ČESKÉ VYSOKÉ UČENÍ TECHNICKÉ V PRAZE

Fakulta jaderná a fyzikálně inženýrská

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Katedra matematiky

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Modely sebeskládajících DNA nanostruktur

Models of self-assembling DNA nanostructures

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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 February 2, 2014

. . . . . .
Jakub Klemsa

Poděkování

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

Jakub Klemsa

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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.

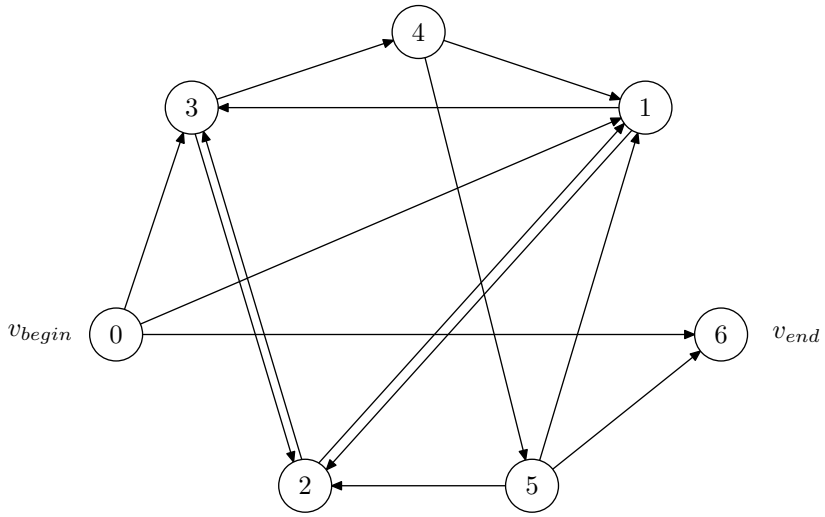


Figure 2.1: Adleman's original graph.

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 $j = end$.

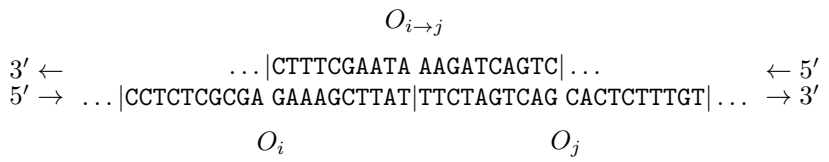


Figure 2.2: Example of assigned sequences.

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*.

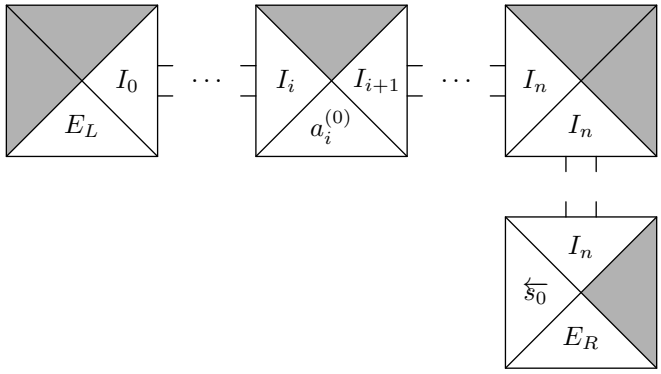
3.2 Computational power

Give table of Turing universality [4].

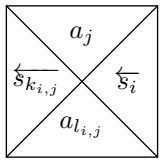
See [11]. Many other results in [4], [3], [10], [1] ...

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

Input tape:



Comes from right, continues left:



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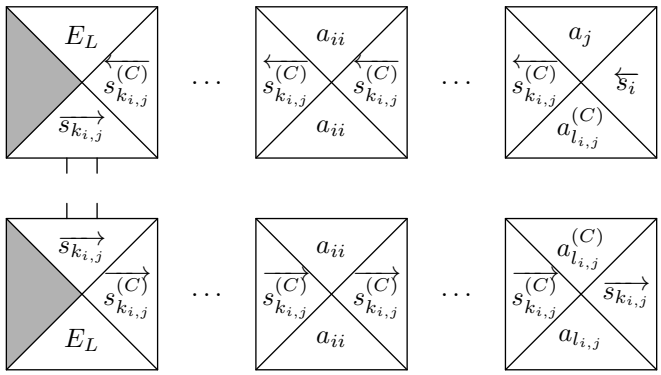
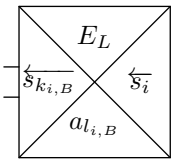
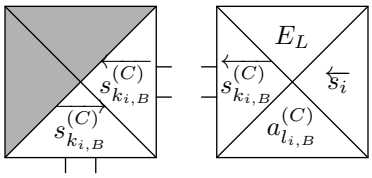


Figure 3.1: Tileset 1/2.

Reads EndLeft, continues left:



Reads EndLeft, continues back to the right:



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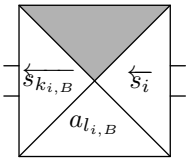


Comes from right and reads Blank, continues back to the right:

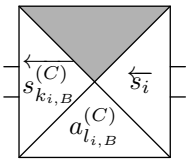


Figure 3.2: Tileset 2/2.

error-tolerant rules – Gacs and Reif, 1988

Chapter 4

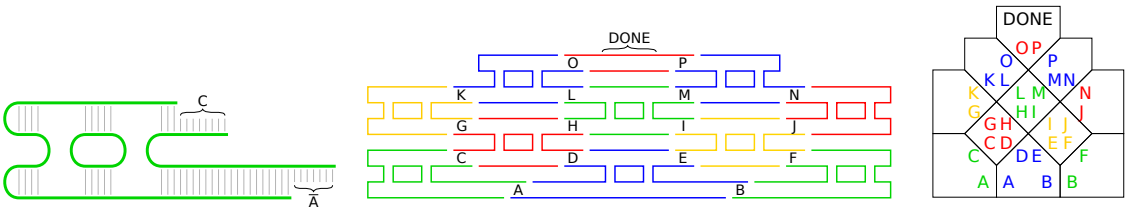
Results

4.1 Abstract model for DAE units

It is better to draw easier-to-understand pictures. Explanation: ... Call those DNA sequences "glues".

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 – biostep complexity is not restrictive[1] and will be required to be $O(1)$ due to its lab complexity. 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.



(a) Corner DAE unit (b) Whole self-assembly (c) Abstract model

Figure 4.1: Evolution of abstract model from DAE units to tiles.

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!

[1] From Turing's thesis, Turing machine is the most universal model.

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 $1\text{1}/2\ n^2$. The improvement decreases it to $1\text{1}/4\ n^2$.

Set of tiles

First of all the graph needs to have even number of vertices, thus one separated non-colored vertex has to be added if applicable. Then follow these rules which are showed in an example, see figure 4.3.

Bottom line For every pair $(2k, 2k+1)$ there will be a bottom-type tile with non-colored numbers $(2k+2, 2k)$ on the bottom and with all feasible[2] color combinations of $(2k+1, 2k)$ on the top. From practical decoding reasons (see Winfree [11]) the sequences encoding colored numbers on the top must be physically present also wherever on the bottom DNA strand, see figure 4.2. $\frac{9n}{2}$ tile types were required.

Bottom corner tiles Both corner tiles are connected on the bottom by the highest and the lowest non-colored number, respectively, and have their special glue (# for $-\infty$ and * for $+\infty$, respectively) on the top. These first two sets of tiles generate all colorings of given graph (without those omitted in previous step) with reverse order of numbers. 2 tile types were required.

Inner tiles These tiles are responsible for ordering[3]. There exist all color combinations for all different numbers with two important exceptions. There *do not* exist tiles with numbers of connected vertices with the same color. Thus, as soon as there appears such forbidden combination, the self assembly cannot continue and reach "DONE". Because the numbers are generated in reverse order they must meet each other – note that they simply cannot "jump" and every number has to exchange with all the higher ones as well as with the lower ones. This implies that every forbidden combination would be revealed, thus it answers correctly if and only if the coloring is correct. The second exception are those described in the following paragraph. $9n^2$ tile types were required.

Border tiles There are two tile types on the borders, one with sharp, one with asterisk. They keep the structure growing up.

Checking tiles As soon as the biggest and the smallest number reach * and #, respectively, there are two special tiles which start checking whether nothing is missing. Note that all tiles had time enough to get into correct order. In this setup checking tiles do not need to check correct order thus there can exist only two types of checking sequences "C" and "D" with all color-number combinations of middle numbers – "D" with the smaller half, "C" with the higher half. $3n$ tile types were required.

[2] If $(2k+1, 2k)$ are connected, same-colored numbers are omitted.

[3] Principially they are the same as in Winfree [11].

DONE tile If everything is checked and checking sequences meet each other, "DONE" tile will be connected to signalize correct solution. 1 tile type was required.

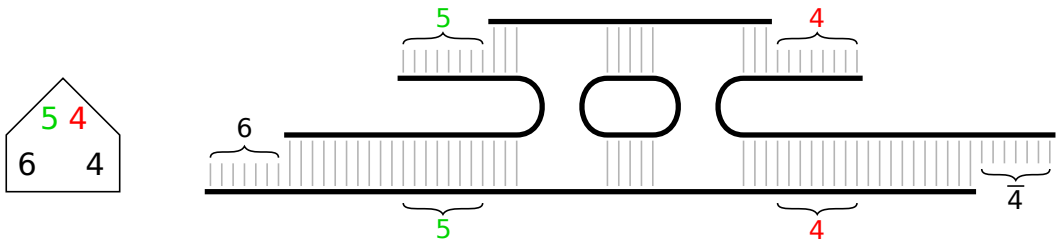


Figure 4.2: Bottom tile with desired sequences in the bottom strand.

Summed up, this DNA algorithm requires $9n^2$ tile types.

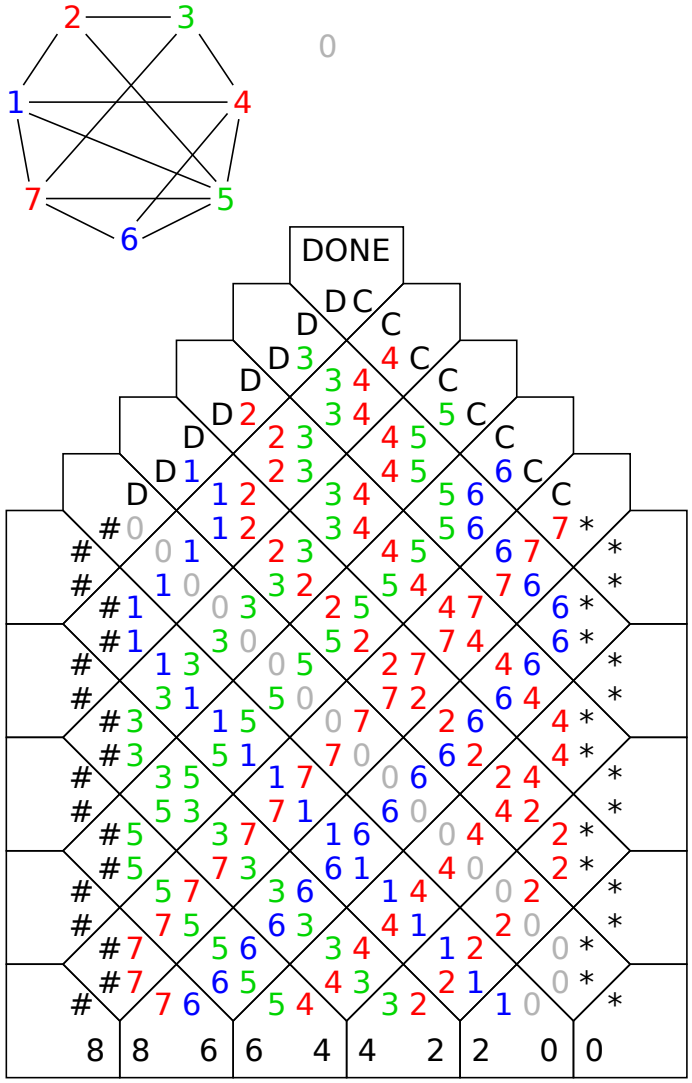


Figure 4.3: 3-color computation.

4.3 Graph isomorphism

Graph isomorphism problem clearly belongs to NP but it does not seem to be NP-hard[4] [**?**]. 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 very special problem.

Surprisingly it is very similar to 3-coloring if we consider n colors instead. The problem can be stated: "For a non-colored graph G and a graph H where every vertex is colored with different color, find a coloring of G with all of those n colors used exactly once (1) such that these colored graphs are isomorphic (2)." Now one has to check that:

1. every "color" was used exactly once so that it is a bijection,
2. edges and non-edges are preserved.

Set of tiles

Like before, the graph needs to have even number of vertices, thus one separated self-bijective vertex has to be added if applicable. An example is given, see figure 4.5.

Bottom line These tiles have almost exactly the same rules as in graph 3-coloring, the difference is that *all* of the same-colored combinations are omitted. $\frac{n^3}{2}$ tile types were required.

Bottom corner tiles Are exactly the same. 2 tile types were required.

Inner tiles There are three types of inner tiles:

Number-ordering tiles These are similar to previous ones, the difference is which do exist and which do not. Let us assume a tile with numbers k and l with colors a and b, respectively. Note that numbers k and l correspond with vertices in graph G and colors a and b correspond with vertices in graph H. This tile must check the isomorphism property – existence or non-existence of edge between appropriate vertices. Thus the tile exists if and only if

$$(\{k, l\} \in E(G) \wedge \{a, b\} \in E(H)) \vee (\{k, l\} \notin E(G) \wedge \{a, b\} \notin E(H)).$$

From similar reasons all pairs of vertices from graph G meet each other, thus every edge is checked so condition number 2 would be done. n^4 tile types were required.

Color extracting tiles Now I have to extract colors (forget numbers) and order them in given order so that I can check that every color is used exactly once. This process will be triggered by a special inner tile with the highest number of arbitrary color and a non-colored asterisk on the bottom. On the top it will have an asterisk of that number's color and a non-colored asterisk. For every other number with arbitrary color there exists a tile with it and an asterisk of an arbitrary but different color on the bottom. On the top it will have two asterisks of these colors in correct order. n^3 tile types were required.

Color-ordering tiles These are similar to those with numbers. Similarly there do not exist tiles with one color. n^2 tile types were required.

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

Border tiles These tiles are exactly the same like for 3-coloring.

Checking tiles As soon as there appears a combination of sharp and most-left-colored asterisk, a checking tile comes having "C" of the second color on the right top. After this initialization there are tiles with colored "C" and same-colored asterisk on the bottom and next-colored "C" on the right top. This ensures that every color was used exactly once. The last color is followed by non-colored "C". n tile types were required.

DONE tile Finally if non-colored "C" meets non-colored asterisk, a "DONE" tile is connected signalizing correct solution. 1 tile type was required.

Summed up, this DNA algorithm requires n^4 tile types.

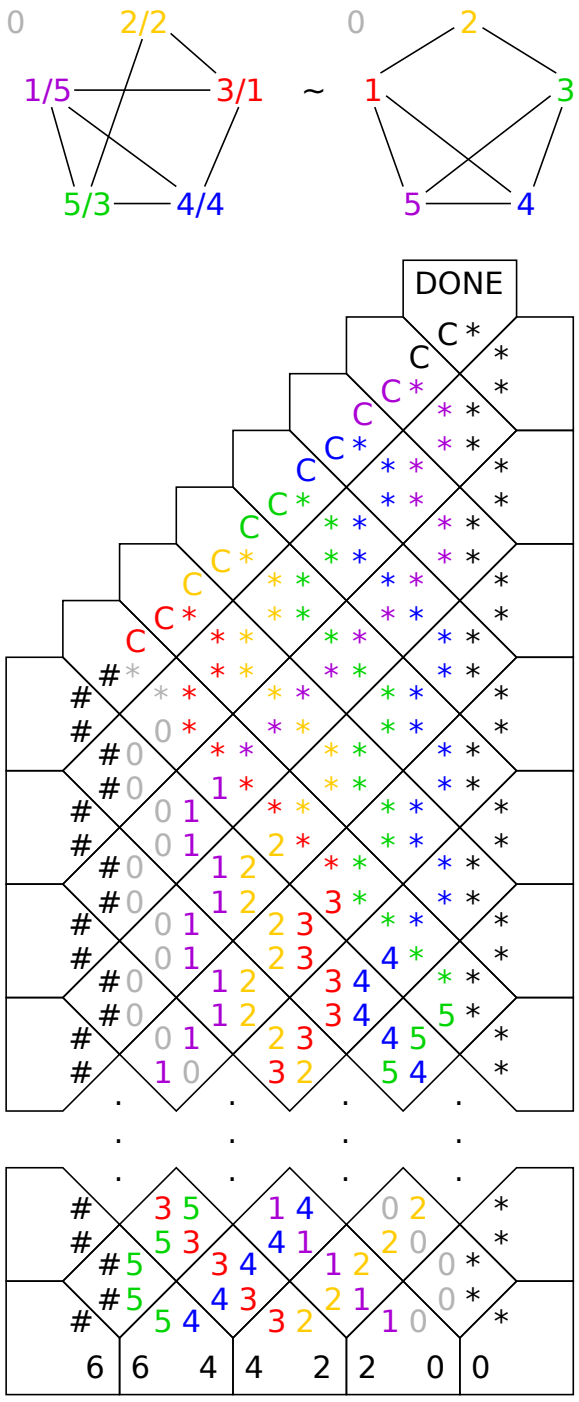


Figure 4.4: Graph isomorphism computation. Color order is defined by their wavelength.

4.4 k-clique

k-clique problem belongs to NP-complete problems. Note that k-clique problem in G is equivalent to $n-k$ independent set in $\overline{G}$ so we can assume $k \leq \frac{n}{2}$. Like before we add an unchecked vertex if k is odd so we will assume k to be even.

Set of tiles

Bottom line For now there are tiles with $2l-2$ and $2l$ $(0 < l \leq \frac{k}{2})$ on the bottom and with an arbitraty ordered[5] pair of different numbers from 1 to n with $k-2l+2$-th and $k-2l+1$-th colors, respectively, on the top. Note that now the order of colors is given and do not forget that they should also contain those upper sequences once more on the bottom strand. $\frac{kn^2}{4}$ tile types were required.

Bottom corner tiles Are exactly the same. 2 tile types were required.

Inner tiles These tiles are now responsible for ordering by color during which they check existence of *every* edge in similar manner to previous problems. And because the first line contains them in reverse order there will meet each other. k^2n^2 tile types were required.

Border tiles These tiles are exactly the same like for 3-coloring.

Checking tiles As soon as the most left color reaches sharp and the most right color reaches asterisk, checking is triggered in similar manner to 3-coloring. kn tile types were required.

DONE tile This is exactly the same like 3-coloring. 1 tile type was required.

Summed up, this DNA algorithm requires k^2n^2 tile types.

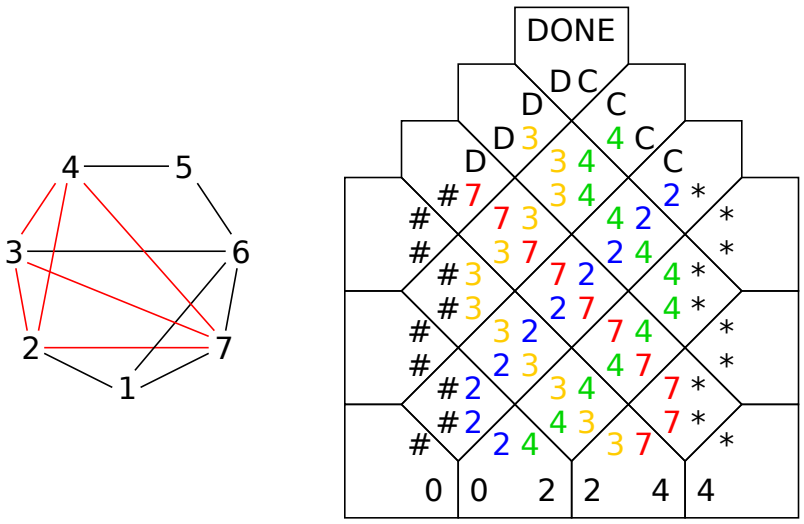


Figure 4.5: k-clique computation. Color order is defined by their wavelength.

[5]Note that this restriction does not reduce the set of possible k-member subsets.

Epilog

The very last section to be done.

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