Graph theoretical tools for DNA self-assembly

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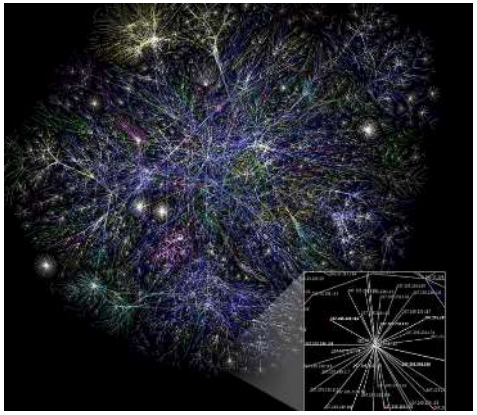
New applications ⟶ New mathematics

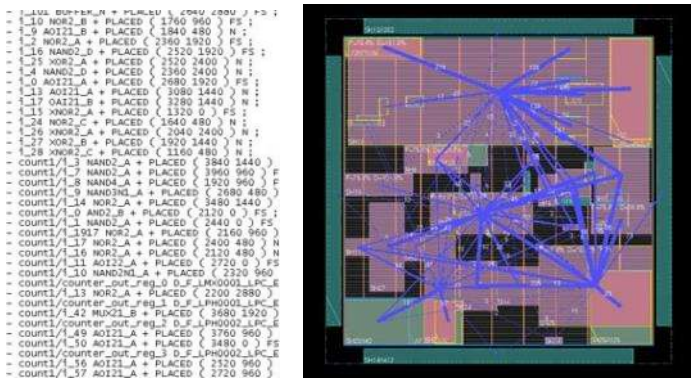


https://en.wikipedia.org/wiki/Random_graph

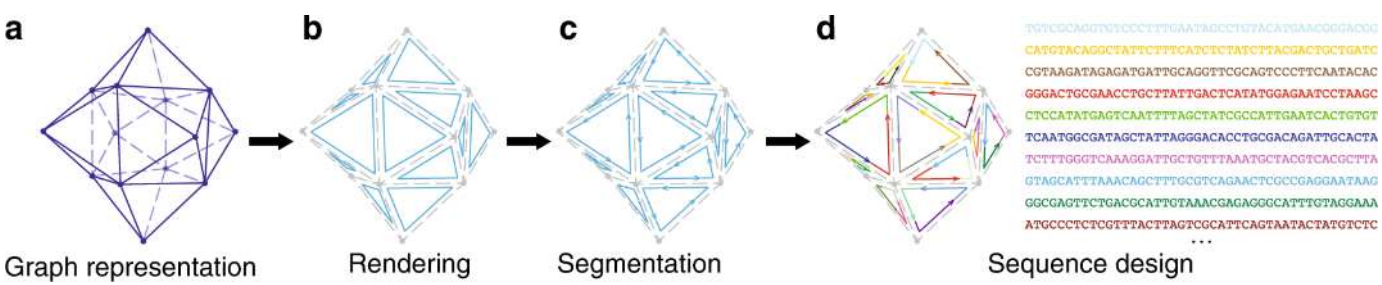
Internet ⟶

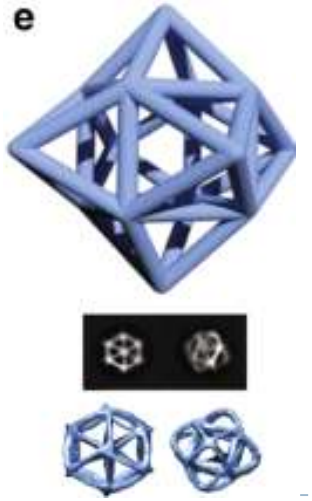
Random Graphs

VLSI ⟶ Graph Drawing



https://www.nature.com/articles/s41467-019-08647-7

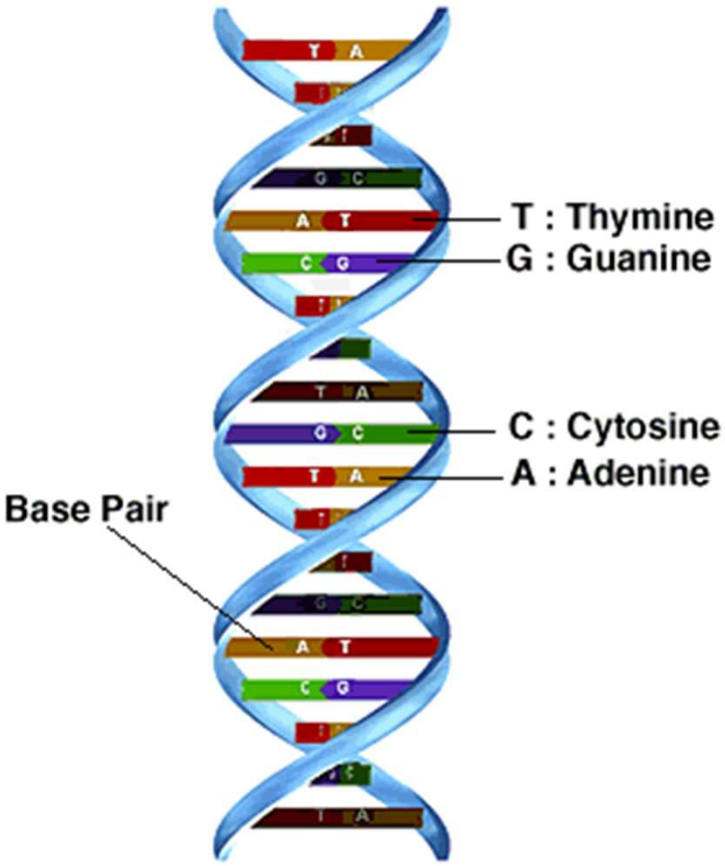




Self-assembly ⟶ Graphical Assembly Design.

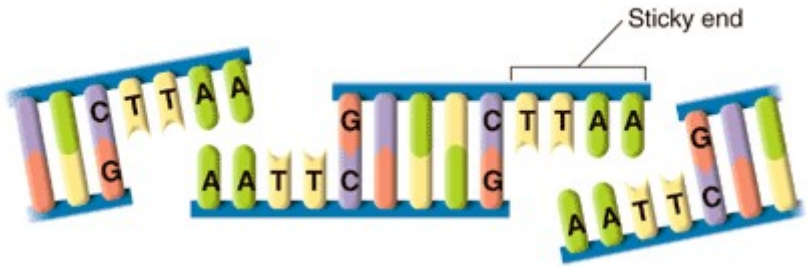
Remember how DNA works:

In Nature

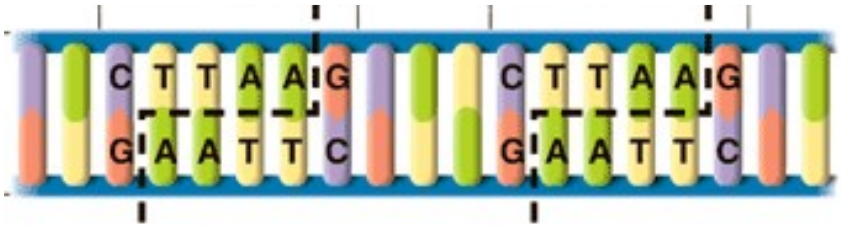


In The Lab

Create fragments of DNA with carefully designed 'sticky ends', or unsatisfied bases.

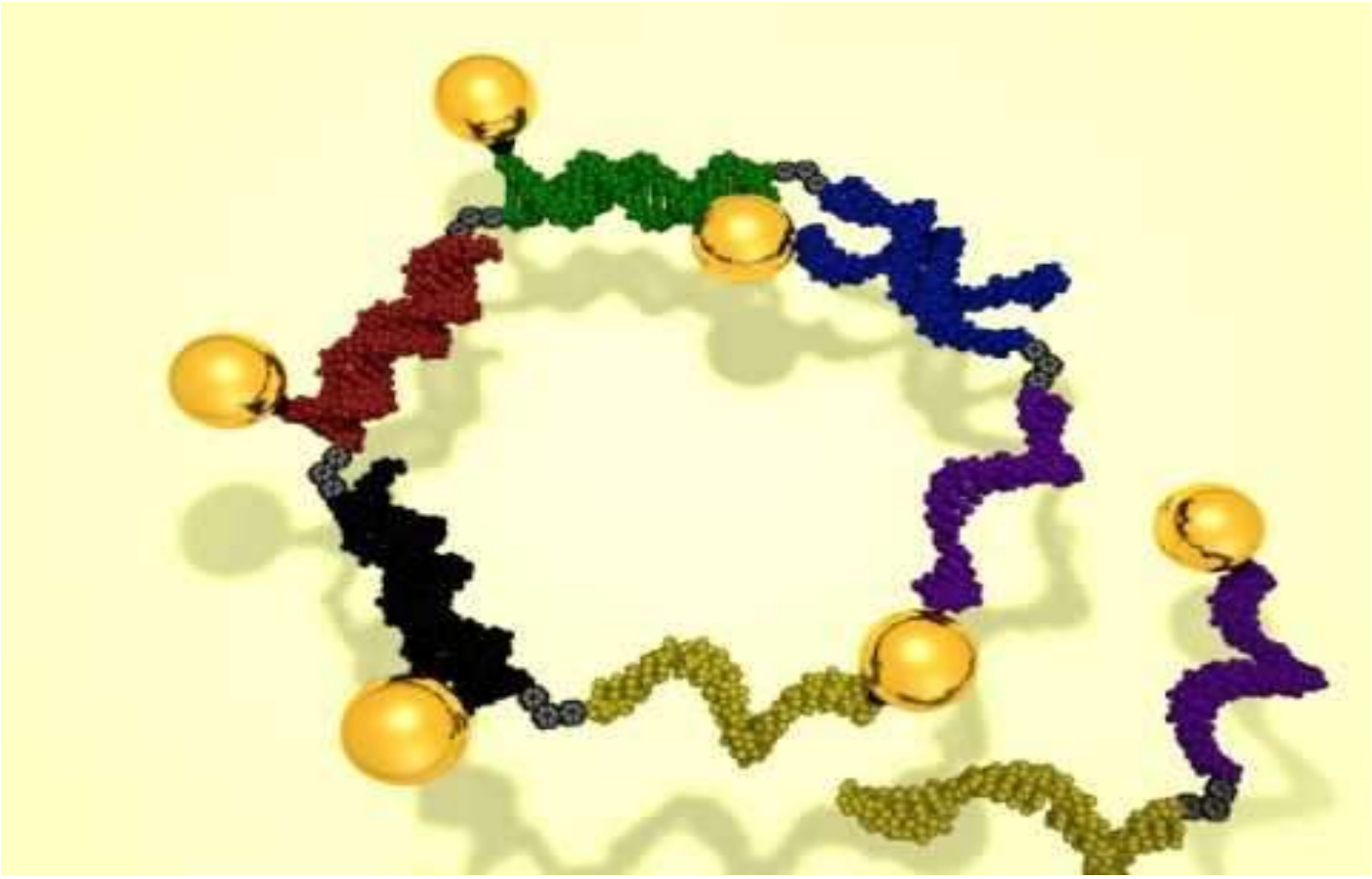


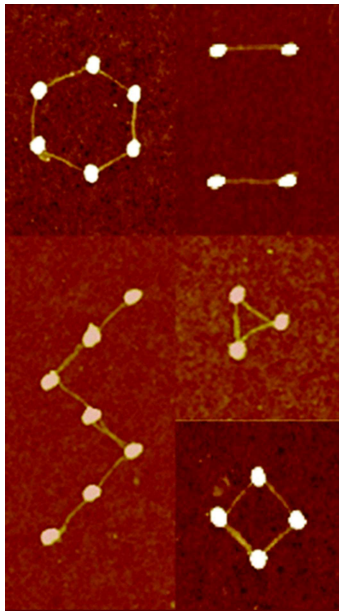
These will stick to each other, self-assembling into the target structure.



DNA self-replicates, so can create more and more of the targets.

Controlling shapes with engineered DNA



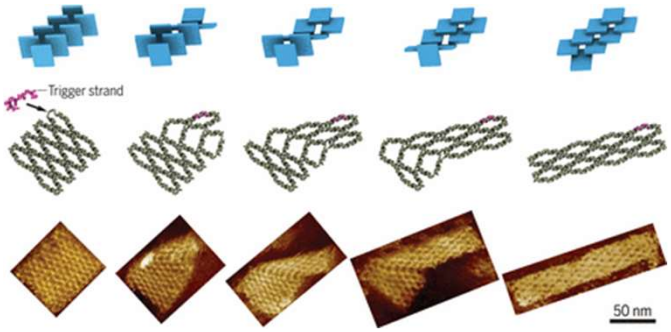


Nano Lett., 2010, *10* (12), pp 5065–5069

http://www.youtube.com/watch?v=6_ewP22n2mg&feature=related

Why self-assembling nanostructures?

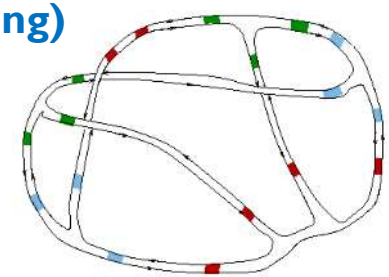
Nano-robotics



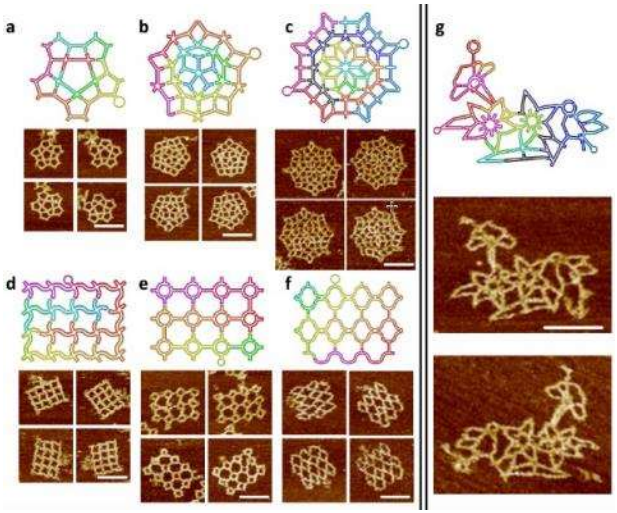
Reconfiguration of DNA molecular arrays driven by information relay. Song, Li, Wang, Mayer, Mao, Ke
Science 28 Jul 2017: Vol. 357, Issue 6349

Biomolecular computing (Hamilton Cycle/3-Sat/Graph Coloring)

http://shell.cas.usf.edu/~jonoska/bio-comp/node4.html

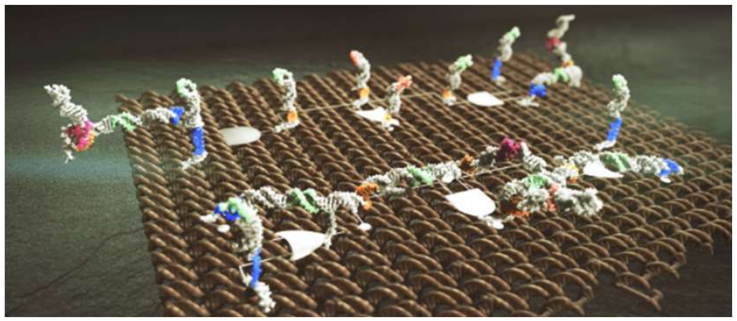


Nano-scale meshes and filters



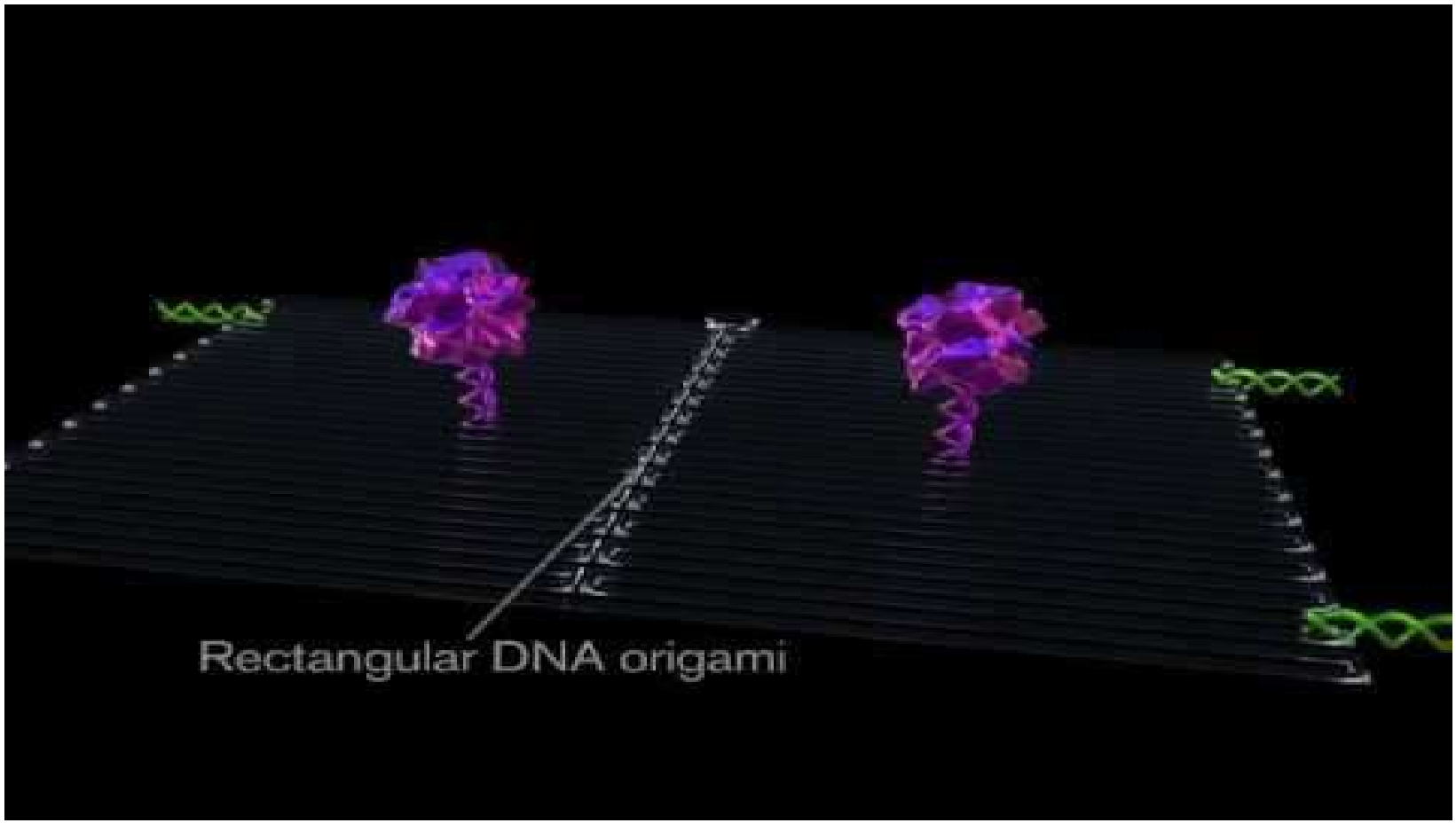
Complex wireframe DNA origami nanostructures with multi-arm junction vertices. Zhang, Jiang, Wu, Li, Mao, Liu, Yan. *Nature Nanotechnology* volume10, pages 779–784 (2015)

Nano-circuitry



https://www.microsoft.com/en-us/research/blog/researchers-build-nanoscale-computational-circuit-boards-dna/

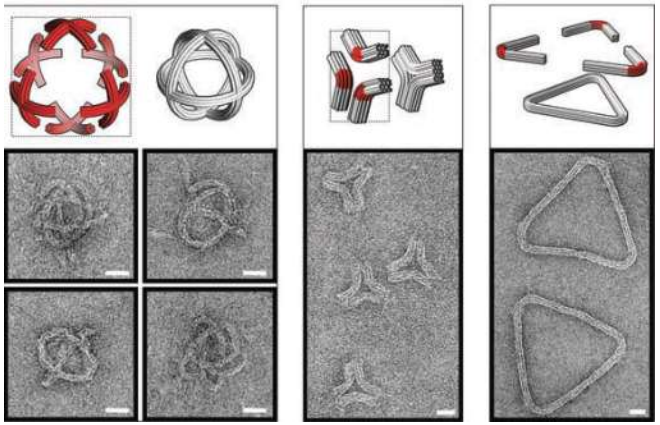
How might this work in the body?



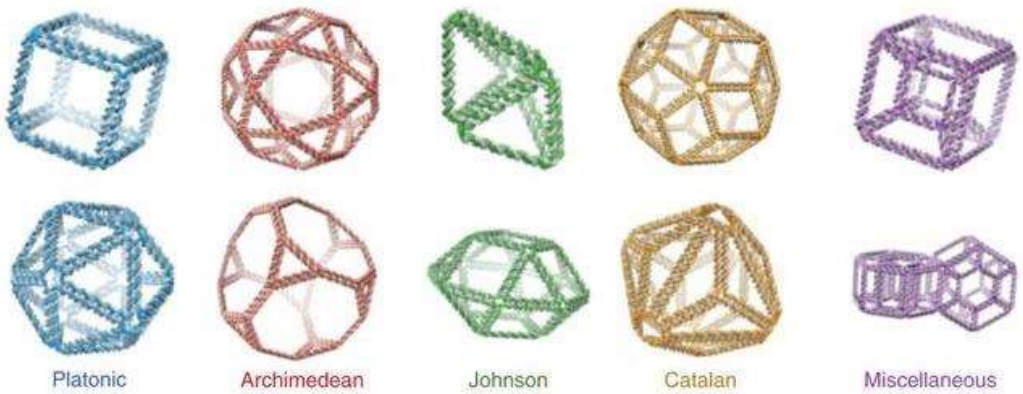
Targeted Drug Delivery

https://www.eurekalert.org/multimedia/pub/162624.php

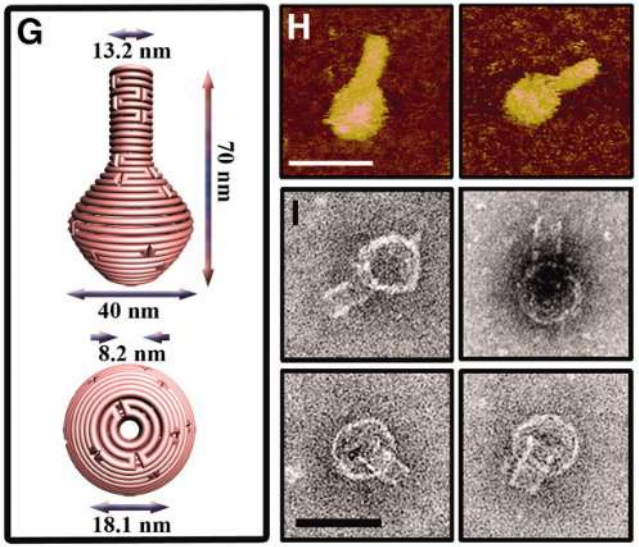
Some state of the art (3D) DNA nano-objects



Dietz, Douglas and Shih, Science, 325, 725



Linko, Kostiainen. Nature Biotechnology volume34, pages826–827 (2016)



Han, Pal, Nangreave, Deng, Liu, and Yan, Science, 333, 342

Benson, Mohammed, Gardell, Masich, Czeizler, Orponen , Högberg. Nature 523, 441–444 (23 July 2015)

Our Objectives

Create new mathematical and computation tools for laboratories producing self-assembled DNA nanostructures.

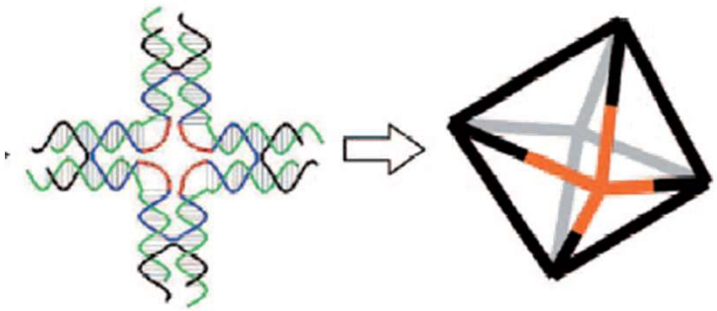
- Several assembly paradigms:

  Tile-based assembly ◆ DNA origami ◆ Reporter strands

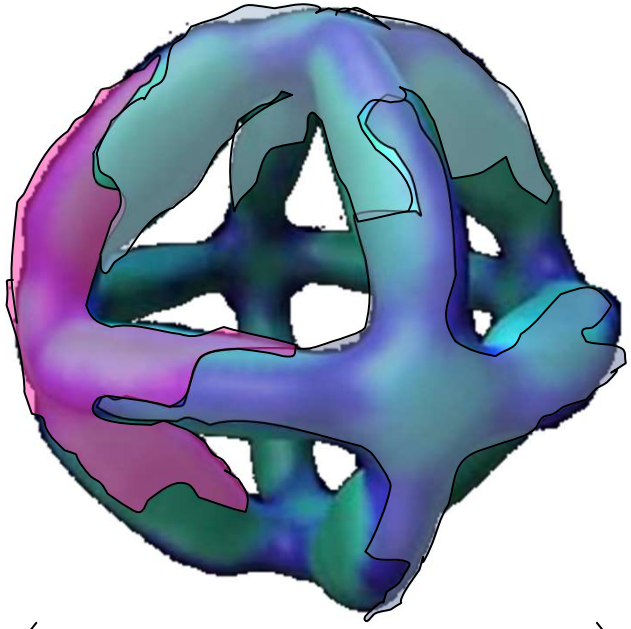
- For each assembly method, usually we get:
  - Problem formulation and mathematical formalism
  - Proofs that design strategies are NP-Hard
  - Pragmatic approaches
  - New mathematical directions arising from the problem

Branched Junction Molecules

A self-assembled octahedron



http://onlinelibrary.wiley.com/doi/10.1002/anie.200904513/pdf



22 nanometers

http://www.scripps.edu/news/press/2004/021104.html

A visualization model

https://www.youtube.com/watch?v=X-8MP7g8XOE

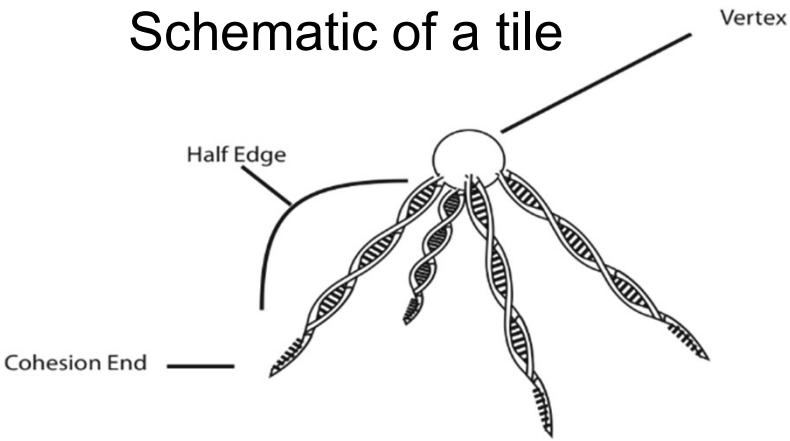
Short and long

https://gulfspecimen.org/specimen/echinodermata/brittle-stars-and-serpent-stars/

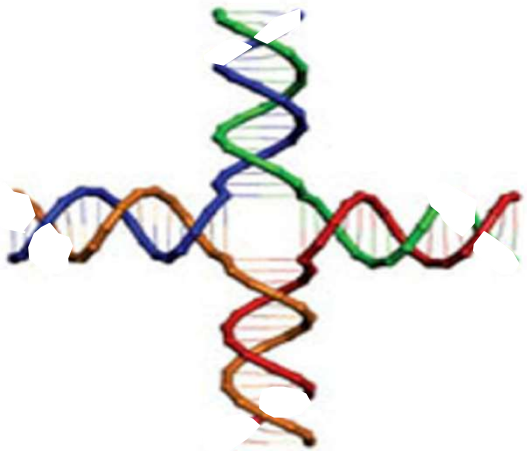
https://www.flickr.com/photos/edbierman/7383798192/

What is a tile?

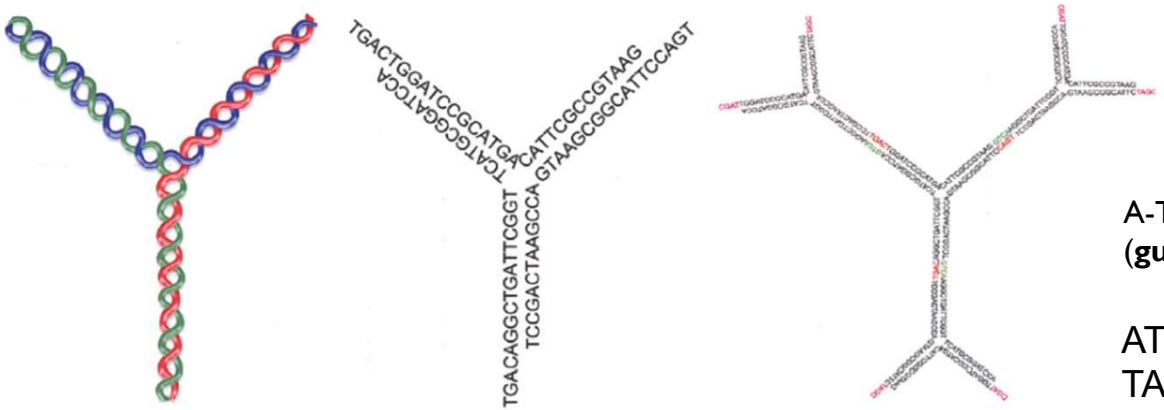
Schematic of a tile



The branched junction molecule



With the bases specified



A-T (**adenine - thymine**) and G-C (**guanine - cytosine**).

ATTCG GGTAACATTCG
TAAGCCCATTG TAAGC

Y-shaped DNA. Schematic diagrams of the structure (left) and sequence (middle) of Y-DNA, and dendrimer-like DNA (right).

D. Luo, "The road from biology to materials," Materials Today, **6** (2003), 38-43

Combinatorial formulation

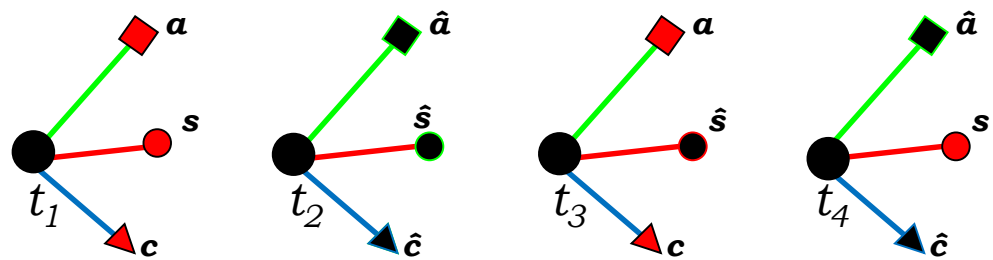
a $\hat{a}$

ATTCG GGTAACATTCG

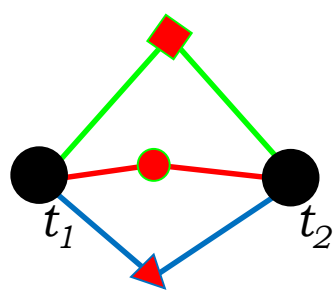
TAAGCCCATTG TAAGC

Both complete complexes and incomplete complexes can be constructed from the this pot P with 4 tiles:

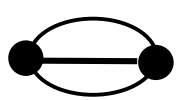
A *pot* P:

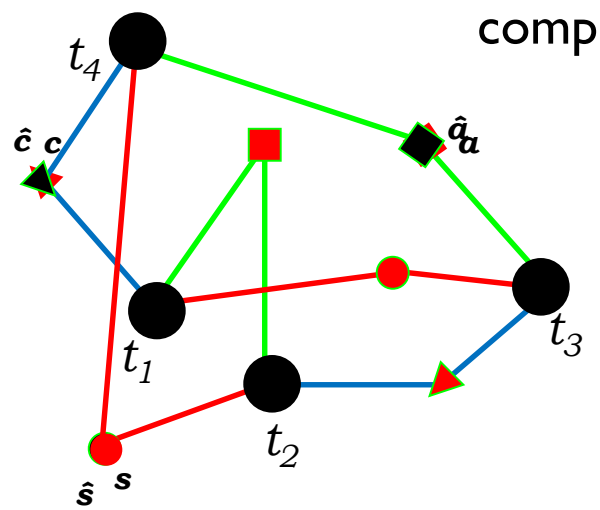


The labs generally want complete complexes

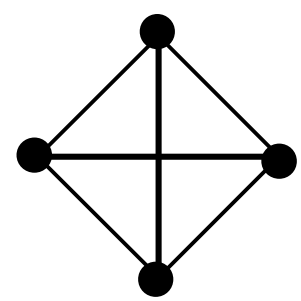


Complete complex



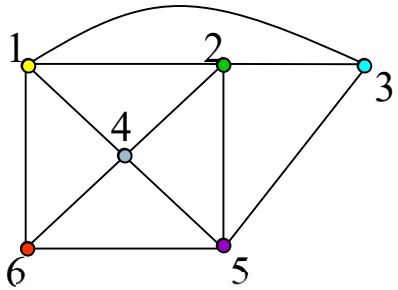


Incomplete complex



Different paradigms:

- Abstract graphs
  - E.g. only care about the connectivity of nodes and edges, not physical location
  - Examples: graphs for biocomputation of colorability.



- Geometric graphs
  - Specific embeddings in space
  - Examples: skeletons of Platonic or Archimedian solids, or crystallographic lattices.

- Constraints
  - The incidental assembly of graphs smaller than the target is acceptable
  - Any graph incidentally assembled must be larger than the target

New graph invariants in each setting

Given a graph G,

1. what is $T(G)$, the minimum number of k-armed branched junction molecules (tiles) that must be designed to create the graph?
2. What is $B(G)$, the minimum number of bond types (size of alphabet) needed?

For *rigid* tiles, description of the pot must also specify the geometric structures of each tile.

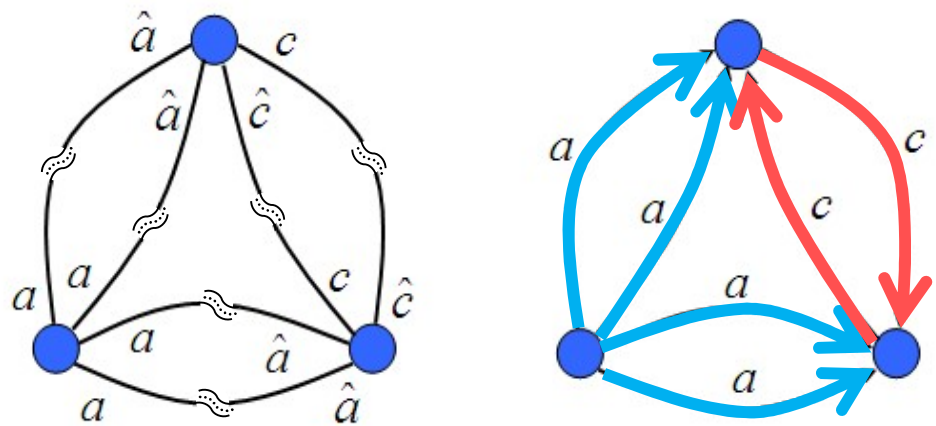
Branched junction methods

- Objectives:
  - Given a graph *G*, find an optimal pot *P* that realizes *G*, *i.e.* minimize the number of branched junction molecules required to assemble the target structure and give their combinatorial specifications.
  - Given a pot *P*, find the set of graphs (up to isomorphism) realized by *P*.
- In both cases need:
  - General theory
  - Optimal solutions or algorithms for application-relevant graphs
  - Computational complexity results
- Existing tools don't help:
  - Coloring? No….
  - List coloring? No….
  - Automorphism group? No….

Again opens new areas of mathematical investigation

Basic Design Strategy

Find an edge labeled/colored orientation of the graph, using a minimal number of colors, with as few different labelings of the half edges about the vertices as possible, and furthermore specifying the set of different vertex types (the resulting tiles).



Such a labeled/colored orientation of a graph G is called an *assembly design of* G and denoted λ, where λ maps half edges to labels.

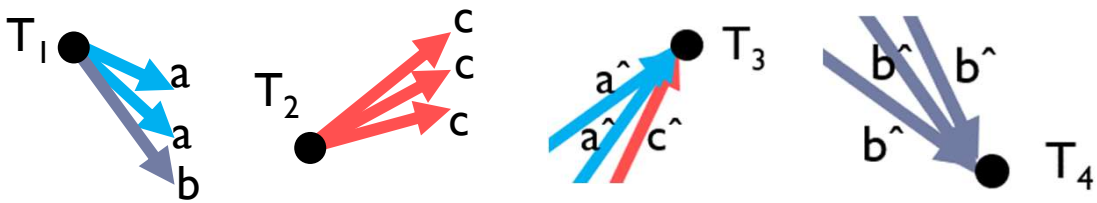
A little linear algebra

Let P be a pot with n tiles labeled $t_1 \ldots t_n$, and let $z_{i,j}$ be the net number of sticky ends of type i on tile t_j

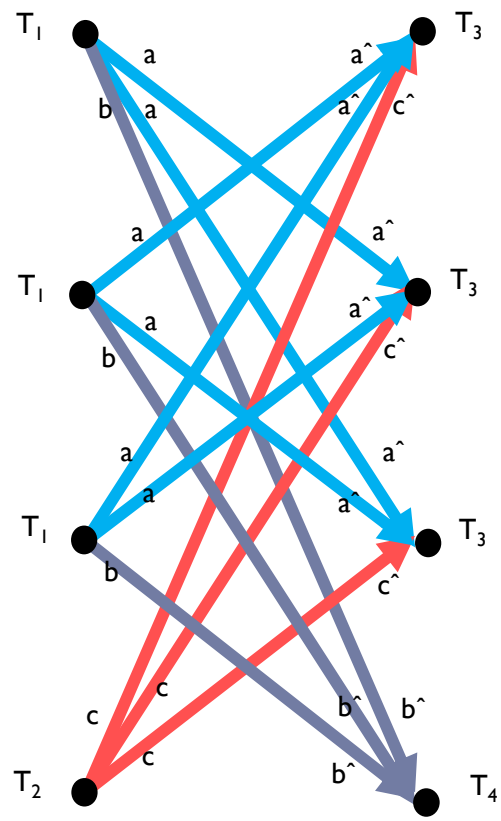
$$M(P) = \begin{bmatrix} z_{11} & z_{12} & \cdots & z_{1n} & 0 \\ \vdots & \vdots & & \vdots & 0 \\ z_{m1} & z_{m2} & \cdots & z_{mn} & 0 \\ 1 & 1 & \ldots & 1 & 1 \end{bmatrix}$$

Theorem: Some graph G with m vertices may be constructed from the pot P if and only if $<r_1 \ldots r_n>$ is a solution of the construction matrix $M(P)$ and $m <r_1 \ldots r_n>$ has integer entries.

Example



$$
\begin{array}{c c}
 & \begin{array}{ccccc} T_1 & T_2 & T_3 & T_4 & \end{array} \\
\begin{array}{c} a \\ b \\ c \end{array} & \begin{bmatrix} 2 & 0 & -2 & 0 & 0 \\ 1 & 0 & 0 & -3 & 0 \\ 0 & 3 & -1 & 0 & 0 \\ 1 & 1 & 1 & 1 & 1 \end{bmatrix}
\end{array}
\quad \text{rref} \rightarrow \quad
\begin{bmatrix} 1 & 0 & 0 & 0 & 3/8 \\ 0 & 1 & 0 & 0 & 1/8 \\ 0 & 0 & 1 & 0 & 3/8 \\ 0 & 0 & 0 & 1 & 1/8 \end{bmatrix}
$$



Thus, there is an 8-vertex complete complex realized by this pot with 3 T_1's, 1 T_2, 3 T_3's, and 1 T_4.

(Example from Harsy group)

Integer linear programing

If we ask for a complete complex of a specific size *k*, this becomes an integer programing problem, since a solution $<r_1 \ldots r_n>$ now is in $\boldsymbol{Z}^n$

$$M(P) = \begin{bmatrix} z_{11} & z_{12} & \cdots & z_{1n} & 0 \\ \vdots & \vdots & & \vdots & 0 \\ z_{m1} & z_{m2} & \cdots & z_{mn} & 0 \\ 1 & 1 & \ldots & 1 & \mathbf{k} \end{bmatrix}$$

All variables are restricted to be non-negative

ILP is NP hard in general, but this is a special case. Is it hard?

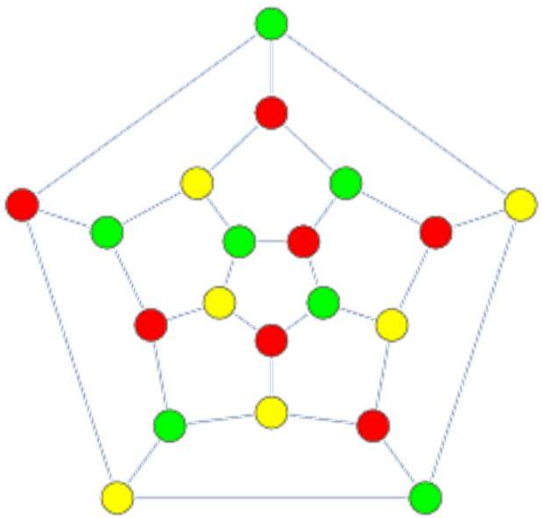
The decision question

- Given a pot *P* and a positive integer *k*, does *P* realize an assembly design for a graph *G* with *k* vertices.

[It is fast, linear in fact, to check that an assembly design is realized by a pot *P*, since you only need to check that each vertex configuration appears as a tile in *P*.]

Three coloring

- ILP is know to be NP hard in general, but this is a special case, so requires an independent proof of hardness—we do this by reduction to 3-coloring.



3-coloring a graph means coloring the vertices with 3 colors so that no pair of adjacent vertices get the same color.

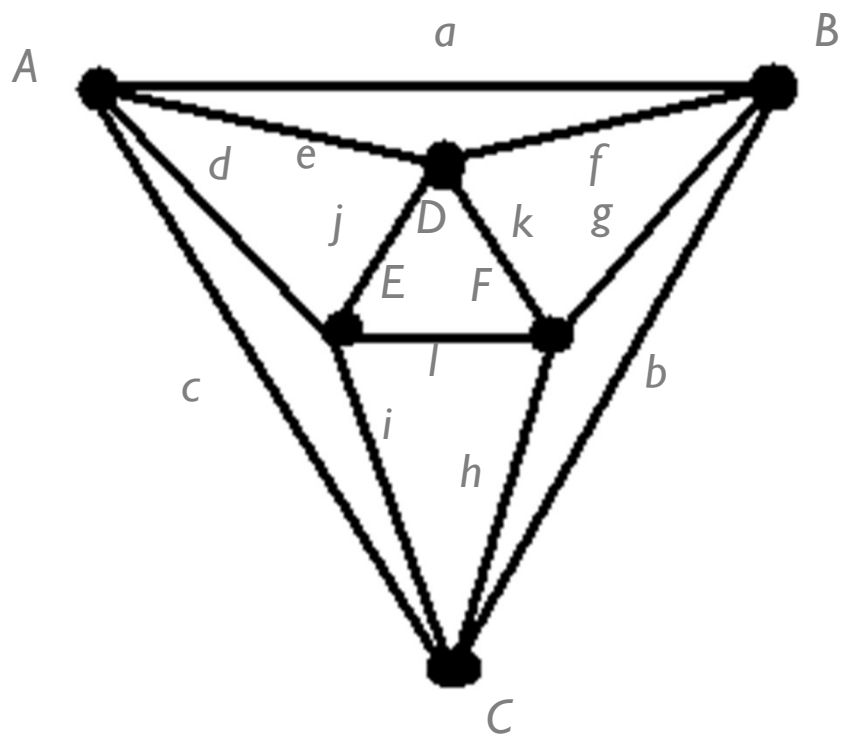
3-coloring is NP-complete even for 4-regular plane graphs

3-coloring reduction to pot problem

Now assume we have a polynomial time algorithm that will tell us if a pot *P* will assemble a graph on *k* vertices, and that we are given a 4-regular plane graph *G* that we want to 3-color.

[If we are able to use this hypothetical algorithm to come up with a 3-coloring, that would mean there is a polynomial time algorithm for 3-coloring. But unless P=NP, there isn't one.]

3-coloring 4-regular plane graphs

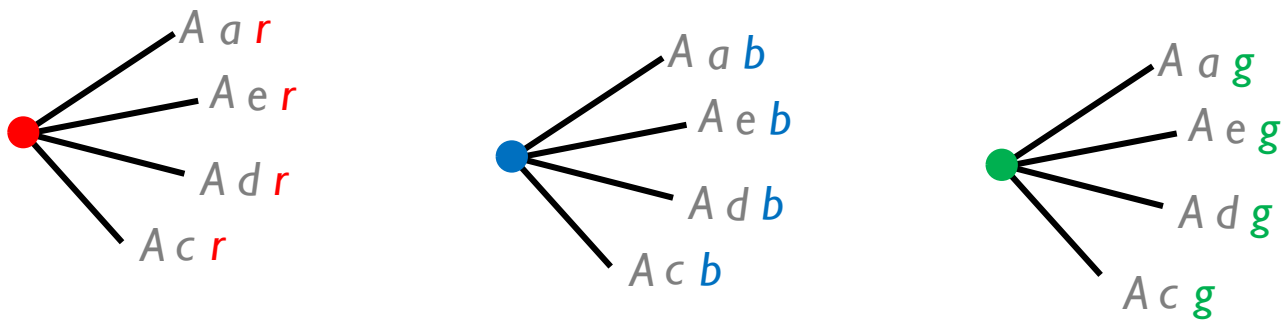


G, with vertices and edges labeled

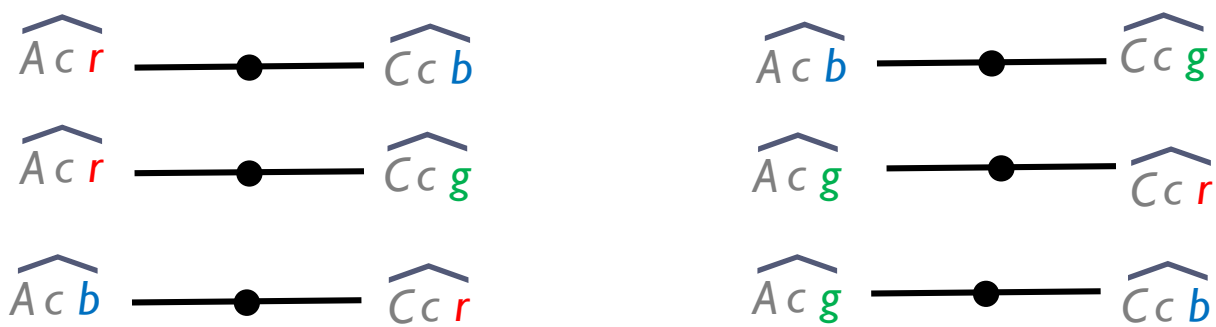
(This follows essential ideas of Jonoska, Sa-Ardyen, Seeman '03 , but adapted to our application and notation)

Create a pot

- For each vertex, create three tiles, one for each color, with sticky end labels recording vertex, edge, and color, e.g. for the vertex *A*:

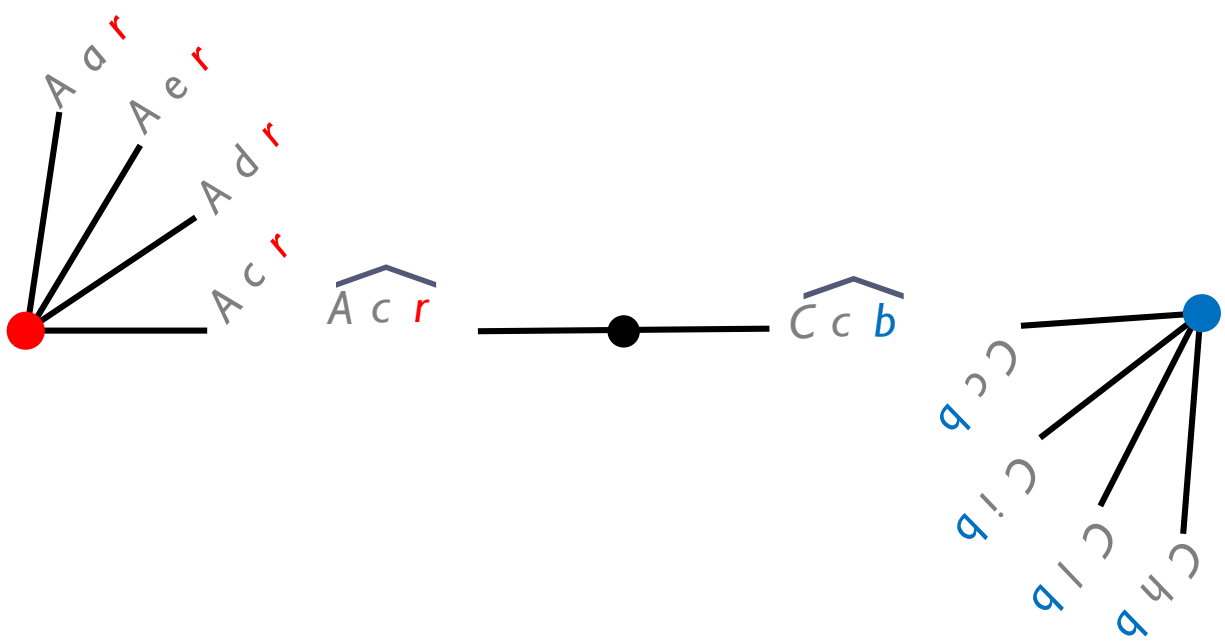


- For each edge create six tiles, one for each proper coloring of the edge's endpoints, with complementary sticky ends, e.g. for edge *c*:



A unique smallest complete complex from this pot

- The original graph (subdivided) is the unique smallest complete complex built from this pot, and that *only* if it is three-colorable:



Complexity summary

- The pot decision problem is in NP, since it is easy to check a solution.
- 3-coloring a 4-regular plane graph is NP-Complete and polynomial reduces to the pot decision problem.
- Therefor the pot-decision problem is also NP-Complete.

Ramifications

- This complexity result has ramifications for both of the fundamental objectives:
  - If you have a pot *P*, in general you can't efficiently determine what graphs it will construct.
  - If you have a graph *G*, in general you can't efficiently determine a pot that will assemble *G*, but not anything smaller.
- This stinks for the labs, as they would really prefer a fast, general purpose algorithm.
- But it is great for mathematicians, since it means this area is a whole new playground of problems: complexity for special classes, pragmatic solutions, approximation algorithms, explicit minimal pots for high-utility graphs, etc.
- Also, exploration of the new graph parameters—what do they reveal about the structure of graphs? Girth? Tree-width?

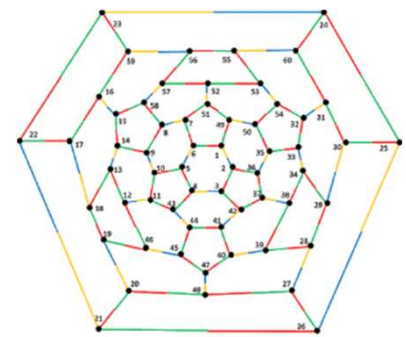
Pragmatic code

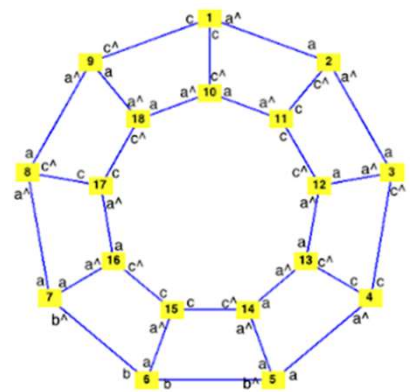
- We can use existing integer linear programing tools for small examples.
- We have specialized code that will handle 2-3 degrees of freedom and can determine if a graph is the unique smallest construct assembled by a pot.
- Lot of sporadic ad hoc cases, but quite difficult to prove optimality.

- More algorithms are needed– for special classes, in restricted settings, and for approximate solutions.

Table A: Minimum Tile Types	
Scenario 1	$T_1(G)$ = Minimum number of tile types required if complexes of smaller size than the target graph are allowed
General graph *G*	The number of different vertex degrees $\leq T_1(G) \leq$ The number of different even vertex degrees + 2*(The number of different odd vertex degrees).
Trees	The number of different vertex degrees $\leq T_1(T) \leq$ The number of different vertex degrees + 1
$\mathbf{C}_n$	$T_1(C_n) = 1$
$\mathbf{K}_n$	$T_1(K_n) = 1$ if n is even, and $T_1(K_n) = 2$ if n is odd
$\mathbf{K}_{n,m}$	$T_1(K_{n,m}) = 1$ if $n=m$ and even, and $T_1(K_{n,m}) = 2$ otherwise
K-regular graphs	$T_1(G) = 1$ if n is even, and $T_1(G) = 2$ if n is odd
Scenario 2	$T_2(G)$ = Minimum number of tile types required if allow complexes of the same size as, but not smaller than, the target graph
Trees	$T_2(T)$ = The number of different lesser size subtree sequences
$\mathbf{C}_n$	$T_2(C_n) = ceiling(n/2)+1$
$\mathbf{K}_n$	$T_2(K_n) = 2$ if n is even, and $T_2(K_n) = 3$ if n is odd
$\mathbf{K}_{n,m}$	$T_2(K_{n,m}) = 2$ if $gcd(m,n)=1$, and $T_2(K_{n,m}) = 3$ if $gcd(m,n)>1$
Scenario 3	$T_3(G)$ = Minimum number of tile types required if do not allow complexes of the same size as (or smaller than) the target graph
Trees	$T_3(T)$ = the number of induced subtree isomorphisms
$\mathbf{C}_n$	$T_3(C_n) = ceiling(n/2)+1$
$\mathbf{K}_n$	$T_3(K_n) = n$
$\mathbf{K}_{n,m}$	$T_3(K_{n,m}) = min(n,m)+1$

Also the Platonic and Archimedean solids



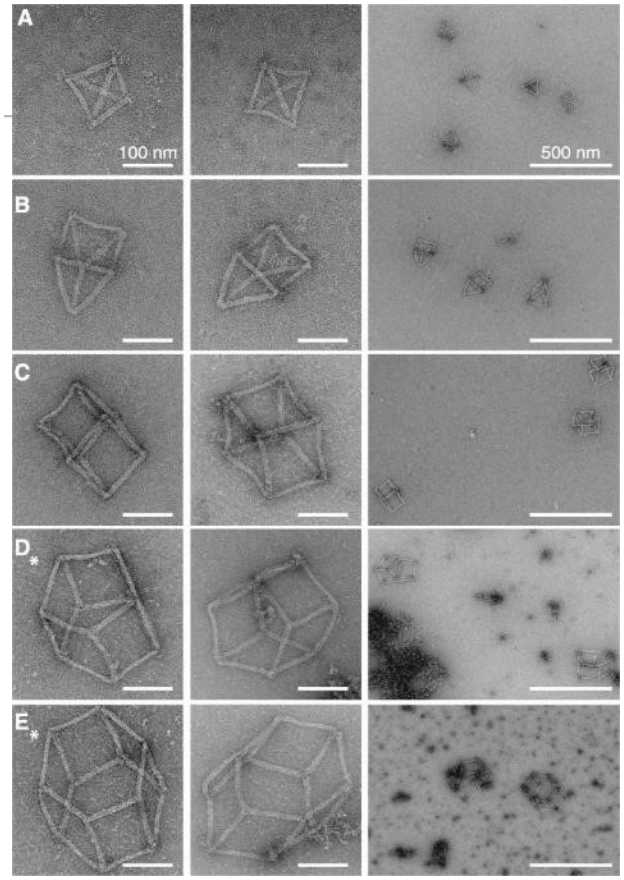


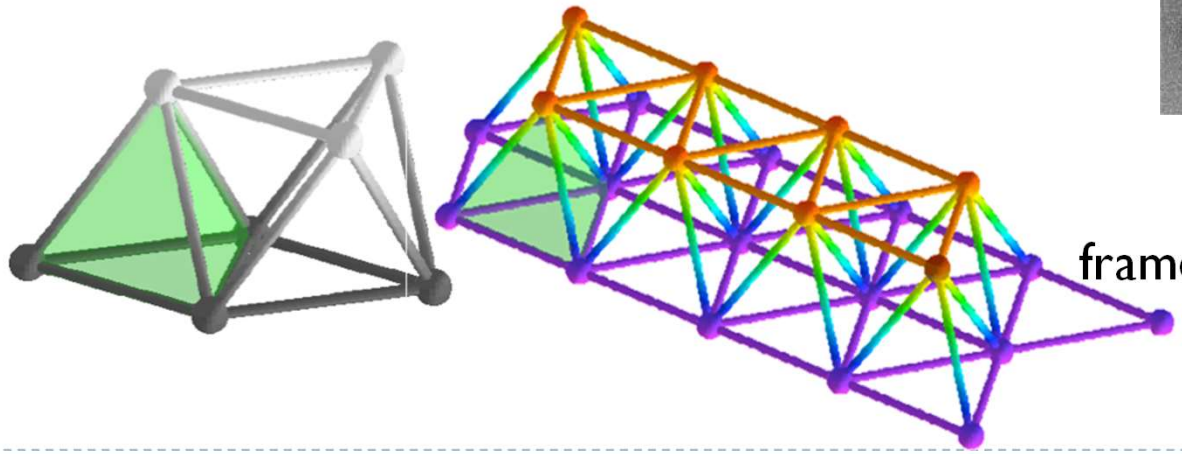
$P = \{\hat{a}c^2, ab^2, \hat{a}a\hat{c}, a^2\hat{b}\}$

Science 4 April 2014:
Vol. 344 no. 6179 pp. 65-69

Rigid Tiles

1. Arms are straight and rigid
2. Arms have integer lengths
3. The positions of the arms are fixed
4. The arms do not bend or twist in order to bond.
5. No molecule has more than 12 or less than 2 arms (branched junction molecules with 2, 4, 5, 6, 8, and 12 arms have been fabricated) .
6. Final DNA structures must be complete.
7. No design may allow structures smaller than the target structure to form.





The octet truss as an ideal framework for this problem = a new setting for grid graph drawing.

Rigid tiles are especially challenging

We have developed a novel *half-lap splice joint model*, inspired by wood-working techniques to accurately model DNA origami assembly with rigid tiles, and used it to determine provably optimal design strategies for various regular polyhedral cages. *(Joint with M. Ferrari and N. Seeman, and students)*

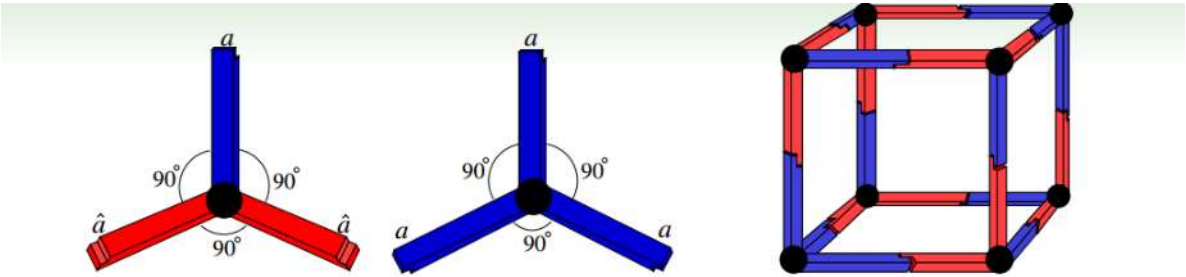


Figure: Tiling the cube

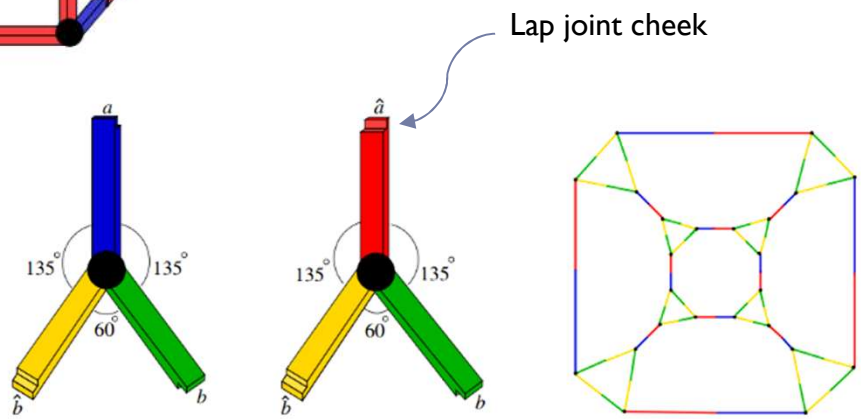
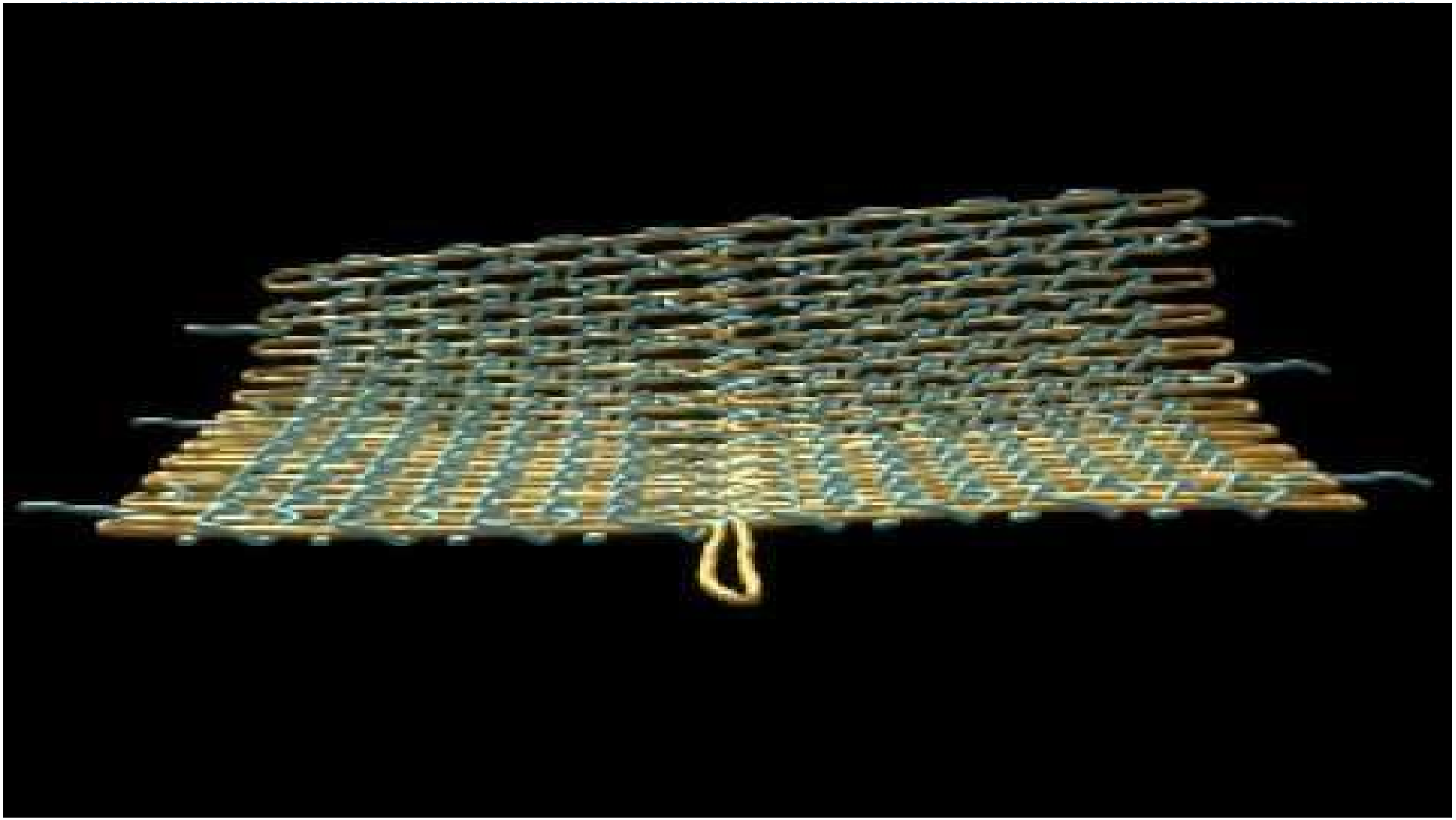


Figure: Tiling the truncated cube

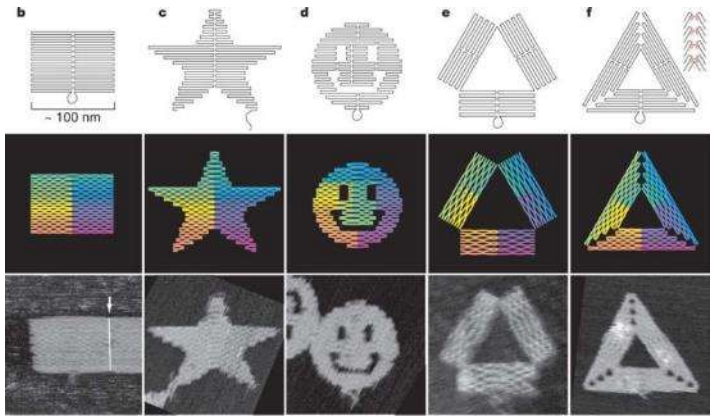
DNA Origami

Paul W. K. Rothemund Nature 440, 297-302 (16 March 2006)

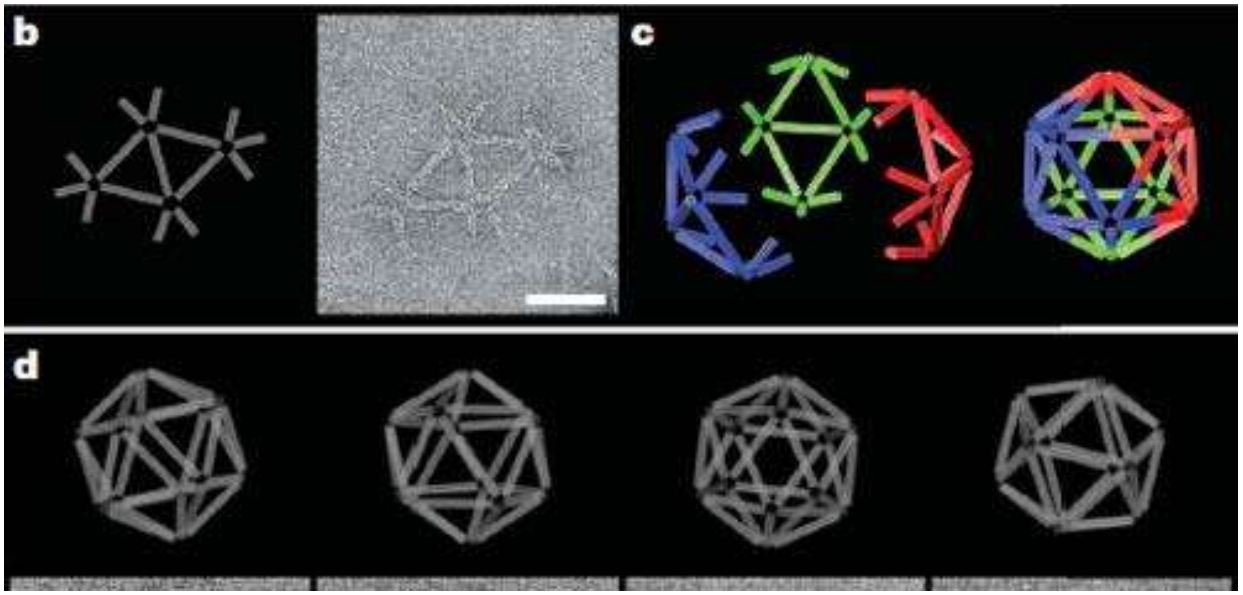


http://www.youtube.com/watch?v=5yH5LTXxFzk&feature=related

DNA Origami—new challenges



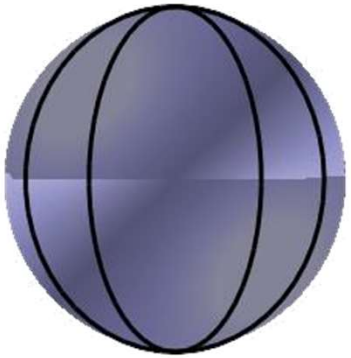
There are techniques, and even software, for flat, filled, objects (which actually come from paper origami)
Woo and Rothemund, Nature Chemistry, 3, 620



Designs for open structures, e.g. cages, graph-like objects, are much more challenging. This is where our work focuses.

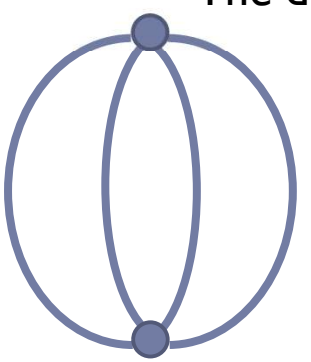
Douglas SM, Dietz H, Liedl T, et al (2009) Self-assembly of DNA into nanoscale three-dimensional shapes. Nature 459:414–418. doi: 10.1038/nature08016

Basic design process for DNA origami

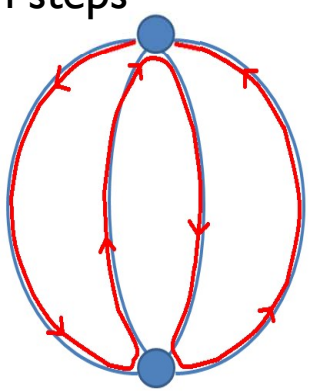


The target

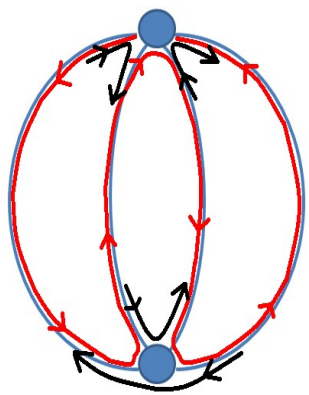
The design steps



Represent the target as a graph



Find an optimal route for the scaffolding strand



Locate the staple strands

MANY constraints:

- Just an **Eulerian circuit** if the target happens to be an **Eulerian graph**.
- For non-Eulerian graphs, must adapt either the graph or the circuit to enable the construction.
- Identify structurally appropriate augmenting edges.
- Constraints on turnings
- No interwoven strands
- Symmetry preferred
- Commensurable edge lengths (full turns of DNA)
- Overall length of strand

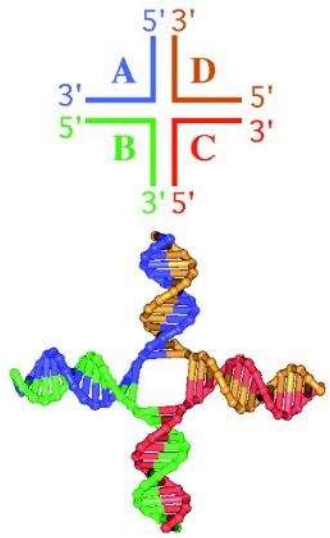
Scaffolding and staple constraints

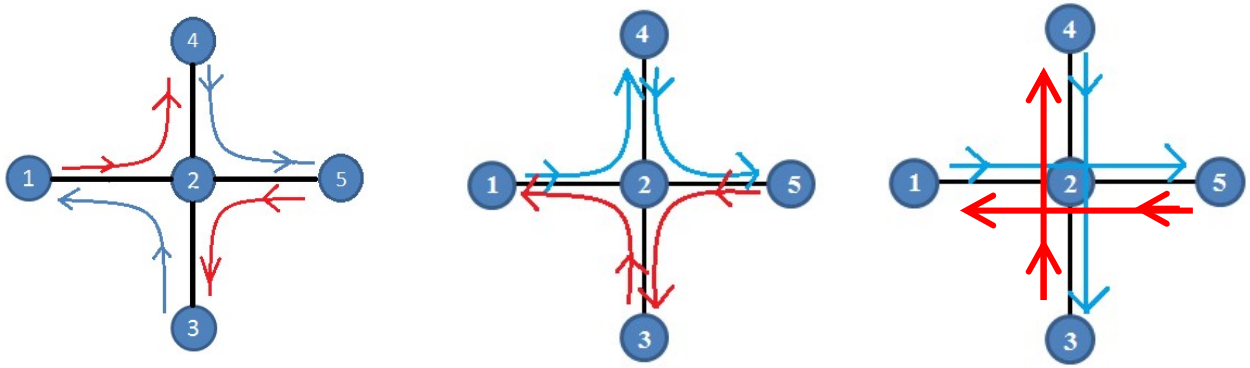
a) Each edge is covered by a scaffolding and staple strand.

b) Scaffolding and staples must run in opposite directions (DNA is directed).

c) Scaffolding and staples cannot cross over each other (DNA strands don't naturally interweave).

d) The configuration must not disconnect the vertex.

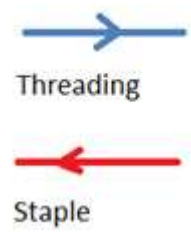




Good

Bad

Bad (crosses and disconnects)



The generic problem from the lab

- We want to build a molecule with the structure of this graph in three space using DNA origami
- We want the scaffolding strand to follow faces as much as possible, but if it can't, we want it at least not to cross-over or interweave. (And, well, these other bizarre configuration are no good either…)

Please provide the best possible route for the scaffolding strand through the graph.

Again, we prove the problem is NP-hard

Reduction to 3-SAT.

Origami methods may not be suitable for efficient biomolecular computing, since they may shift the complexity issue from the computation to the input.

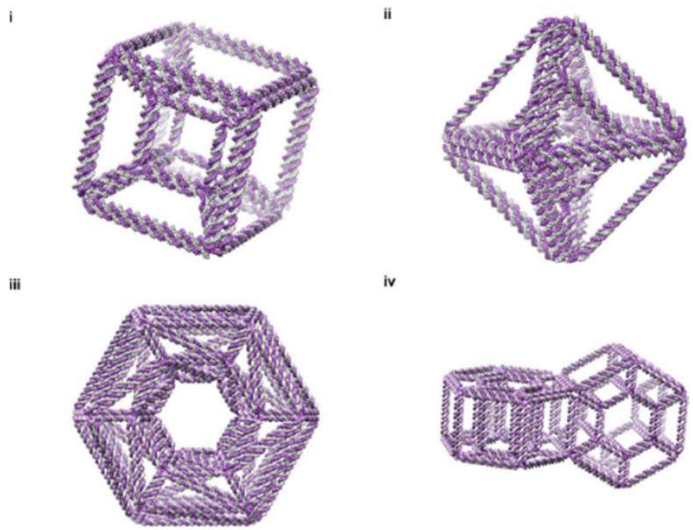
Telling the lab folks that their problem is provably hard doesn't really help them conduct the next experiment.

Need pragmatic solutions.

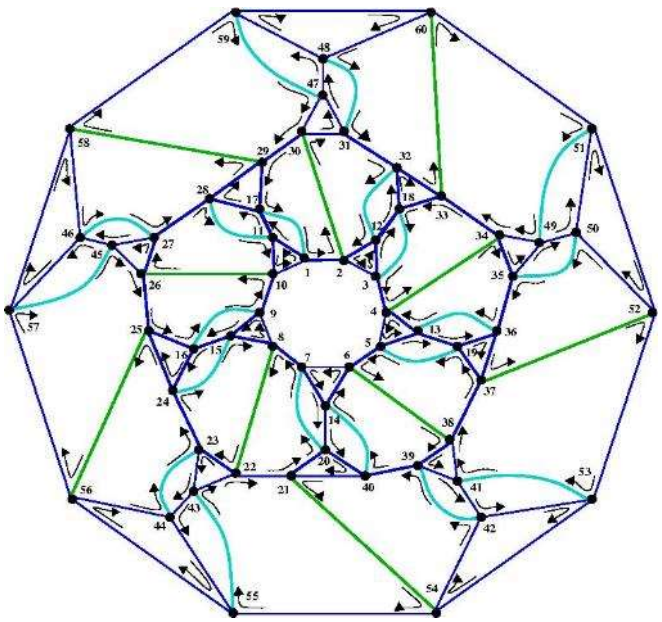
General Principle: An NP-Hard problem is often a 'place marker' for a rich field of related problems– approximation algorithms, special classes that are tractable, tractable variations of the problem, etc.

Other complications: no knotting…

- Designs are increasingly complex
- As are topologies



Veneziano et al. Designer nanoscale DNA assemblies programmed from the top down, *Science* 2016

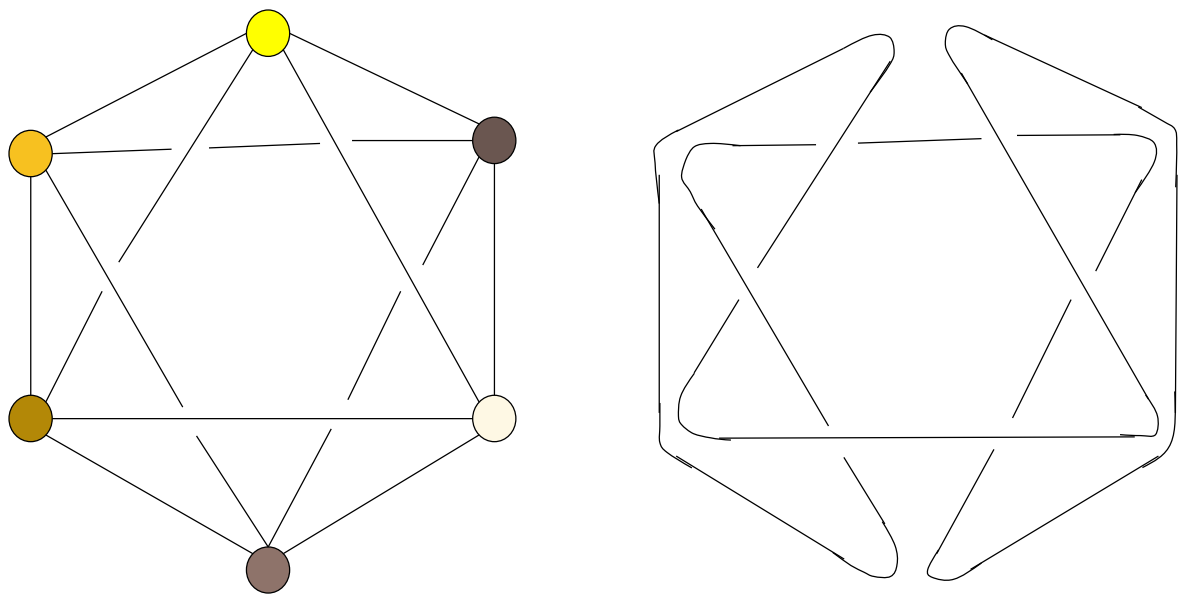


Truncated Dodecahedron

- Knots can confound assembly, so need to be sure they aren't inadvertently introduced.

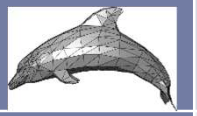
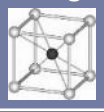
New DNA-driven area: knotted Eulerian circuits

- The Eulerian circuit needed for DNA origami traces each edge exactly once, but can end up knotted.



Can we prevent this?

Settings for new area of origami knotting

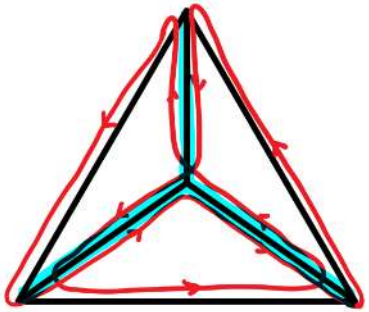
	Trail	No trail	All trails unknotted	At least one unknotted trail	At least one knotted trail	All trails knotted
Cellularly embedded 	A-trail	Incon-structable	Strongly origami constructable	Origami constructable	Origami surface knotted	Strongly origami surface knotted
Straight-edge 	O-trail	Inconstructable	Strongly origami constructable	Origami constructable	Origami stick knotted	Strongly origami stick knotted
Spatially embed-ded 	O-trail	Inconstructable	Strongly origami constructable	Origami constructable	Origami knotted	Strongly origami knotted
Abstract Graph	Euler Circuit	Non Eulerian	There exists an embedding with no knotted O-trails: Intrinsically strongly origami constructable	Every embedding has at least one unknotted O-trail: Intrinsically origami constructable	Every embedding has at least one knotted O-trail: Intrinsically Origami knotted	Every embedding has all O-trails knotted: Intrinsically strongly origami knotted

The routing problem on the backend

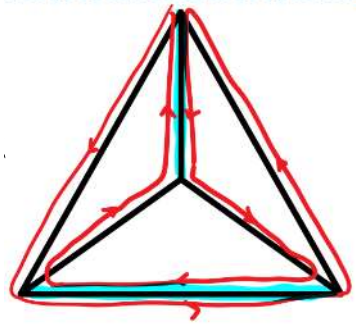
- The preceding were examples of 'front end' design problems.
- But we also need good routes, called ***reporter strands*** for reading the output from biomolecular computing or other experiments.
- Reporter strands may be used following other assembly methods, e.g. branched junction molecules, or tiles.
- The graph may not be Eulerian, and in this case, some edges may need to be repeated.

Example

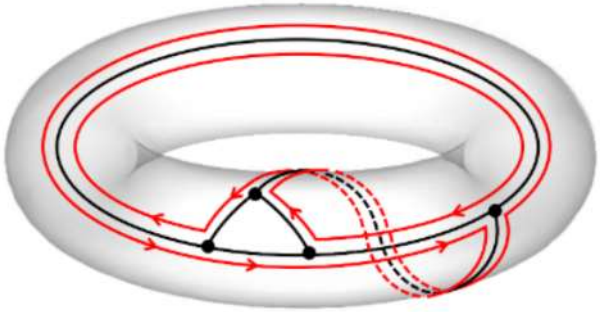
GOOD

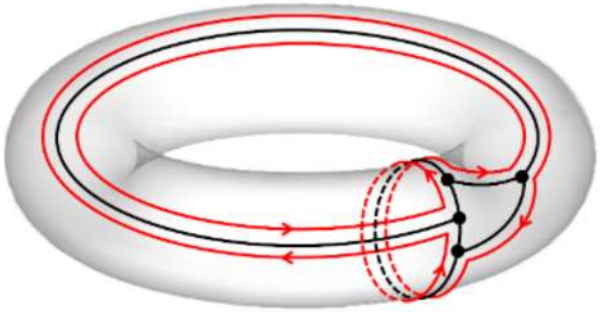


Reporter strand walks in K_4. Double traced edges are highlighted



BEST





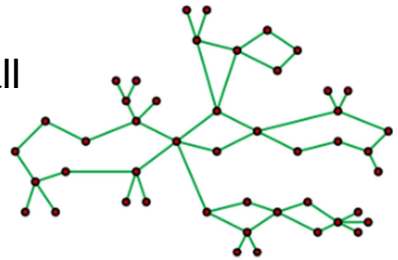
Corresponding edge-outer embedding in the torus, with facial walks around the outer face.

- We want the shortest possible reporter strands
- For cubic graphs, the theoretical minimum is $|E| + \frac{1}{2}|V|$

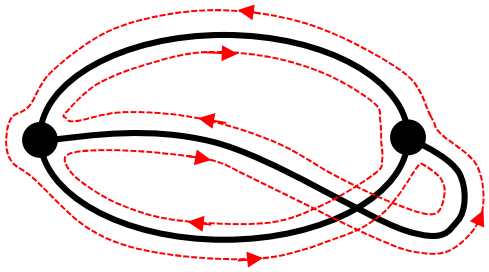
This problem also generated many new questions in graph theory

- For both scaffolding and reporting, we need a walk that covers every edge at least once, at most twice, and if twice, once in each direction (DNA is directed).
- Existing results in the literature are not quite what we need for the DNA application.
  - Outer planar graphs? No… (need edges, not vertices on the outer face)
  - Upper embeddable graphs? No… (covers *every* edge twice, and we want as few as possible double covered)
- So we need new theory and new results.

An outer planar graph: vertices all on one face



Upper embedding of the theta graph on a torus: only one face



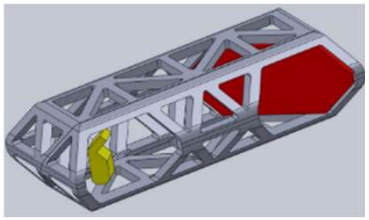
New directions

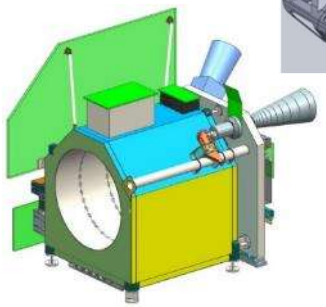
Edge outer embeddability is a natural area of investigation with many open questions:

1. Approximation algorithms? Is there an algorithm that will return a route that is within x% of minimum length?
2. Special classes of graphs? Are there classes of graphs where it is polynomial time to find a minimum solution? Eulerian graphs are one such class. What others might there be?
3. What can be said about the genus range of embeddings that yield reporter strand walks, or reporter strand walks of minimum length? Are these ranges intervals? (All the usual genus questions can be reformulated for edge outer embeddings)
4. For a given graph, what is the minimum genus surface on which it is edge outer embeddable?

Graphical self-assembly design is a rich new area

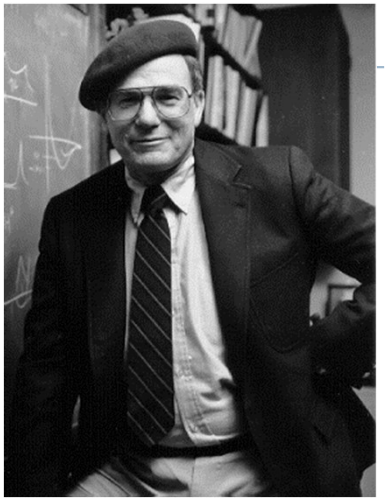
- DNA self-assembly opens whole new mathematical vistas--
  - Algorithms, approximations, tractable classes,
  - General theory (need much more of this!) in several settings
- The work involves broad synthesis
  - Mathematics (topology, combinatorics, algebra, geometry, knot theory…)
  - Operations research and computer science
  - Chemistry, biology, and physics
  - Art
  - Sheer creative ingenuity



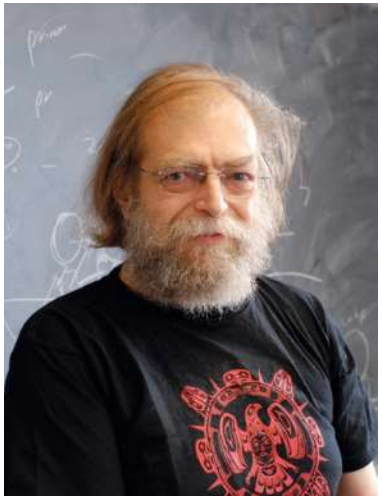


NASA ATLAS Utilizing the Octet Truss in the Design of Lateral Transfer Retroreflectors

PI's & senior personnel (design problems)

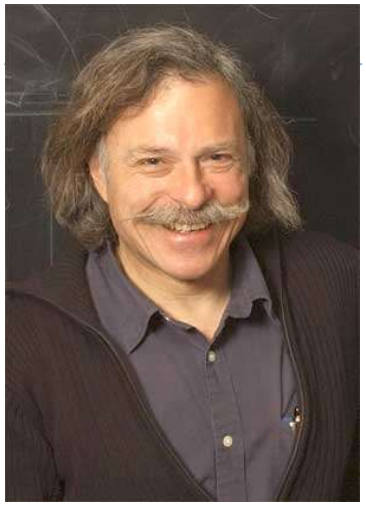


Bill Goddard (PI)



Ned Seeman

Lisa Scherer



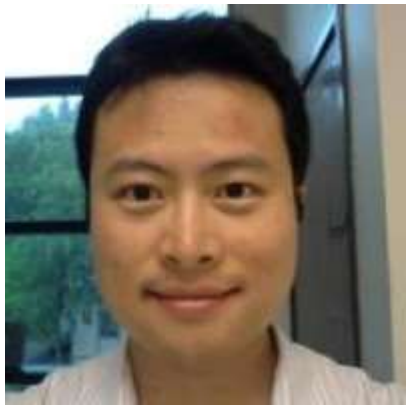
Paul Chaikin

John Rossi

Jo Ellis-Monaghan

Greta Pangborn

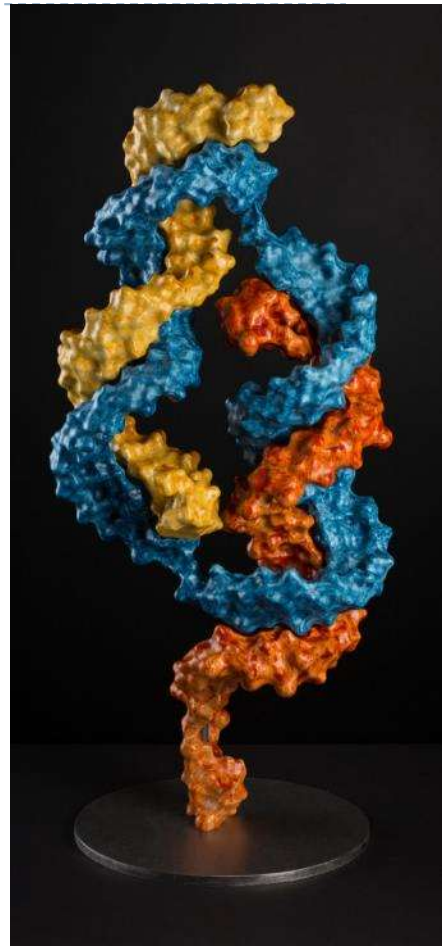
Si-Ping Han



Julian Voss-Andreae

Jim Canary

Get to collaborate with a sculptor!



https://julianvossandreae.com/

Current collaboration

Microsystems and MechanoBiology Lab

- Rebecca Taylor (Carnegie Melon University)
- http://www.andrew.cmu.edu/user/bex/
- PNA assembly (a synthetic molecule that bonds more strongly than DNA).

https://www.meche.engineering.cmu.edu/directory/bios/taylor-rebecca.html

ICERM-supported REUF Junior Faculty

Jessica Williams
Cory Johnson
Leyda Almodovar Velazquez
Amanda Harsy

Some recent graduate and undergraduate students

Ada Morse

Rebecca Rouleau,
Margherita Ferrari

Brenna Smith, Anna Cook, David Perry, Jessica Greene

Self-Assembly Design Strategies

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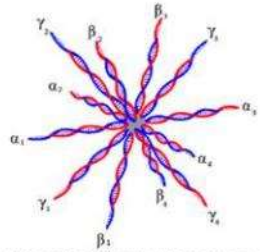
A number of exciting new laboratory techniques have been developed using the Watson-Crick complementarity properties of DNA strands to achieve the self-assembly of graphical complexes.

For all of these methods, an essential step in building the self-assembling nanostructures is designing the component molecular building blocks.

These design strategy problems fall naturally into the realm of graph theory.

There are many open questions associated with these applications, many of which are accessible to students and offer the possibility of exciting undergraduate research experiences in applied graph theory.



A 12-armed, single-vertex in the octet truss

This work has been supported by the NSF through award 1001408.

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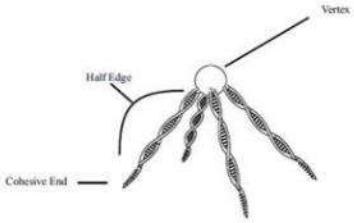
molecules that have rigid
s are fixed with respect to
tions of the arms are fixed
ms are fixed with respect to

position by twisting (arms

strand as a result of external
either too short to curve, or



A depiction of the typical four-armed tile.

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- No branched junction molecule has more than 12 arms or less than 2 arms
- Final DNA structures must be complete
- No design may allow structures smaller than the target structure to form

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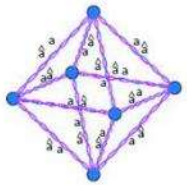
Octahedron



Summary of Results fo

Octahedron: *1 tile required*	
Tile Type Used in Co	
α_1	α_4
a	*a*

Theorem *An octahedron may be constructed with a minimu*

Proof. The octahedron is made up of six vertices, twelve edg
six tiles with four arms each. We now present a construction

Self-Assembly Design Strategies

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Branched Junction Molecule

One construction method for self-assembly of DNA structures uses *k*-armed **branched junction molecules**, star-shaped molecules whose centers form the vertices of the structure, and whose arms are double strands of DNA with one strand extending beyond the other. The longer strand forms a cohesive end at the end of the arm that can bond to any other cohesive end with complementary Watson-Crick bases, as in Figure 1, thus forming the edge of the graph.

```
AATTCCGGAATT          GGCCTTAAGGAATTCCGGTTTAA
TTAAGGCCTTAACCGGAATTC          CTTAAGGCCAAATT

AATTCCGGAATTGGCCTTAAGGAATTCCGGTTTAA
TTAAGGCCTTAACCGGAATTCCTTAAGGCCAAATT
```

Figure 1: Joining two cohesive ends

Constructing the Graph A target graph is constructed from these branched molecules, with a vertex of degree *k* realized by a *k*-armed branched molecule, and where two vertices in the target graph have an edge between them if and only if their two branched molecules have an arm joined between them via the complementary bases on the cohesive ends. Thus, the joined arms form the edges of the target graph.

Some resources

- J. Ellis-Monaghan, N. Jonoska, G. Pangborn, "Tile-based DNA Nanostructures: Mathematical Design and Problem Encoding", Algebraic and Combinatorial Computational Biology, R. Robeva & M. Macauley, eds. Elsevier. 2019.
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THANK YOU!