ČESKÉ VYSOKÉ UČENÍ TECHNICKÉ V PRAZE

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Modely sebeskládajících DNA nanostruktur

Models of self-assembling DNA nanostructures

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V Praze dne February 21, 2014

. . . . . .
Jakub Klemsa

Poděkování

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

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Contents

Chapter 1

Introduction to DNA computation

1959: Feynman's visionary talk, [7]; pros: extreme paralelism, cons: reliability.

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

1.1 Basic DNA principles

DNA (deoxyribonucleic acid) is a large biomolecule carrying living organisms' genetic information. Its most common structure is well known double-helix which consists of two strands connected by hydrogen bonds. These strands are biopolymers built up by *polymerase chain reaction* (PCR) from small units – nucleotides. Each nucleotide consists of two parts: nitrogenous base and backbone molecules.

Nitrogenous bases There are 4 nucleobases in DNA (+1 in RNA): Adenine (**A**), Thymine (**T**), Cytosine (**C**), Guanine (**G**) and Uracil (**U**) in RNA instead of Thymine in DNA. These molecules are responsible for making hydrogen bonds between strands in a manner following Watson-Crick complementarity: only **A** – **T** and **C** – **G** pairs can be formed.

Backbone molecules Backbone of DNA strand is made of alternating deoxyriboses and phosphates. Phosphates only hold adjacent deoxyriboses, each deoxyribose moreover holds one nucleobase. Due to deoxyribose carbon numbering, DNA backbone has so called $5'$ and $3'$ ends, default reading order is $5' \to 3'$. DNA strands must be antiparallel so that nucleobases can connect.

1.2 Complexity, languages

1.2.1 O and other notations

Let us briefly remind O-, o-, Ω-, ω- and Θ-notations for $f, g : \mathbb{N} \to \mathbb{N}$. We will denote $(\exists n_0 \in \mathbb{N})(\forall n > n_0)$ shortly by $(\forall^* n)$ which can be read "for almost all n". Also $(\forall n_0 \in \mathbb{N})(\exists n > n_0)$ will be denoted by $(\exists^\infty n)$ which can be read "there exist infinitedly many n".

Definition 1.1.

$$g \in O(f) \Leftrightarrow (\exists C > 0)(\forall^* n)\big(g(n) < Cf(n)\big)$$
$$g \in \omega^{(1)}(f) \Leftrightarrow (\forall C > 0)(\exists^\infty n)\big(g(n) > Cf(n)\big)$$
$$g \in \omega^{(2)}(f) \Leftrightarrow (\forall C > 0)(\forall^* n)\big(g(n) > Cf(n)\big)$$
$$g \in \Omega^{(1)}(f) \Leftrightarrow (\exists C > 0)(\exists^\infty n)\big(g(n) > Cf(n)\big)$$
$$g \in \Omega^{(2)}(f) \Leftrightarrow (\exists C > 0)(\forall^* n)\big(g(n) > Cf(n)\big)$$
$$g \in o(f) \Leftrightarrow (\forall C > 0)(\forall^* n)\big(g(n) < Cf(n)\big)$$
$$g \in \Theta(f) \Leftrightarrow (\exists C_1, C_2 > 0)(\forall^* n)\big(C_1 f(n) \le g(n) \le C_2 f(n)\big)$$
$$g \sim f \Leftrightarrow \lim_{n\to\infty} \frac{g(n)}{f(n)} = 1$$

Remark 1.1. Note that there are two different definitions for omegas. $\Omega^{(1)}$ is equivalent to the orgininal definition introduced by Hardy [9] which states

$$f \in \Omega(g) \Leftrightarrow \limsup_{n\to\infty} \frac{f(n)}{g(n)} > 0. \tag{1.1}$$

The other, $\Omega^{(2)}$, was introduced by Knuth from good reasons described in [10]. In similar manner there are two definitions for ω.

Note that there are also some relations: the condition for $\Omega^{(1)}$ is negation of the condition for o so these sets are complementary for given function f, similarly for $\omega^{(1)}$ and O. For the second variant one can easily check that $f \in \Omega^{(2)}(g) \Leftrightarrow g \in O(f)$ and $f \in \omega^{(2)}(g) \Leftrightarrow g \in o(f)$. There is also an equivalent condition for Θ:

$$g \in \Theta(f) \Leftrightarrow g \in O(f) \wedge f \in O(g) \Leftrightarrow g \in O(f) \wedge g \in \Omega^{(2)}(f). \tag{1.2}$$

The condition for $g \sim f$ can be easily seen to be equivalent to $|f - g| \in o(g)$. In chapter 2 we will be mostly interested in this relation because it specifies the function better than Θ. For example, $2n \in \Theta(n)$ but $2n \not\sim n$.

1.2.2 Studied complexities

Definition 1.2. All the following complexities are considered as functions of problem size n:

Biostep complexity will refer to the number of laboratory steps required to handle the computation, denoted by $Bs(n)$.

Binding complexity will refer to the number of bindings in given computation, denoted by $Bnd(n)$.

Tile complexity will refer to the number of different DNA tiles, denoted by $Ti(n)$.

Glue complexity will refer to the number of different sticky-end sequences (commonly referred to as *glues*), denoted by $Gl(n)$. Each sequence with its Watson-Crick complement is considered as one glue.

Remark 1.2. Note some properties of proposed complexities.

Ad biostep complexity Adleman [3] describes formally in his *unrestricted model* few types of such lab procedures – *Separate, Merge, Detect* and *Amplify*, Winfree [14] adds another – *Append*. And both of them remind that one biostep takes tens of minutes. Thus the only practically feasible DNA algorithms are those with $O(1)$ biostep complexity.

Ad binding complexity Too high binding complexity leads to lower probability of correct computation P_c because it holds $P_c(n) = (1 - p_e)^{Bnd(n)} \approx^{1} 1 - p_e \cdot Bnd(n)$ where p_e denotes probability of erroneous binding.

Ad tile complexity The higher tile complexity the more demanding it is to prepare required tiles.

Ad glue complexity Higher glue complexity will require longer DNA sequences in the sticky ends.

1.2.3 Languages

Definition 1.3. Let Σ be an nonempty and finite set of *characters* which will be referred to as *alphabet*. Define set of *words* over alphabet Σ as $\Sigma^* = \bigcup_{n\in\mathbb{N}_0} \Sigma^n$ and set of nonempty words as $\Sigma^+ = \bigcup_{n\in\mathbb{N}} \Sigma^n$. Empty word will be denoted by ε. *Language* $\mathcal{L}$ over alphabet Σ is then just a set of words: $\mathcal{L} \subseteq \Sigma^*$. *Complement* of language $\mathcal{L}$ will be denoted by $\overline{\mathcal{L}} = \Sigma^* \setminus \mathcal{L}$.

Let us briefly remind Chomsky hierarchy of languages generated by generative grammars. Denote alphabet of non-terminals by N, alphabet of terminals by Σ and initial symbol by I.

Recursively enumerable (type 0) Generated by unrestricted grammar rules.

Context-sensitive (type 1) Grammar rules are either all of the form $\alpha A\beta \to \alpha\eta\beta$ where $\alpha, \beta \in (N \cup \Sigma)^*$, $A \in N$ and $\eta \in (N \cup \Sigma)^+$. Note that η cannot be empty. Or, if we assume these rules without those having I on the right hand side, then there is allowed also the rule $I \to \varepsilon$.

Context-free (type 2) All grammar rules are of the form $A \to \eta$ where $A \in N$ and $\eta \in (N \cup \Sigma)^*$. Note that η can be empty.

Regular (type 3) Grammar rules are either all of the forms $A \to bB$ and $A \to b$ where $A, B \in N$ and $b \in \Sigma$. Or, if we assume these rules without those having I on the right hand side, then there is allowed also the rule $I \to \varepsilon$.

[1] If reasonable.

Remark 1.3. Note that given an alphabet Σ the set of all words Σ^* is countable. Moreover, one can sort Σ^* first by word length, then lexicographically thus it is easy to define desired bijection $f : \mathbb{N} \leftrightarrow \Sigma^*$.

Formal language $\mathcal{L}$ can then be viewed as a boolean function $g : \mathbb{N} \to \{0, 1\}$ defined as $g(n) = 1 \Leftrightarrow f(n) \in \mathcal{L}$.

1.2.4 P, NP and other

This section describes some classes of languages from the resource-consumption point of view. Note that all of these sets are a subset of recursively enumerable languages.

There exist many equivalent definitions, these are taken from [4]. The first set of definitions is very straightforward and thus can be used for propositions.

Definition 1.4. $\mathcal{L} \subseteq \Sigma^*$. $\mathcal{L} \in \mathsf{P} \Leftrightarrow \big(\exists p \in \mathcal{P}\big)\big(\exists$ deterministic Turing machine $M\big)$ $\big(\forall x \in \Sigma^*\big)\big(x \in \mathcal{L} \Leftrightarrow M$ accepts x in time $\leq p(|x|)\big)$.

Definition 1.5. $\mathcal{L} \subseteq \Sigma^*$. $\mathcal{L} \in \mathsf{NP} \Leftrightarrow \big(\exists p, q \in \mathcal{P}\big)\big(\exists$ deterministic Turing machine $M\big)$ $\Big(\forall x \in \Sigma^*\Big)\Big(x \in \mathcal{L} \Leftrightarrow \big(\exists y \in \Sigma^{p(|x|)}\big)\big(M$ accepts (x, y) in time $\leq q(|x| + |y|)\big)\Big)$.
Such y will be referred to as *certificate* for x (with respect to $\mathcal{L}$ and M).

Definition 1.6. $\mathcal{L} \subseteq \Sigma^*$. $\mathcal{L} \in \mathsf{co\text{-}NP} \Leftrightarrow \big(\exists p, q \in \mathcal{P}\big)\big(\exists$ deterministic Turing machine $M\big)$ $\Big(\forall x \in \Sigma^*\Big)\Big(x \in \mathcal{L} \Leftrightarrow \big(\forall y \in \Sigma^{p(|x|)}\big)\big(M$ accepts (x, y) in time $\leq q(|x| + |y|)\big)\Big)$.

The second possibility is to first define general classes DTime, NTime, DSpace and NSpace and after that to use their special case. Remind how Non-deterministic Turing machine (NTM) differs from Deterministic Turing machine (DTM):

- it is allowed to have ambiguous transition function,
- it has two types of terminal states: accepting q_{accept} and halting without accepting q_{halt} (not rejecting!). We say it accepts input x iff there *exists* a sequence of decisions ending in q_{accept}, it declines x iff *for every* sequence of decisions reaches q_{halt}.

Definition 1.7. $\mathsf{DTime}\big(f(n)\big) = \big\{\mathcal{L}$ language $\big|\ (\exists$ deterministic Turing machine $M)$ $(\forall x \in \Sigma^*)\big(x \in \mathcal{L} \Leftrightarrow M$ accepts x in time $\leq f(|x|)\big)\big\}$.
Other classes are defined in a very similar manner: time $\leftrightarrow$ space, deterministic $\leftrightarrow$ non-deterministic.

Definition 1.8. $\mathsf{P} = \bigcup_{k \in \mathbb{N}} \mathsf{DTime}(n^k)$ and $\mathsf{NP} = \bigcup_{k \in \mathbb{N}} \mathsf{NTime}(n^k)$.

Definition 1.9. $\mathcal{L} \in \mathsf{co\text{-}NP} \Leftrightarrow \overline{\mathcal{L}} \in \mathsf{NP}$

Note 1.4. $\mathsf{NP} \subseteq \mathcal{P}(\Sigma^*)$ so the notation co-NP might be confusing. Note that co-NP is *not* a complement to NP as a set of languages.

Remark 1.5. In case of P there is no "co" version. It leads from $\mathcal{L} \in \mathsf{P} \Leftrightarrow \overline{\mathcal{L}} \in \mathsf{P}$. This can be easily seen because deterministic Turing machine is capable of negation with the same time resources, non-deterministic is not known to. Note that Immerman–Szelepcsényi theorem states possibility of non-deterministic Turing machine negation in limited *space*: $\mathcal{L} \in \mathsf{NSpace}(s(n)) \Leftrightarrow \overline{\mathcal{L}} \in \mathsf{NSpace}(s(n))$ for $s(n) \geq \log(n)$.

Theorem 1.1. All of the previous definitions of P, NP and co-NP are equivalent, see [4].

To define probabilistic classes of languages (BPP, RP, co-RP and ZPP) we will remind the concept of Probabilistic Turing machine (PTM). Like NTM it is allowed to have ambiguous transition function, moreover, in every state there is defined a transition probability. We say that PTM M decides language $\mathcal{L}$ iff for every $x \in \Sigma^*$ the probability of halting in correct state (i.e. q_{accept} for $x \in \mathcal{L}$ and q_{reject} for $x \notin \mathcal{L}$) is higher than $2/3$. Now we can define those classes, note that it would be possible to use again two types of definition like above.

Definition 1.10. $\mathsf{BPTime}\big(f(n)\big) = \big\{\mathcal{L} \text{ language} \,\big|\, (\exists \text{ probabilistic Turing machine } M)$ $\big(M \text{ decides } \mathcal{L} \text{ in time } \leq f(|x|)\big)\big\}$.

Definition 1.11. $\mathsf{BPP} = \bigcup_{k\in\mathbb{N}} \mathsf{BPTime}(n^k)$.

SAT: Lipton's contribution using m biosteps ($m = \#clauses$), [12], Lipton's set of speedup problems, [11].

Energy efficiency (Adleman).

1.3 Strand models

There exist (can be synthesized) many types of molecules, well described by Winfree [14] even with their inception reaction. These can form linear strands (sections 1.3.1, 1.3.2), dendrimer structures (section 1.3.3) or 2D tilings (section 1.3.4).

1.3.1 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.

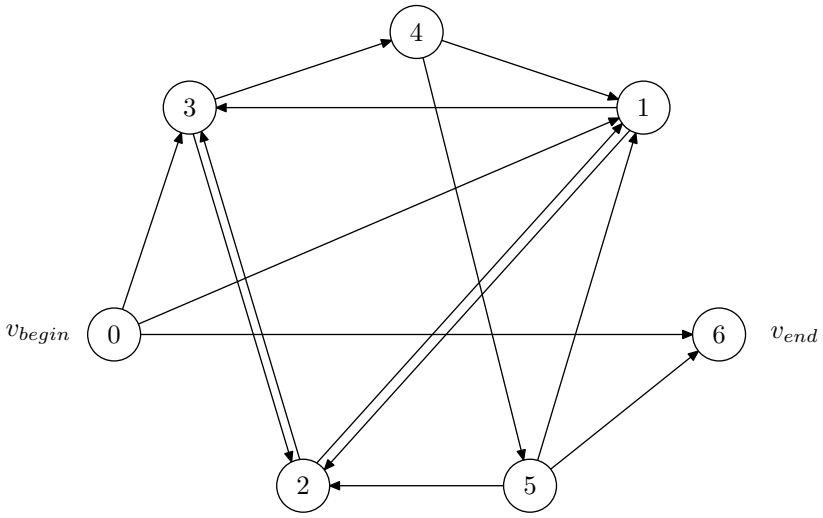


Figure 1.1: Adleman's original graph.

Adleman originally used a graph with seven vertices shown in figure 1.1. It can be seen that the path $0 \to 1 \to 2 \to 3 \to 4 \to 5 \to 6$ is Hamiltonian[2].

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."[3]

To see how DNA can compute, let us describe this example more precisely. The computation itself (meaning the inception of the final solution) is hidden in Step 1. Each vertex i is associated with a random[4] 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 $j = end$.

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

[3]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 it may happen that there exists a valid path but unfortunately it did not assemble or got lost. Note the similarity to NP versus co-NP, see section 1.2.4.

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

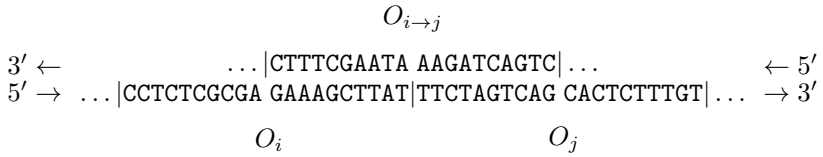


Figure 1.2: Example of assigned sequences.

It can be easily seen that all correctly bonded double-strands correspond with a valid walk through G_n. Moreover, all complete double-strands represent a valid walk 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 this algorithm has biostep complexity $O(n)$ which we considered unfeasible. Better solution with biostep complexity $O(1)$ was brought by Winfree [14], see section 1.3.4.

1.3.2 Linear strands

Equivalent to regular languages.

1.3.3 Dendrimer structures

Equivalent to context-free languages.

1.3.4 Double crossover molecules

DAO vs. DAE units. Winfree 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 [8], is the picture of DAO strange?

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.

1.4 Wang-tile models

1.4.1 Definition

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

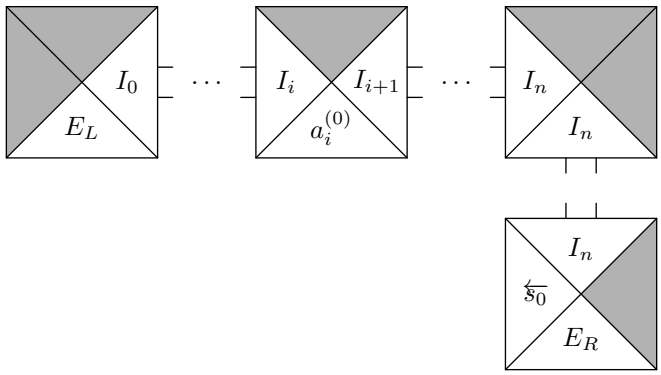
1.4.2 Computational power

Give table of Turing universality [6].

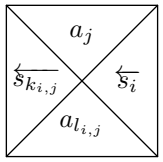
See [14]. Many other results in [6], [5], [13], [1] ...

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

Input tape:



Comes from right, continues left:



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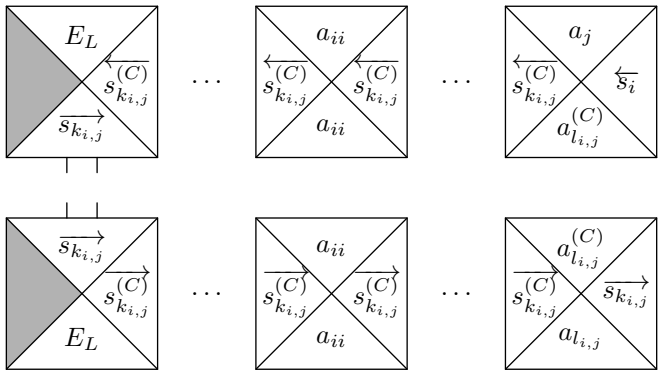
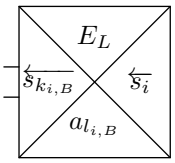
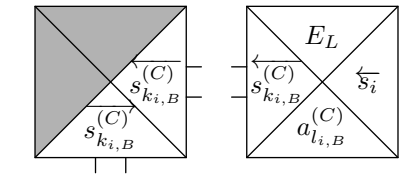


Figure 1.3: Tileset 1/2.

Reads EndLeft, continues left:



Reads EndLeft, continues back to the right:



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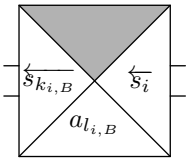

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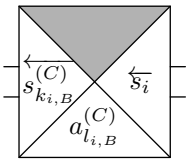


Figure 1.4: Tileset 2/2.

error-tolerant rules – Gacs and Reif, 1988

Chapter 2

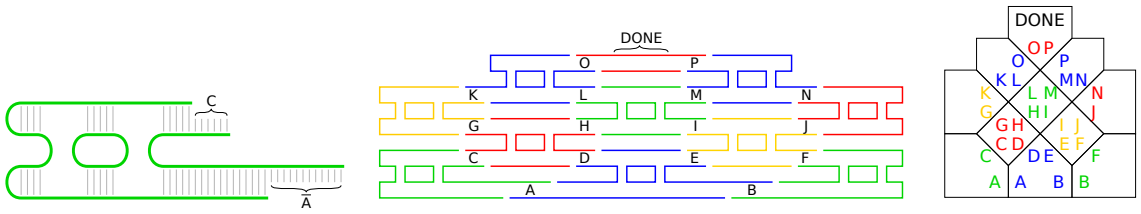
Solutions to NP problems

2.1 Abstract model for DAE units

It is better to draw easier-to-understand pictures. Explanation: ... Call those DNA sequences "glues". Binding, tile and glue complexity. Note those twice longer sticky ends on the bottom line.

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.

Note that the word on the bottom line can be restricted to belong to arbitrary regular language.



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

Figure 2.1: Evolution of abstract model from DAE units to tiles.

2.2 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! Robusticity?

[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.

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 2.3.

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 [14]) the sequences encoding colored numbers on the top must be physically present also wherever on the bottom DNA strand, see figure 2.2. $\frac{9n}{2}$ 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.

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.

[2] If $(2k+1, 2k)$ are connected, same-colored numbers are omitted.
[3] Principially they are the same as in Winfree [14].

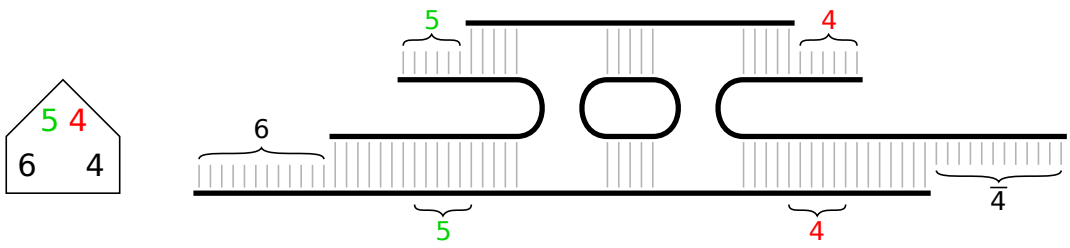


Figure 2.2: Bottom tile with desired sequences in the bottom strand.

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

The first idea's binding complexity was like $O(n^4)$, the second is already $O(n^2)$, the binding complexity is $1^1/_2\ n^2$. The improvement decreases it to $1^1/_4\ n^2$.

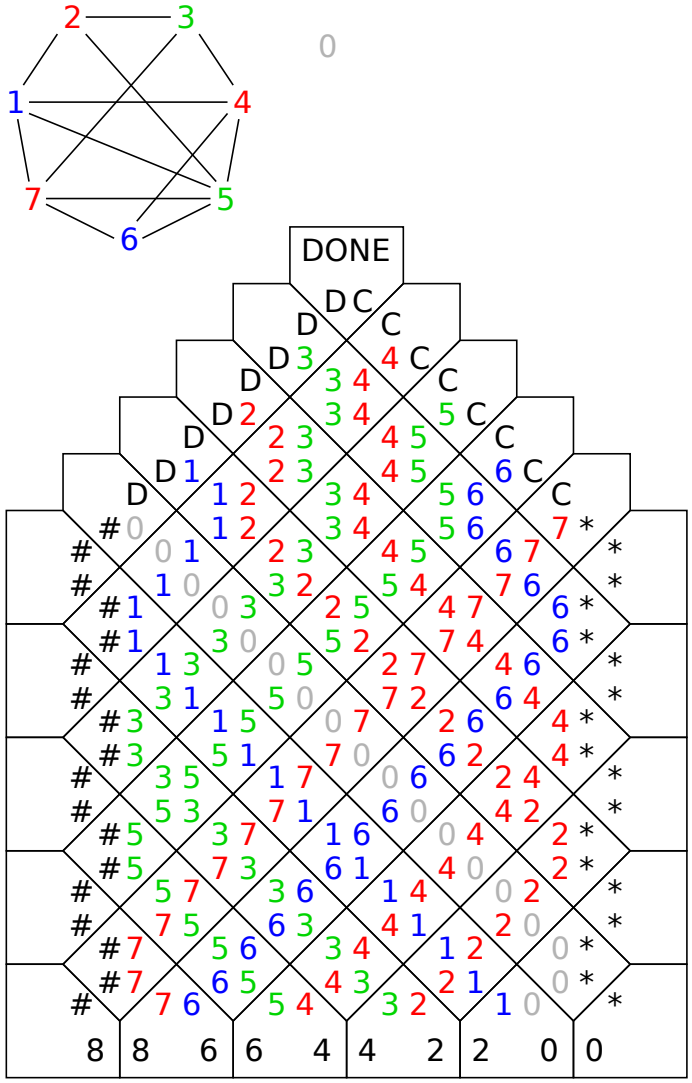


Figure 2.3: 3-color computation.

2.3 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 we 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 2.5.

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 we have to extract colors (forget numbers) and order them in given order so that we 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 and its binding complexity is $2^1/_2\, n^2$. Glue complexity is ...

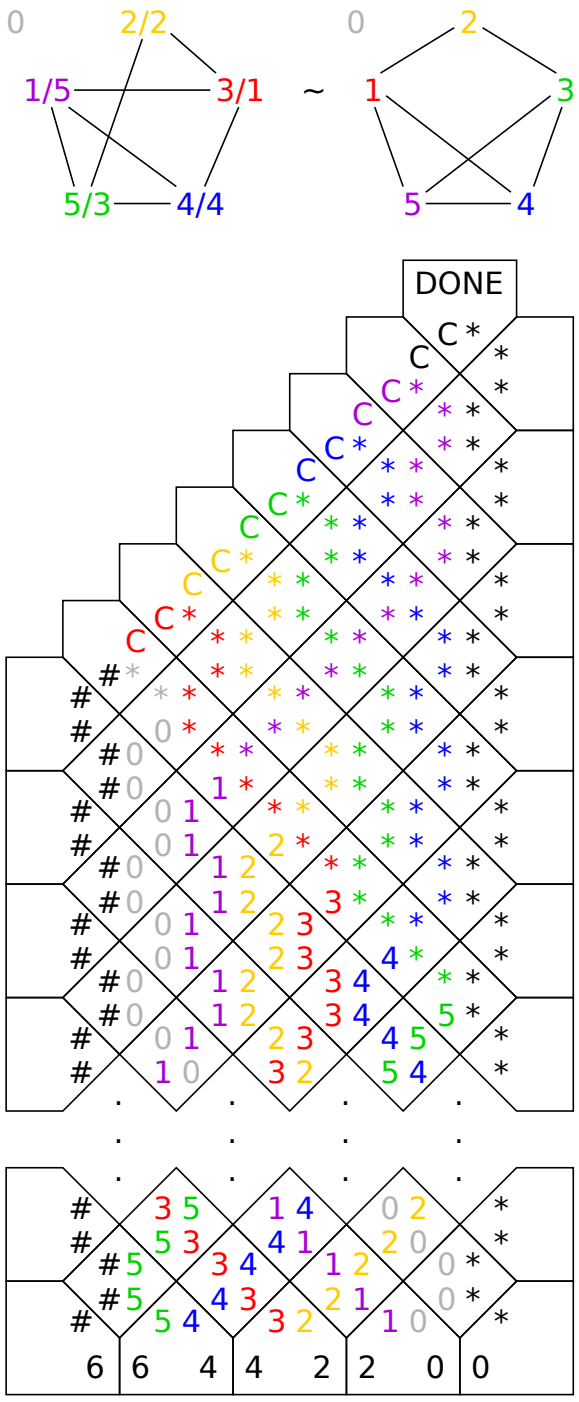


Figure 2.4: Graph isomorphism computation. Color order is defined by their wavelength.

2.4 k-clique

k-clique problem belongs to NP-complete problems. Note that k-clique problem in G is equivalent to k-independent set in $\overline{G}$ and that is equivalent to $n-k$-vertex cover of $\overline{G}$ 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. Binding complexity is $1^1/_4$ $\min\{k^2, (n-k)^2\}$ Glue complexity is ...

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

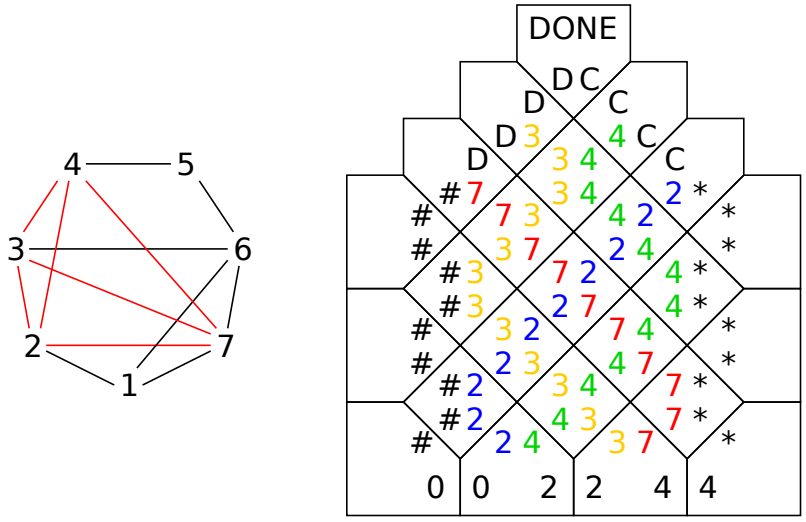


Figure 2.5: k-clique computation. Color order is defined by their wavelength.

2.5 DNA computation feasibility

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