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Master Thesis

Predicting Hi-C contact matrices using machine learning approaches

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Abstract

Harhar!

Zusammenfassung

Hohoho!

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Abschlussarbeit selbständig verfasst habe, keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe und alle Stellen, die wörtlich oder sinngemäß aus anderen Werken entnommen wurden, als solche kenntlich gemacht habe. Darüber hinaus erkläre ich, dass die eingereichte Masterarbeit weder vollständig, noch in wesentlichen Teilen Gegenstand eines anderen Prüfungsverfahrens war oder ist.

Bad Krozingen, den 12. Januar 2021

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Contents

1 Introduction

In recent years, the three-dimensional organization of DNA has been shown to be a key factor for important processes in molecular biology. However, even with the most advanced experimental methods, it remains comparatively expensive to determine the spatial folding of DNA directly, so that current knowledge of three-dimensional DNA organization is still sketchy. In the last five years, several methods have thus been proposed to improve on this situation by determining DNA-DNA interactions *in-silico* All of these are using existing experimental data which is easier to obtain than spatial data, but correlates with spatial structure in certain ways. However, most current in-silico approaches have disadvantages and shortcomings, and the current thesis attempts to improve on these.

1.1 Spatial structure of DNA

In the late 1970s, Watson and Crick XXXdiscovered the now well-known double helix structure of DNA molecules. However, this is not the only relevant spatial structure of genomes. At larger scales, DNA molecules can be wound around certain proteins, so-called histones, forming DNA-protein complexes named nucleosomes. Several of these can further be compacted into fibres, which in turn can be "supercoiled" into the also well-known chromosomes. XXXhier muss das bild hin XXX

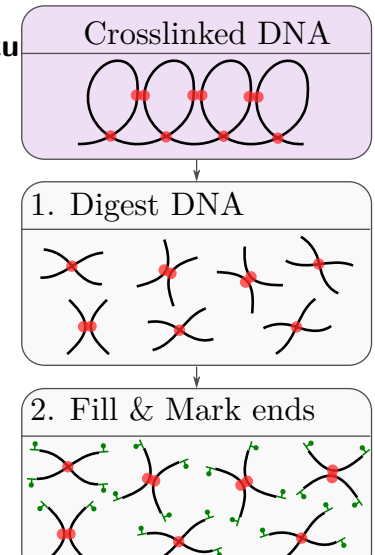
While the spatial structure of chromatin outlined above brings along compaction (fig. XXXfrom left to right), e. g. to make chromosomes fit into eucaryotic cell nuclei, it also has other functional implications. One well known effect of spatial structure is the regulation of gene transcription by establishing or releasing contacts between gene enhancers and the relevant promoters [1, 2]. Since enhancers can be up to a million basepairs away from the promoters, the two can only interact by means of spatial DNA structure. Many effects of spatial structure are still under investigation, two recent studies have for example found dependencies between chromatin conformation and cell differentiation in Drosophila Melanogaster [3] and investigated spatial structure dynamics during phase transitions in murine cells [4].

While the driving mechanisms behind the formation of spatial chromatin structures are partially still under research, certain proteins like CTCF or modified histones are already well known to mediate or prevent DNA-DNA contacts [5, 6, 7].

In the last two decades, DNA-sequencing-based techniques have increasingly been utilized to capture the spatial structure of DNA experimentally. The method of choice within this thesis is called Hi-C and shall be explained in the following section.

1.2 The Hi-C process for determining spatial DNA structu

The Hi-C process is an elaborate biochemical procedure for investigating the spatial structure of DNA by detecting DNA-DNA interactions within and across chromosomes. The original Hi-C workflow has been developed by Lieberman-Aiden et al. in 2009 [8] and is depicted in simplified form in fig. 1.



The typical input (In) to Hi-C consists of several millions of cells, which are treated chemically to fix existing DNA-DNA contacts, commoly using formaldehyde, before they are lysed. Next, the DNA is extracted and cut into fragments by certain restriction enzymes (1), usually HindIII or DpnII, and the cut ends are repaired with nucleotides, some of which are marked by biotin (2). The free ends are then joined (3) under conditions which prefer ligations among open ends over ligations between different fragments. Originally, such conditions were achieved by high dilution of the fragments in solvents, but especially this part of the protocol has been replaced by more efficient methods in later works [9, 10]. The ligated fragments are then purified and cut into shorter sequences, some of which contain biotinylated nucleotides and some not (4). The fragments of interest – the ones containing biotinylated nucleotides – are then selected by pulling down biotin (5), for example using magnetic tags, and subjected to paired-end DNA-sequencing (6). In the end, the output of the Hi-C lab process is a large number of short genomic "reads", which are subsequently processed in the bioinformatics part of the Hi-C protocol outlined in the following section.

On the software side of the protocol, the reads first need to be mapped to the corresponding reference genome. Here, only reads are kept where the "left" sequence (6)(a) uniquely maps to a different region of the reference genome than the "right" sequence (6)(b). These so-called chimeric reads are subjected to quality control, and those passing are counted as an interaction between the two genomic positions (1)(a) and (1)(b) to which the two ends belong. However, at reasonable read coverages, interactions cannot be counted per base pair. Instead, the reference genome is split into equally sized bins (or regions), and the reads are counted for those regions where they belong. The final outcome of a Hi-C experiment is then a sparse matrix, henceforth referred to as "Hi-C matrix", which records the interaction count for all possible pairs of regions in the reference genome.

For the thesis at hand, Hi-C matrices can abstractly be considered as sets of sparse, square matrices; one matrix for each chromosome. The individual elements $m_{i,j}$ of the matrices are counts of interactions between the bins with indices $i, j \in \{0, 1, ..., l\}$, where the last index l is given by the chromosome size cs and the binsize b in basepairs as $l = \left\lceil \frac{cs}{b} \right\rceil - 1$. Because interaction counts do not have a "direction", it holds that $m_{i,j} = m_{j,i}$, so Hi-C matrices are always symmetric.

A bin with index n then corresponds to the genomic region $p_n = [\, n \cdot b,\ (n+1) \cdot b \,)$, except the last bin l, where $p_l = [\, l \cdot b,\ cs \,]$, with l, b, cs as above. As an example, if $m_{0,10} = 22$ for a matrix with binsize $b = 25\,\text{kbp}$, this means that in the underlying experiment, 22 interactions have been counted between region p_0, ranging from 0 to 24 999 bp and region p_{10}, ranging from 250000 to 274 999 bp. Due to insufficient read coverage, $b = 1\,\text{bp}$ is impossible in practice. Instead, common values include $b \in \{1, 5, 10, 25, 50, 100, 1000\}\,\text{kbp}$.

In the bioinformatics part of the Hi-C protocol, often just a small fraction of all reads fulfill the selection criteria outlined above, for example due to reads not being chimeric or uniquely mappable. This makes Hi-C a comparatively inefficient, slow and thus expensive process. For

example, the well-known dataset by Rao et al. [9] with matrix bin sizes down to 1 kbp, required several *billions* of reads being made.

Parts of fig. 1 and the process description above have been adapted from the preceding study project [11].

XXXmod input steps in graph XXXmark regions a, b throughout the graph

1.3 The ChIP-seq process for determining protein binding sites

The ChIP-seq process is a combination of Chromatin-Immunoprecipitation (ChIP) and DNA-sequencing, designed for investigating DNA-protein interactions [12, 13]. As with Hi-C, the input consists of a sufficient number of cells, which are first fixed with formaldehyde. The cells are then lysed, the DNA-protein structure is extracted and cut into fragments, usually by sonication (2). Next, specific antibodies are added, designed to bind only to a certain protein of interest (3). These antibodies are additionally equipped with a tag, for example a magnetic one, so that the DNA-protein-antibody structures can be precipitated, while fragments without antibodies are discarded (4). The proteins and antibodies are then removed (5), the DNA is purified and finally sequenced (6). Typically, a control experiment is performed together with the ChIP-seq process, which comprises all steps described above, except the immunoprecipitation (3),(4).

The outcome of the ChIP-seq lab process is again a bunch of short genomic sequences, which are then fed into the bioinformatics part of the pipeline.

On the software side of the process, the reads are filtered for quality and mapped to an appropriate reference genome. The number of mapped reads per genomic position can then be simply be counted. It is common to process reads from the control experiment in the same way as reads from the ChIP-seq experiment and then use special software to call "peaks", i. e. protein binding sites, at those genomic positions where the read count from ChIP-seq is statistically significant compared to the read count from the control group.

For the thesis at hand, the reads from the ChIP-seq experiment have been used directly and binned by taking the mean over all reads inside each bin. For n ChIP-seq experiments, given chromsize cs and binsize b, this corresponds to an $l \times n$ array with $l = \lceil \frac{cs}{b} \rceil - 1$. The element $m_{i,j}$ in this array is then the mean read count of the j-th ChIP-seq experiment in genomic region $[\, i \cdot b,\ (i+1) \cdot b \,)$, or $[\, l \cdot b,\ cs \,]$ in case $i = l$. For ChIP-seq experiments, taking a binsize of one is in principle possible, but yields very sparse arrays. Thus, binsizes that evenly divide the binsizes of the corresponding matrices have been chosen for this thesis, namely 5 kbp and 25 kbp.

1.4 Motivation and goal of the thesis

Due to the high effort, Hi-C experiments have been conducted only by few labs and for comparatively few organisms and cell lines so far. For example, as of January 2021, Hi-C assays are available for just 26 of more than 150 human cell lines listed in the Encyclopedia of DNA elements [14, 15], and these have been produced by only five university labs.

cell line	TF ChIP-seq	Histone ChIP-seq	Dnase-seq	Hi-C
K562	680	20	10	1
HepG2	668	15	3	1
A549	251	87	14	6
HEK293	231	6		
GM12878	211	15	3	7
MCF-7	155	18	8	
H1	88	55	3	
HeLa-S3	77	15	4	1
SK-N-SH	62	21	2	

However, investigations and experiments with the available Hi-C data have shown correlations between the spatial DNA structure and the binding sites of certain transcription factors and histone modifications [9, 16]. Since these binding sites can be detected with the less costly ChIP-seq method, a computational method able to predict contact matrices from DNA-protein bindings would be very helpful.

The goal of this master thesis is thus to predict missing Hi-C data from existing ChIP-seq data, making use of the known correlations between the binding sites of transcription factors and histone modifications of the one hand and Hi-C interaction counts on the other hand. Because this is a wide field and lead time for a master thesis is limited, the present work will focus on machine learning techniques, which have proven a good choice for exploiting complex patterns and relationships in various kinds of data. XXXcitations needed More specifically, the goal of this thesis is to develop an easy-to-use machine learning approach for predicting Hi-C interaction matrices from ChIP-seq data, using standard in- and output formats with minimal pre- and postprocessing.

To underscore the usefulness of such an approach, table 1 to the side shows the first 16 human cell lines in ENCODE, sorted by total number of selected assays available. It is obvious that even otherwise well-investigated cell lines like HEK293, MCF-7 and H1 lack Hi-C data, while ChIP-seq data is mostly available.

2 Related work

In the last five years, several approaches have been presented to determine DNA-DNA interactions *in silico*, using existing data from various experiments. Section 2.1 gives an overview about these methods. Furthermore, some methods originally developed for image synthesis and similar tasks in computer vision might also be useful in the field of Hi-C matrix generation and are thus summarized in subsection 2.2.

2.1 Methods for predicting DNA-DNA interactions and contact matrices

As of 2020, there is quite a body of existing work in the field of predicting DNA-DNA interactions, using various approaches and different types of input data.

Two conceptually similar methods have been proposed by Brackley et al. in 2016 and MacPherson et al. in 2018 [17, 18]. In both approaches, DNA is modeled as a "beads-on-a-string" polymer, and simulation techniques are employed to find energy-optimal spatial structures of these polymers. Apart from constraints derived from the molecule's DNA sequence itself, the models also consider spatial contact constraints derived from ChIP-seq experiments of chromatin factors which are known to mediate such DNA-DNA contacts. The interaction matrices derived from the simulations look interesting, but the paper from Brackley et al. [17] is unfortunately lacking a comparison with "true" experimentally measured Hi-C matrices, and the results from MacPherson et al. [18] seem inferior to most other ones presented in this section.

Another simulation-based method has been developed by di Pierro et al. in 2017 [19] and later extended by Qi and Zhang [20]. In both cases, a convolutional neural network (CNN) is trained to learn different "open" and "closed" chromatin states from 11 chromatin factors, and the predicted chromatin states are then taken as constraints for beads-on-a-string models. The difference between [19] and [20] lies mainly in the number of states considered and the simulation methods applied; the results are mathematically convincing in both cases.

A further approach using chromatin states is due to Farrè and Emberly [21]. Here, the conditional probability of two genomic regions being in contact, given their distance and the chromatin state around them, is estimated using Bayes' rule. In this case, the chromatin state – reduced to active or inactive – is derived from DNA adenine methyltransferase identification (DamID) signals of 53 chromatin factors using probabilistic methods [22]. The conditional probabilities on the right side of Bayes' rule are either computed from training data or estimated with different probabilistic approaches, too. While the predicted contact matrices do not look like real Hi-C matrices with this approach, highly interacting regions are still often well identifiable.

Three further approaches in the field make use of random forests. 3DEpiLoop by Bkhetan and Plewczynski and Lollipop by Kai et al., both from 2018, use a random forest classifier to predict DNA loops, but differ in input data and preprocessing [23, 24]. While 3DEpiLoop is using only ChIP-seq data of histone modifications and transcription factors [23], Lollipop additionally takes ChIA-PET-, RNA-seq- and DNase-seq-data, CTCF motif orientation and loop length as inputs [24]. Both approaches show good coincidence of predicted loops with experimental data, but their output is binary and rather sparse. Contrary to these two, the third random-forest-based approach, HiC-Reg by Zhang et al. from 2019, allows predicting real-valued Hi-C interaction matrices directly [25]. To this end, it employs random forest regression to predict interactions

between two genomic "windows", using ChIP-seq data of 13 chromatin factors and the genomic distance of the two windows. The published results for five human cell lines look interesting, but could not be reproduced in two study projects at the university of Freiburg for unknown reasons [11, 26]

Another recent method which investigated decision-tree-based algorithms is due to Martens et al. (2020) [27]. Here, gradient boosted decision trees, logistic regression and neural networks were used to predict highly interacting chromatin regions and TAD domain boundaries from histone modifications and CTCF ChIP-seq data. However, in this setup, the neural network approach yielded the best, overall acceptable results of the three approaches, but again in form of a binary classifications. A neural-network approach with comparable input data, but without the restriction to binary classifications has been presented by Farrè et al. in 2018 [28]. Here, a one-dimensional convolutional filter is used to convert ChIP-seq data from 50 chromatin factors into a one-dimensional chromatin vector, which is then processed by a dense neural network (DNN). This allows predicting real-valued Hi-C interaction matrices, which resemble the general structure of experimentally derived matrices quite well.

While the approaches discussed so far have either modeled DNA as a "beads-on-a-string" polymer or not used it explicitly at all, there are also several machine-learning approaches which directly consider DNA sequence without a need for polymer modeling. In 2019, Singh et al. presented SPEID [29], an approach to predict promoter-enhancer interactions from DNA sequence, using a combination of CNNs, a recurrent network (LSTM) and a DNN. The results match well with experimental data, but are limited to promoter and enhancer loci by design, disallowing predictions of complete Hi-C contact matrices. Other researchers have tried to design similar methods without such limitations. The work by Peng from 2017 [30] is an extension of SPEID, based on a 2016 preprint [31], additionally taking into account a "middle sequence" between enhancer- and promoter sequences, CTCF motif counts within the sequences and genomic distance between two sequence snippets. However, the network lacks generalization, i. e. the results are only good in training regions [30, figs. 4, 5]. A conceptually similar method to the one by Peng [30], but with a different neural network design has been presented by Schreiber et al., also in 2017, named Rambutan [32]. It accepts sequence, DNase-seq data and distance between two genomic loci as inputs and then uses a combination of CNNs and a DNN to predict whether the given two loci interact or not. Unfortunately, it is difficult to decide whether the results of Schreiber et al. are useful for the task at hand, since the evaluation is done only by statistical means and no actual Hi-C matrices have been published. The original paper [32] also contains a known error and seems not to have appeared in a peer-reviewed journal in improved form yet. A probably more promising method working on DNA sequence, Akita, has been published by Fudenberg et al. in 2020 [33]. It is based on two rather involved convolutional neural networks. While the first one, "trunk", processes one-dimensional, one-hot encoded DNA sequence input through convolutional filters, the second one, "head", converts one-dimensional representations to 2D, further processes the data with convolutional filters and enforces symmetry. Although Fudenberg et al. initally seemed to focus on determining the influence of DNA modifications on spatial structure [34], predicting complete Hi-C matrices is an integral part of their work, and a large number of images of Hi-C matrices from the test set has been published alongside the article. The predicted matrices often hardly look like experimental Hi-C matrices, but mostly still indicate highly interacting regions quite well.

A further method by Schwessinger et al. [35] also makes use of DNA sequence and additional

epigenetic data for its predictions, but is conceptually different from the ones presented so far. Here, ChIP-seq tracks are initially used to train a CNN on the relationship between sequence and the corresponding chromatin factors. The weights of this first network are then used to seed another convolutional neural network, which is responsible for predicting DNA-DNA interactions from DNA sequence. In this case, the results were blurry, but generally in good accordance with experimental Hi-C data. However, the neural network has a large number of weights and thus requires long training times at very small batch sizes.

Yet another machine-learning concept based on sequence data, Samarth, has been proposed by Nikumbh and Pfeifer in 2017 [36]. Here, a support vector machine is trained on 5C data, using a specific representation for DNA sequence called oligomer distance histograms. The results showed acceptable consensus with experimental Hi-C data and allowed some interesting conclusions about the importance of certain k-mers for DNA folding. Unfortunately, none of the predicted matrices used for statistical evaluation has been published alongside the paper, making an assessment of the usefulness for the task at hand again difficult.

2.2 Image synthesis techniques from computer vision

With the advent of deep learning, both the number of oppurtunities and the demand for using machine learning techniques in image synthesis tasks have risen, as recently summarized by Tsirikoglou et al. [37]. Since Hi-C contact matrices can be seen as are square grayscale images, such techniques can also be relevant for this thesis.

One of the first applications of computer vision methods for Hi-C matrices was presented by Liu and Wang in 2019 [38]. Here, deep convolutional neural networks – modified from established image super-resolution networks XXX– have been used to enhance low-resolution Hi-C matrices.

Another technique from computer vision that has been transferred to Hi-C matrices are conditional generative adversarial networks (GANs), invented by Goodfellow, Mirza and colleagues in 2014 [39, 40]. Again, several works have employed this comparatively new and involved method to increase the resolution of given Hi-C matrices, including the ones by Liu and colleagues [41], Hong et al. [42] and Dimmick et al. [43]. In general, all three works feature the typical GAN setup with two competitive networks – a generator, which is trained to produce realistic high-resolution Hi-C matrices from its low-resolution inputs, and a discriminator, which tries to distinguish real Hi-C matrices from generated ones and thus serves as a "critique", an additional loss function, for the generator. While the convolutional building blocks for the discriminators and the residual building blocks for the generators are conceptually similar in all cases, the three works differ in the number of building blocks used and the activation functions applied within the blocks. Furthermore, Dimmick et al. and Hong et al. include additional loss functions beyond standard generator- and adversarial losses. This includes perceptual losses derived from other (pre-trained) neural networks to obtain "visually good" Hi-C matrices and total variation loss to suppress noise while maintaining edges. The method by Dimmick et al. outperformed the others for most test cases, but it is also the most elaborated.

Since all of the methods presented above require existing Hi-C matrices for training *and* prediction, none of them is suitable for the task at hand. However, some of the concepts mentioned might still be useful, cf. section 3.2.

3 Advancing predictions of Hi-C interaction matrices

3.1 Deep Neural Network approach

3.1.1 Basic network setup

3.1.2 Modifying the convolutional part of the network

3.1.3 Modifying the loss function

3.1.4 Modifying resolution and windowsize

3.1.5 DNA sequence as an additional network input branch

3.2 Hi-cGAN approach

3.2.1 Pix2Pix as a generic generative network

3.2.2 Using a DNN for 1D - 2D conversion

3.2.3 Using a CNN for 1D - 2D conversion

4 Method details

4.1 Input data

4.1.1 Hi-C matrices

4.1.2 ChIP-seq data

4.2 Deep Neural Network approach

4.2.1 Modifying kernel size, number of filter layers and filters

4.2.2 Modifying input resolution

4.2.3 Custom loss function based on TAD insulation score

4.2.4 Combination of mean squared error, perception loss and TV loss

4.3 HiC-GAN approach

4.3.1 Using a DNN for 1D-2D conversion

4.3.2 Using a pre-trained DNN for 1D-2D conversion

4.3.3 Using a CNN for 1D-2D conversion

5 Results

5.1 Deep Neural Network approaches

5.2 HiC-GAN approaches

6 Discussion and Outlook

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Acronyms

ChIA-PET chromatin interaction analysis by paired-end tag sequencing.

ChIP-seq chromatin immunoprecipitation followed by sequencing.

CNN convolutional neural network.

DamID DNA adenine methyltransferase identification.

DNN dense neural network.

GAN generative adversarial network.

LSTM long-short-term memory.

TAD topologically associating domain.