# DNA Computing: Theory, Models and Wet lab Experiments

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DNA Computing is a field mixing theory, models and wet lab experiments that emerged at the end of the 1990s. The goal is to design nanoscale DNA/RNA-based molecular computing devices for real. Achievements of the field includes: reliable processes to design shapes (namely, DNA origami) [20], DNA-based implementation of cellular automata [21, 9], nano robotics [24], fast boolean circuit [28, 16, 23], implementation of a 6-bit universal computer as a DNA nanotube [27]. An important challenge of the field is to move to reconfigurable devices allowing reversible in-place computation.

Theory plays a key role in this field as it allows to explore much faster than experiments the potential of a given experimental setup (e.g. [25, 22, 1, 2, 3, 4, 5, 7, 8]). It also allows to improve the reliability and efficiency of experiments. Theory borrows mainly from cellular automata, tilings, dynamical system, and probability.

Regarding wet lab, thanks to the nice behavior of DNA, experiments in this field do not require any particular skills. Any computer scientist with no wet lab training but good will (as I and many main actors of the field were) will be able to conduct experiment after few days of training. We have an agreement with the ENS biology lab (lab bench) and the ENS physics lab (atomic force microscopy) to conduct our experiment in an ideal setting.

Here are some examples of the research that we conduct here in this field.

**Theory and Models.** We are currently studying the Oritatami system (OS) model which aims at understanding the computing power of molecular cotranscriptional folding in nature. Wet-lab experimental work in [12] showed that RNA cotranscriptional folding can be used to built regular hexagonal grid at constant human-compatible temperature ($\sim 37°C$), as opposed to "classic" DNA based tiles or DNA origami that require higher temperatures and annealing (from $65°C$ to $45°C$) [20, 26]. Oritatami systems were introduced in [11, 10, 14] to explore the computation capabilities of these experimental systems. It consists in a "molecule" made of "beads" that attract each other. The molecule grows by one bead at each step and at each step, the $\delta$ most recently produced beads are allowed to move around to look for the position that maximizes the number of bonds they can make (hence the folding is co-transcriptional). This process ends up

self-assembling a shape incrementally. We have first proposed an OS implementing a binary counter [10] and then showed that there is a Turing complete OS [13] simulating arbitrary tag systems. We recently gave a much simpler construction simulating any 1D cellular automata [18] by defining elegant simple "mechanical" tools that have their own interest. Oritatami are somehow hard to program as is, but we are currently working on a new theoretical model (*Turedos*, related to Turmites) together with a corresponding OS simulation (a kind of *compiler*) that will considerably simplify the programmation of oritatami systems. One of the main objectives of the DNA computing field is also the construction of nanoscaled shapes. We have obtained an algorithm to build OS that self-assembles into an arbitrary shape at scale 3 [6]; [17] exhibits an OS that self-assembles into a complex fractal (Heighway dragon). Several questions such as the equivalence of two OS have been proved to be (co)NP-complete [15].

**Experimental work under development.** We are currently running several experimental projects in collaboration with various teams in France and Ireland, namely: Y. Rondelez' team at ESPCI (Paris); G. Bellot's team at CBS, U. Montpellier; A. Genot's team at LIMMS, CNRS & Tokyo U. (Japon); D. Woods' team at Hamilton I., Maynooth U. (Ireland); M. Leocmach's team at iLM, Lyon I U. One aims at solving mazes with a DNA strand system, an other at designing a DNA gel with shape-learning capacities, the next one at studying the mechanical properties of aperiodic DNA gels, finally at designing a complete 3D software solution for designing DNA nanoobjects, validated by experiments. Taking part to the development of one of these projects could be the experimental part of this internship (see bellow).

**Example of open questions:** Many questions are open in this field:

**Theory and Models:** Most of the questions below concern Oritatami model

- We know that there are shapes that cannot be self-assembled using an OS at scale 1. What about scale 2? We believe that there are shapes impossible to self-assemble using any OS at scale 2 but are currently unable to prove it. We believe that proving this will require the development of new and interesting technics.
- Our Turing-universal OS simulating arbitrary tag systems is quite sophisticated and geometrically intricate. Moreover tag systems are a non-intuitive model for computation. We have recently provided a simple and direct enough cellular automata intrinsic simulation [18]. However, we would like to design an OS programming system which is closer to classic programing models, including `for` loops, random access memory, composition, etc.
- There are several parameters in OS, namely the delay $\delta$ and the arity (the maximum number of bonds that can be made between beads). Some work have started to study the influence of these parameters [19] but these are still widely not understood. For instance, no one knows whether increasing/decreasing the delay, yields a more/less powerful OS. One approach to

this question would be to show that some OS can simulate whole classes of other *intrinsically*. We propose to study the existence of an intrinsically universal OS, that is an OS that could simulated any other OS.

- Describing random shapes produced by random Oritatami systems is a challenging direction to explore that would have important impact on our understanding or co-transcriptional folding in biology
- Finally, several extensions of the Oritatami model should be considered: introducing probabilistic local rearrangements or extending to 3D would be a decisive step into making the model closer to nature.

**Software design:** The help of softwares is critical in design biomolecular devices to help predict correctly their shape and behavior. Most of the current softwares are quite unsatisfying and unmaintained which makes them hard to use. We are currently developing in `Rust` a complete high-performance software suite `icedNano`, a powerful alternative to the current classic origami design softwares such as `CADnano`,[1] `Scadnano`, [2] the free-form DNA-structure design software `vHelix`,[3] and the folding prediction software `CanDo`[4] whose usage is widely spread in this field, but which are also notably hard to use. Many other softwares are needed, in particular, to simulate efficiently the kinetic of the reactions/folding.

**Wetlab experiments:** The most challenging questions we would like to address concern the design of configurable biomolecular devices which would allow in-place computation.

- *Oritatami modules implementation:* Our new Oritatami cellular automata intrinsic simulation uses very simple key modules. We believe that some simplified version of them could be implemented in DNA/RNA. In particular, we would be interested in implementing in DNA/RNA the speed bumps in particular, because this would be a important, simple enough yet interesting, first step towards reconfigurable biomolecular devices.
- *Learning biomolecular devices:* We would like to design devices that are able to learn from their environment as, for instance, our immune system does. We are currently running an experimental project with Yannick Rondelez (ESPCI) and Anthony Genot (LIMMS, Japan) to get a DNA gel to "learn" a shape and replicate it. We would like to investigate other settings where learning could be involved in biomolecular chemistry such as learning how to solve an (easy!) problem using a "self-reconfiguring" biomolecular boolean circuit.

[1] `https://cadnano.org/`
[2] `https://scadnano.org/`
[3] `http://www.vhelix.net/`
[4] `https://cando-dna-origami.org/`

- *Mechanical properties of DNA Gels:* We would like to design DNA gels that self-assembles as quasi-crystals (aperiodic tiling) to study their mechanical properties (rupture, etc.).
- *Implementing algorithms in DNA:* We are currently developping an experimental setting to break the scalability barrier of the current DNA implementations of algorithms. Our framework relies on a small fixed number of strands or complexes, independent of the size of the input. We will focus on a basic problem, maze solving, and focus on designing a framework that allows to solve instances several orders of magnitude larger than the current known solutions.

**The internship** will take place in the MC2 Team at the LIP (UMR 5668), ENS de Lyon. ENS de Lyon provides an ideal and stimulating environment to conduct this type of interdisciplinary research. In particular, we have an agreement with O. Gandrillon's team at the biology lab LBMC, for the lab bench and work, and the physics lab, for the atomic force microscopy, that guarantees us to have access to top lab equipments, just a few meters from our offices.

Our research receives strong financial supports from the CNRS and the ENS de Lyon.

Lyon is a very welcoming city, which combines both the advantages of large cities (excellent subway and bus system; bike lines everywhere) together with reasonable size (everything is at walking distance from the center), excellent and reasonably priced food, reasonably priced accommodations and very close to Paris, the mountain and the sea by fast train.

**Current and past students in the field.** N. Levy (M2, 2020; PhD, 2020–); P. Marcus (M2, 2020); D. Pchelina (M1, 2019).

**Regular Collaborators.** Shinnosuke Seki (UEC, Tokyo, Japan); Guillaume Theyssier (CNRS, I2M, Marseille); Damien Woods (Maynooth U., Ireland); Yannick Rondelez (CNRS, ESPCI, Paris); Gaëtan Bellot (CNRS, CBS, Montpellier); Anthony Genot (CNRS, LIMMS, Tokyo U., Japan); Matthieu Leocmach (iLM, U. Lyon 1); Cendrine Moskalenko (Phys lab, ENS de Lyon); Matthew Patitz (Arkansas U., USA); Cody Geary (Caltech, USA); Pierre-Étienne Meunier (Maynooth U., Ireland); Damien Regnault (Evry Corbeille Essonne U.) Olivier Gandrillon (CNRS, LBMC, ENS de Lyon);

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