ČESKÉ VYSOKÉ UČENÍ TECHNICKÉ V PRAZE

Fakulta jaderná a fyzikálně inženýrská

VÝZKUMNÝ ÚKOL

Praha, 2014

Jakub Klemsa

ČESKÉ VYSOKÉ UČENÍ TECHNICKÉ V PRAZE

Fakulta jaderná a fyzikálně inženýrská

Katedra matematiky

VÝZKUMNÝ ÚKOL

Modely sebeskládajících DNA nanostruktur

Models of self-assembling DNA nanostructures

Vypracoval: Jakub Klemsa

Školitel: Ing. Štěpán Starosta, Ph.D.

Akademický rok: 2013/2014

Na toto místo přijde svázat **zadání mého výzkumného úkolu**!

V jednom z výtisků musí být **originál** zadání, v ostatních kopie.

Čestné prohlášení

Prohlašuji na tomto místě, že jsem předloženou práci vypracoval samostatně a že jsem uvedl veškerou použitou literaturu.

V Praze dne January 31, 2014

. . . . . .
Jakub Klemsa

Poděkování

Děkuji Ing. Štěpánu Starostovi, Ph.D., za vedení mého výzkumného úkolu a za podnětné návrhy, které ho obohatily.

Jakub Klemsa

Název práce:	**Modely sebeskládajících DNA nanostruktur**
Autor:	Jakub Klemsa
Obor:	Inženýrská informatika
Zaměření:	Matematická informatika
Druh práce:	Výzkumný úkol
Vedoucí práce:	Ing. Štěpán Starosta, Ph.D.,
Konzultant:	—
Abstrakt:	Abstrakt CZ.
Klíčová slova:	Klíčová.

Title:	**Models of self-assembling DNA nanostructures**
Author:	Jakub Klemsa
Abstract:	Abstrakt EN.
Key words:	Keywords.

Contents

Prolog

1959: Feynman's visionary talk, [5];

The ground-breaking work was carried out by Adleman, [2], who showed that DNA computation is practically feasible. In his experiment, Adleman used special DNA sequences for solving Hamiltonian Path Problem, one of the most typical NP-complete problems.

... Extreme parallelism! But also possibility of errors.

Work overview

Chapter 1: Intro.
Chapter 2: First of all I will describe models which exploit specific DNA structure.
Chapter 3: Abstract Tile Assembly Model, temperature, 2D vs. 3D.
Positive integers $\mathbb{N}$.

Chapter 1

Introduction to DNA computation

1.1 Basic DNA principles

Backbone: deoxyribose + phosphate; $5' \to 3'$ ends (due to deoxyribose atoms numbering); bases: adenine, thymine, cytosine, guanine; Watson-Crick complementarity; Polymerase chain reaction; Gel electrophoresis; biostep; hairpin;

1.2 Complexity, languages

P, NP, co-NP, PP, #P, PSpace. Enough? Maybe also polynomial hierarchy: $\Sigma_k P$ and $\Pi_k P$ languages (alternating Turing machine with bounded alternation, [7]).

Regular languages, context-free languages, recursively enumerable languages.

HPP: Adleman uses $O(n)$ biosteps, Winfree one. SAT: Lipton's contribution using m biosteps ($m = \#clauses$), [9], Lipton's set of speedup problems, [8]. Lipton 95 describes basic DNA operations. Energy efficiency (Adleman). NP definition?

Chapter 2

Strand models

Quick overview of considered structures. Winfree's overview (pg 29 – considered molecules, pg 36 – sizes of DAE and a better picture, pg 37 – comparison of DAO/DAE in a lattice, explanation pg 43).

Seeman, Fu and their DAO/DAE in [6], is the picture of DAO strange?

2.1 Adleman's experiment

Adleman showed in his ground-breaking work, [2], that DNA molecules are really capable of computation. He exploited that huge parallelism possible in DNA computation for one of the most fundamental NP-complete problems – the Hamiltonian Path Problem (HPP) in directed graph with designated vertices v_{begin} and v_{end}.

Let us remind this type of HPP. Given a directed graph G_n with n vertices and two designated vertices v_{begin} and v_{end}, the problem is to answer whether there exists an oriented path from v_{begin} to v_{end} through the graph such that the path visits every vertex. Note that *path* cannot visit any vertex more than once from definition.

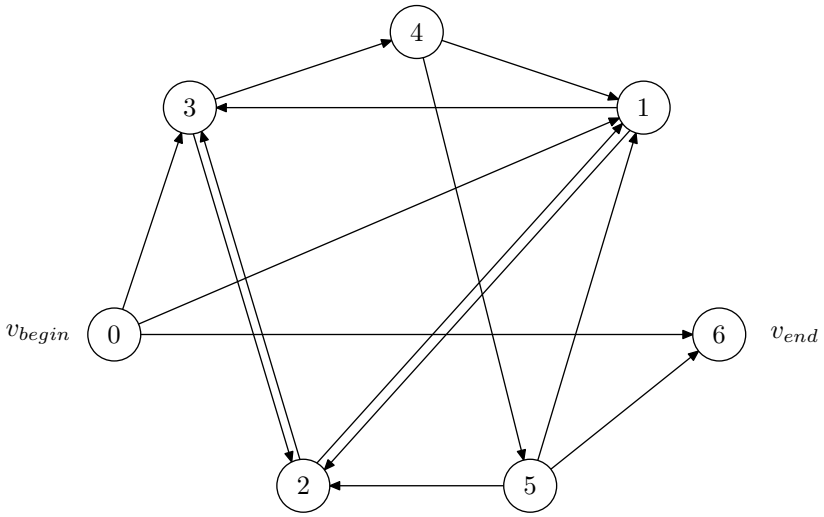


Figure 2.1: Adleman's original graph.

Adleman originally used a graph with seven vertices shown in figure 2.1. It can be seen that the path $0 \to 1 \to 2 \to 3 \to 4 \to 5 \to 6$ is Hamiltonian[1].

Adleman first presents this non-deterministic five-step algorithm, whose steps are then described in terms of DNA manipulations:

Step 1 Generate random paths through the graph.

Step 2 Keep only those paths that begin with v_{begin} and end with v_{end}.

Step 3 If the graph has n vertices, then keep only those paths that enter exactly n vertices.

Step 4 Keep only those paths that enter all of the vertices of the graph at least once.

Step 5 If any paths remain, say "Yes"; otherwise, say "No."[2]

To see how DNA can compute, let us describe this example more precisely. The computation itself (I mean the inception of the final solution) is hidden in Step 1. Each vertex i is associated with a random[3] 20-mer sequence of DNA, let us denote its $5' \to 3'$ orientation by O_i, its 10-mer prefix by p_i and its 10-mer suffix by q_i. Each edge $i \to j$ is then associated with $\overline{q_i p_j}$ sequence with reverse backbone orientation ($3' \to 5'$) where $\overline{q_i}$ stands for Watson-Crick complementary word. There is an exception for $i = begin$ and $j = end$: instead of $\overline{q_{begin} p_j}$ there is $\overline{O_{begin} p_j}$ and in a similar way for $j = end$.

$$
\begin{array}{lc}
 & O_{i\to j} \\
3' \leftarrow & \ldots|\texttt{CTTTCGAATA AAGATCAGTC}|\ldots \quad \leftarrow 5' \\
5' \to & \ldots|\texttt{CCTCTCGCGA GAAAGCTTAT}|\texttt{TTCTAGTCAG CACTCTTTGT}|\ldots \quad \to 3' \\
 & O_i \qquad\qquad\qquad O_j
\end{array}
$$

Figure 2.2: Example of assigned sequences.

It can be easily seen that all correctly bonded double-strands correspond with a valid path in G_n. Moreover, all complete double-strands represent a valid path from v_{begin} to v_{end} through G_n.

All the other steps are fully described in [2]. The most important thing is that the most time-demanding step is Step 4. In this step one has to purify the product of Step 3 with a biotin-avidin magnetic beads system. This process extracts consequently for every vertex i only those DNA strands which contain a substring representing vertex i. Thus its biostep complexity is $O(n)$. If we assume that one biostep takes at least tens of minutes and it should be performed repeatedly to avoid errors, we can conclude that $O(n)$ is just too much[4].

2.2 Single-stranded molecules

SAT in $O(1)$ biosteps etc.

[1] Note that it can be re-labelled such a nice way without loss of generality.

[2] This is the original version, I would rectify the fifth step: If any paths remain, say "Yes"; otherwise, say "*I do not know.*" That is because NP problem gives answer "Yes" iff there *exists* supporting solution. To say "No" one needs to show that *all* solutions do not satisfy. That is exactly the difference between NP and co-NP.

[3] We will expect those sequences to be different enough.

[4] Winfree, [11], gives a positive solution.

2.3 Double-stranded molecules

2.3.1 Linear strands

Equivalent to regular languages.

2.3.2 Dendrimer structures

Equivalent to context-free languages.

2.4 Double crossover molecules

Equivalent to recursively enumerable languages (Turing universal). Important notes in 3.2.5 Winfree – single side hybridization – how to avoid. Tricky solution of Hamiltonian Path Problem.

Chapter 3

Wang tile models

3.1 Definition

More abstract model where one handles only with "glues" on edges of Wang tiles. Define *temperature*.

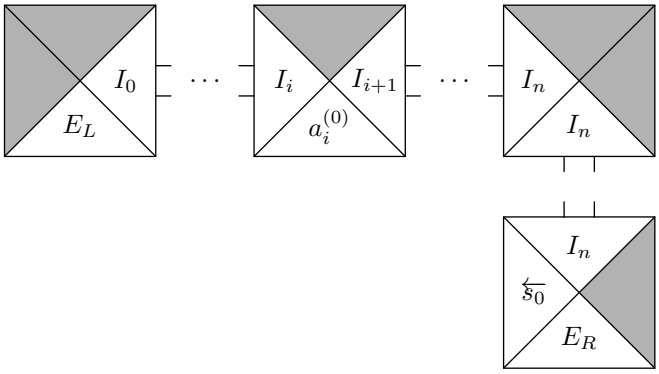
3.2 Computational power

Give table of Turing universality [4].

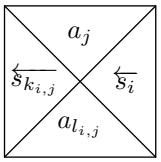
See [11]. Many other results in [4], [3], [10], [1] ...

3.2.1 Turing universality of 2D tiles at $T = 2$

Input tape:



Comes from right, continues left:



Comes from right, continues back to the right:

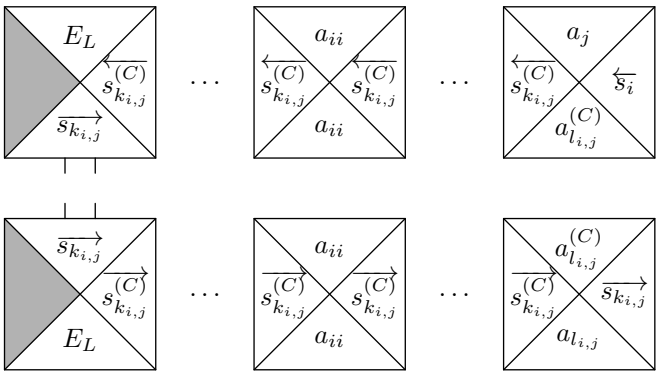
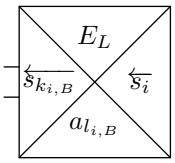
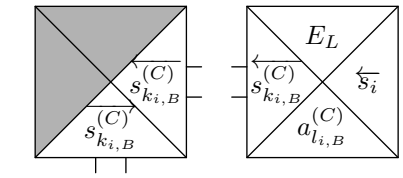


Figure 3.1: Tileset 1/2

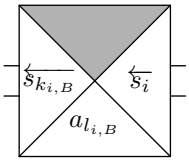
Reads EndLeft, continues left:



Reads EndLeft, continues back to the right:



Comes from right and reads Blank, continues left:



Comes from right and reads Blank, continues back to the right:

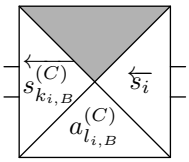


Figure 3.2: Tileset 2/2

error-tolerant rules – Gacs and Reif, 1988

Chapter 4

Results

4.1 Abstract model for DAO units

It is better to draw easier-to-understand pictures. Explanation: ...

In following examples this model will be set up to act similarly like NP: $\exists y \ R(x, y)$. Although existence is not sure it is very likely. Predicate R will be enumerable in polynomial time for $x \in L$. In this context, *enumerable in polynomial time* will mean number of bindings, not number of biosteps. This can be assumed due to Turing universality of this model in $O(1)$ biosteps, thus biostep complexity is not restrictive and will be required to be $O(1)$. On the other hand the binding complexity will be very important, we will be interested even in constants. This is because the less binding complexity, the less probability of error.

Define (slightly more correctly) binding complexity of this model as the number of bindings. Only the biggest term will be considered but even with constant.

4.2 Graph 3-coloring

Remind original Knuth's algorithm at `http://www.iti.fh-flensburg.de/lang/algorithmen/sortieren/networks/oetsen.htm`! And prove that everything goes fine!

First idea: Generate all bonds with colored atoms and check the entire system (haha, complexity like $O(n^4)$ because $|E| \in O(n^2)$). Second solution: Generate a reverse-order sequence of vertices and let it order in the correct order. All pairs should meet each other, the problem to solve is whether all pairs really meet each other. After that check that the area is full like Winfree – from one side to the other. Improvement: the check can be triggered from both sides simultaneously.

The first idea was like $O(n^4)$, the second one is already $O(n^2)$, the binding complexity is $1\frac{1}{2}\, n^2$. The improvement decreases it to $1\frac{1}{4}\, n^2$.

4.3 Graph isomorphism

Graph isomorphism problem clearly belongs to NP but it does not seem to be NP-hard[1] [**?**]. Thus it seems that it is neither P nor NP-complete. From this reason it seems to belong to a special class and thus I will describe a DNA system which solves this problem.

[1] Clearly, if P = NP it would even belong to P.

Surprisingly it is very similar to 3-coloring if we consider n colors instead. Each color will be assigned to concrete vertex. But there are slight differences, one has to check whether:

1. edges and non-edges are preserved,
2. every "color" was used exactly once.

In the first step the difference is that one checks coincidence of more cases. In the second step a similar check procedure is to be performed.

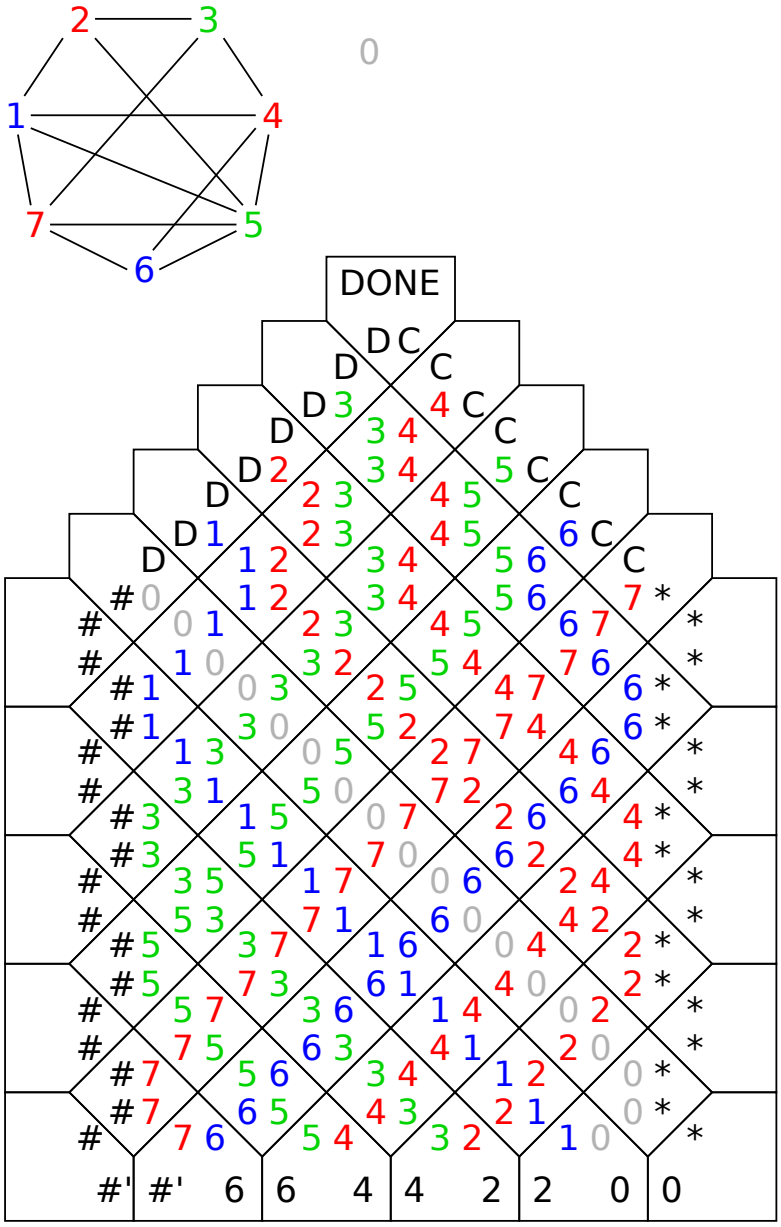


Figure 4.1: 3-color computation

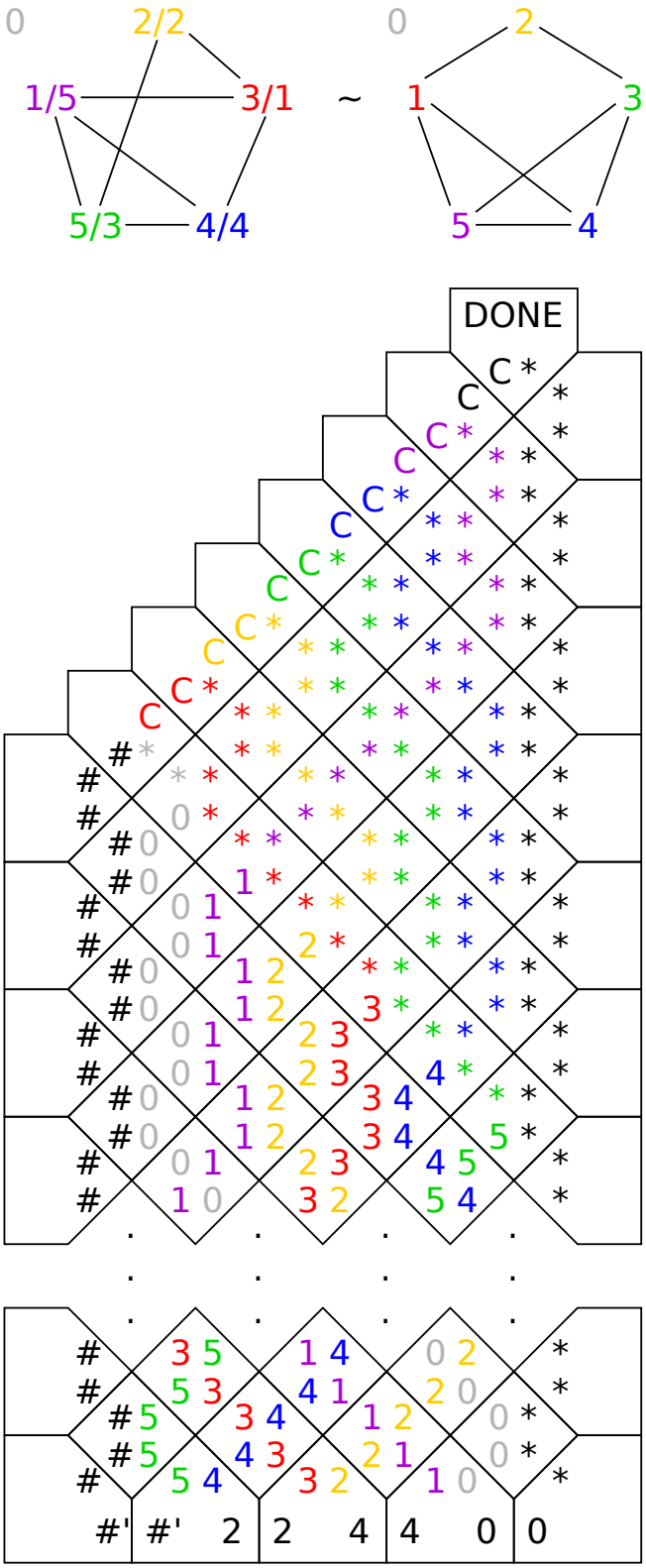


Figure 4.2: Graph isomorphism

Epilog

The very last section to be done.

Bibliography

[1] Leonard Adleman, Qi Cheng, Ashish Goel, and Ming-Deh Huang. Running time and program size for self-assembled squares. In *Proceedings of the thirty-third annual ACM symposium on Theory of computing*, pages 740–748. ACM, 2001.

[2] Leonard M Adleman. Molecular computation of solutions to combinatorial problems. *Science - New York then Washington*, pages 1021–1024, 1994.

[3] Bahar Behsaz, Ján Maňuch, and Ladislav Stacho. Turing universality of step-wise and stage assembly at temperature 1. In *DNA Computing and Molecular Programming*, pages 1–11. Springer, 2012.

[4] Matthew Cook, Yunhui Fu, and Robert Schweller. Temperature 1 self-assembly: Deterministic assembly in 3d and probabilistic assembly in 2d. In *Proceedings of the Twenty-Second Annual ACM-SIAM Symposium on Discrete Algorithms*, pages 570–589. SIAM, 2011.

[5] Richard P Feynman. There's plenty of room at the bottom. *Engineering and Science*, 23(5):22–36, 1960.

[6] Tsu Ju Fu and Nadrian C Seeman. Dna double-crossover molecules. *Biochemistry*, 32(13):3211–3220, 1993.

[7] Dexter Kozen. *Theory of computation*. Springer, 2006.

[8] Richard J Lipton. Speeding up computations via molecular biology. *DNA Based Computers*, 27:67–74, 1996.

[9] Richard J Lipton et al. Dna solution of hard computational problems. *Science*, 268(5210):542–545, 1995.

[10] Paul WK Rothemund and Erik Winfree. The program-size complexity of self-assembled squares. In *Proceedings of the thirty-second annual ACM symposium on Theory of computing*, pages 459–468. ACM, 2000.

[11] Erik Winfree. *Algorithmic self-assembly of DNA*. PhD thesis, California Institute of Technology, 1998.