

SCAI 2022

Generation of DNA sequences that position nucleosomes with Generative Adversarial Networks

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February 3, 2022

The improvement of DNA sequencing techniques lead to an explosion in the number and completeness of fully sequenced genomes (i.e. stretched of billions of A/C/T/G letters). However the mere genome sequence of an organism is far to little to understand how this sequence is interpreted by the molecular machinery within the cell. In eukaryotes, organisms in which the genome is sequestered inside a micron size nucleus, the long DNA molecule (sometimes up to meters) that constitute the chromosomes is wrapped around protein complexes, called nucleosomes, to form a bead on a string array. Nucleosomes have two roles. The first role is structural: 147 base pairs of DNA are wrapped within a nucleosome and this wrapping softens the DNA molecule, reducing its persistence length by a factor of ten and allowing these long DNA molecules to be compacted in small volumes. The second role is functional: nucleosomes occupy specific positions on the genome sequence and they can locally modify the binding affinity between DNA and transcription factors, the proteins that read the DNA motifs and regulate the expression of the genes. In cells expressing the same genes, nucleosomes occupy the same positions [1] and an important question in the field is to understand the mapping that relates the DNA sequence and the position of nucleosomes along this sequence. This function cannot be explicitly described using a mathematical formula but we have recently shown that a deep neural network can be used to model it [2].

As Early as 2015, pioneering studies [3, 4] demonstrated the efficiency of deep neural networks to learn protein binding site, or more generally any type of annotation, directly from DNA sequencing experiments. The application of deep neural networks to genomics has been since growing at high a pace and it can now be considered as a state of the art computational approach to learn and predict genomic annotations at the genome wide level [5, 6, 7, 8, 9]. Deep Convolution Neural Networks (CNN) are in particular very efficient at detecting sequence features since they rely on the optimisation of convolution filters that can be directly matched to DNA motifs [10]. Stacking several of these convolutional layers together can lead to the detection of nested motifs at larger scales. A game changing advantage of these tools is their

ability to predict a learned annotation on a variation of the genome, i.e. to predict the effect of mutations. As a first proof of concept of the ability to predict mutations on large scales, we developed the *mutasome* approach, in which all bp of a single genome are mutated individually to see the effect on a given genome annotation. In our case we successfully predicted the effect of all the possible mutations on the nucleosome positions on the yeast *Saccharomyces cerevisiae* genome [2]. We then used this information to identify the sequence motifs that were responsible for the precise positioning of nucleosomes.

The first part of this PhD project is to extend this study using a larger variety of species in order to understand the evolution of nucleosome positioning rules. While the yeast has been under detailed scrutinising in the past, few nucleosome positioning data-sets exist for other species. In order to increase this number we will rely on the Museum's RBCell collections and will focus our analysis on unicellular eukaryotes and fungal strains. The collections of the RBCell ensemble is dedicated to the conservation of the diversity of living things. These collections come from samples taken from the environment and stored in a functional form (e.g. living or cryopreserved cells). They are the support for research activities on the cellular mechanisms of living organisms, including not only genetic information, but also all the cellular and metabolic potential of cells or organisms. Experiments that will reveal the nucleosome positions on the genome of these organisms will be carried in the group of our collaborator Jean Baptiste Boulé (JBB) at MNHN. This unique opportunity to bring together Julien Mozziconacci's (JM) expertise on deep genomics, JBB's expertise on yeast genetics and the use of the MNHN collection resources will empower us to decipher the rules of nucleosome positioning in many diverse unicellular organisms.

The second part of the PhD project will go beyond the mere prediction of the effect of mutations on nucleosome positions. The rationale behind this extension of the project is that if one can successfully predict the effect of mutations, it becomes also possible to design new sequences with controlled properties, a field now known as *genome writing* [11]. Genome writing is in its early years and our group is involved in the international GP-write consortium which aims at designing synthetic pieces of genomes that will be synthesised and tested experimentally. In the present project, we wish to leverage the use of Generative Adversarial Networks (GANs) for genome writing. Our goal is to design short (200bp) sequences that will position nucleosomes precisely in their centre *in vivo*. A typical GAN model is composed of the input random vector, the generator, and the discriminator. Among them, the generator and discriminator are implicit function expressions, here implemented by deep neural networks. In short, the generator used will be a network that generates a DNA sequence of the given length from random variables. The generator will use two cost functions. The first will be given by the predicted density on the sequence and will be minimum when this density will display a peak at the sequence centre. The second cost function will be given by a discriminator network. The discriminator will try to discriminate these generated sequences from real yeast DNA sequences of the same length. The parameters of both networks will be optimised alternatively while keeping the other network fixed. We will thus train the generator to generate yeast-like sequences that will position one nucleosome in their centre. This strategy has been recently proposed on theoretical grounds [12] and has been applied to generate artificial variations of human splice sites [13]. It requires the use of the Wasserstein algorithm [14] in order to efficiently sample the sequence space. We plan

to leverage this strategy in order to generate sequences (of varying length from 167 to 237 bp) that will position one nucleosomes using a network trained on yeast *Saccharomyces cerevisiae* nucleosome position data. These sequences will be then assembled as tandem arrays of hundreds of repeats to form regular nucleosomal array with different spacing between nucleosomes. We thus expect to form regular arrays of nucleosome with various spacing between them *in vivo*. The efficiency of the design, will be experimentally tested in collaboration with JBB at MNHN who will co-supervise this thesis.

The recruited PhD student will be involved both in training the neural networks on multi species nucleosome data (first part) and training the GANs to generate synthetic DNA sequences (second part) in JM team as well as analysing the experimental results obtained in the JBB team. The project lies at the frontiers between synthetic biology and computer science. It will require strong computational and theoretical skills. We will therefore seek for a candidate with background either in computer science or bioinformatics that will acquire the relevant knowledge in deep learning and biology in our two groups. This project will be one of the very first world-wide that uses deep learning techniques to design *in silico* an entirely new DNA sequence with desired properties and to test these properties in living organisms.

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