that could attain the high level of structural integration of active components seen in biology, such as in muscle tissue. We polymerized a variant of the dynamic switch from Figs. 1 and 2 into 2D lattices, using hybridization-based interactions. These lattices contained up to 1000 switch particles (Fig. 3F and figs. S87 to S90) arranged in a regular fashion. The lattices could be reversibly expanded and contracted simply by decreasing and increasing the concentration of cations in the solution, respectively.

Finally, we illustrate the opportunities for creating various reversibly reconfigurable DNA devices with arbitrary shapes when using our shape recognition scheme. We designed and self-assembled a reconfigurable gear that can be switched between a pinionrack-like shape and a gearlike shape (Fig. 4A and figs. S91 and S92). We also designed a reconfigurable nanobook that can reversibly fold and unfold (Fig. 4B and figs. S93 to S95). As for all other objects shown in this work, the conformational equilibrium of the reconfigurable gear and the nanobook can be adjusted by the cation concentration in solution. Both devices provide starting points for objects that can serve encapsulation purposes. In addition, we produced a heterotrimeric 15 MD complex comprising three asymmetric subunits that assemble specifically on the basis of shape recognition (Fig. 4C and figs. S96 to S100) to form a nanorobot. Two modules form the robot's torso, and one module forms its legs. The torso modules each feature an armlike domain hooked up to a shoulderlike protrusion via a pivot similar to the pivot in the switch. The arms can switch between open and closed states, where the closed states are stabilized by shape-complementary stacking bonds between the forearm and the hip of the robot. We used cation concentration as a control parameter; a designed hierarchy of strengths between the various stacking bonds within the robot allows it to be tasked to self-assemble, open its arms, close its arms, split up into its modules, and reassemble (Fig. 4C). We controlled the sequence of events by the temporal pattern of cation concentrations.

Taken together, the methods put forward herein provide ready access to a diversity of dynamic DNA-based devices and assemblies. By simply considering geometry in 3D space, as exemplified here with differently shaped multilayer DNA origami objects in honeycomb-lattice packing as well as square-lattice packing (Fig. 4D and figs. S101 to S103), and minimized nucleobase stacking interactions as a universal molecular glue, a designer can encode complex higher-order objects and also dynamic objects in DNA sequences (see movies S1 to S7).

Discussion

In computer science, high-level languages use an interpreter to enable the creation of complex software without having to deal with detailed machine code. By analogy, DNA sequences may be considered as the machine code used to create structural modules. Our shape recognition method expands the palette of potential interactions for
DNA-based nanotechnology and adds a layer of abstraction in which components may be treated conceptually as objects that interact in shape space, rather than in sequence space. This property enables the design on a higher structural level without having to program the detailed DNA strand sequences for connecting components. We anticipate that our findings will help in creating dynamic macromolecular devices and assemblies as scaffolds for various purposes. Specifically, we envision potential applications in advanced therapeutics, biosensing, active plasmonics, and responsive nanoscale assemblies as scaffolds for various purposes. We thank E. Stahl, T. Martin, I. Furke, M. Schickinger, F. Kliuchir, C. Wachau, L. Meregalli, and V. Hechtl for technical assistance.

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Supplementary Materials

www.sciencemag.org/content/347/6229/1464/suppl/DC1

CONFIRM no competing financial interests. The data reported in this paper are tabulated in the supplementary materials.

The existence and stability of atoms rely on the fact that neutrons are more massive than protons. The measured mass difference is only 0.14% of the average of the two masses. A slightly smaller or larger value would have led to a dramatically different universe. Here, we show that this difference results from the competition between electromagnetic and mass isospin breaking effects. We performed lattice quantum-chromodynamics and quantum-electrodynamics computations with four nondegenerate Wilson fermion flavors and computed the neutron-proton mass-splitting with an accuracy of 300 kiloelectron-volts, which is greater than 0 by 5 standard deviations. We also determine the splittings in the \( S, S', D, \) and \( \Xi_{cc} \) isospin multiplets, exceeding in some cases the precision of experimental measurements.

The Standard Model of Particle Physics is a \( SU(3) \times SU(2) \times U(1) \) gauge theory with massless fermions. During the expansion of the early universe, the Higgs mechanism broke this symmetry down to \( SU(3) \times U(1) \), and elementary particles acquired masses proportional to their couplings to the Higgs field. As the universe continued to expand, a QCD transition took place, confining quarks and gluons into hadrons and giving those particles most of their mass. This same theory today is believed to be responsible for the tiny isospin splittings, which are the subject of this paper. At the level of precision that we aim for here, the effects of the weak interaction, of leptons, and of the two heaviest quarks can either be neglected or absorbed into the remaining parameters of the theory. The resulting theory is one of \( u, d, s \), and \( \epsilon \) (up, down, strange, and charm, respectively) quarks, gluons, photons, and their interactions. The

drogen than it did in our universe. As a result, stars would not have ignited in the way they did. On the other hand, a value considerably larger than 0.14% would have resulted in a much faster beta decay for neutrons. This would have led to far fewer neutrons at the end of the BBN epoch and would have made the burning of hydrogen in stars and the synthesis of heavy elements more difficult. We show here that this tiny mass splitting is the result of a subtle cancellation between electromagnetic and quark mass difference effects.

The mass of the universe is a consequence of the strong interaction (\( S \)), which is the force that binds together quarks into protons and neutrons. To establish this with percent-level accuracy, very precise calculations based on the lattice formulation of quantum chromodynamics (QCD), the theory of the strong interaction, were needed. Going beyond such calculations to control much finer effects that are at the per mil (\( \% \)) level is necessary to, for instance, account for the relative neutron-proton mass difference, which was experimentally measured to be close to 0.14% (2). Precisely, this difference is needed to explain the physical world as we know it today (3). For example, a relative neutron-proton mass difference smaller than about one third of the observed 0.14% would cause hydrogen atoms to undergo inverse beta decay, leaving predominantly neutrons. A value somewhat larger than 0.05% would have resulted in the Big Bang Nucleosynthesis (BBN), producing much more helium-4 and far less hydrogen than it did in our universe. As a result, stars would not have ignited in the way they did. On the other hand, a value considerably larger than 0.14% would have resulted in a much faster beta decay for neutrons. This would have led to far fewer neutrons at the end of the BBN epoch and would have made the burning of hydrogen in stars and the synthesis of heavy elements more difficult. We show here that this tiny mass splitting is the result of a subtle cancellation between electromagnetic and quark mass difference effects.

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Science 347, 1446 (2015);
DOI: 10.1126/science.aaa5372

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