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Type	Oral communication
Session	Genome Organization and Gene Regulation
Title	Chromatin 3D reconstruction with ChromStruct: a method integrating Hi-C, ChIP-Seq and RNA-Seq data
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Motivation

Knowledge of the three-dimensional structure of chromatin inside the cellular nucleus has proved to be of great importance, because it is connected with physiological and pathological correlates and dysfunctional cell behaviours. Several techniques have been proposed that can provide geometric information on the spacial distribution of the DNA filaments inside the cell;most of these methods are based on the elaboration of data derived from Hi-C and related experiments. The method proposed here integrates not only information deriving from Hi-C, but also data from RNA sequencing (RNA-seq) and Chromatin Immunoprecipitation Sequencing (ChIP-seq), and infer the geometrical characteristics of the three-dimensional structure of chromatin, providing a picture which is more realistic and informative.

Methods

The method ChromStruct, to infer a set of spatial chromatin conformations starting from the contact information obtained through Hi-C experiments, was introduced in previous work (Caudai et al. BMC Bioinformatics 2015 and Caudai et al. IEEE / ACM-TCBB 2018). ChromStruct is based on a multi-scale chromatin chain model built with consecutive and partially penetrable beads. The algorithm automatically divides the contact matrix into diagonal blocks, corresponding to TADs (Topologically Associating Domains, Dixon et al., Nature 2012) and reconstructs their 3D structures independently of each other. The reconstructions are estimated by sampling a solution space defined by a score function based on both data-fit and implicit, soft, geometrical constraints. The sub-chains thus obtained are then modelled as single beads in a coarser-scale chain, which is again divided into blocks, and so on, iteratively, until diagonal blocks are no longer detected. The method is implemented in Python and equipped with a GUI, through which it is possible to generate populations of chromatin chains compatible with experimental data and with all plausible geometric constraints included in the score-function.

Results

In this work, we present an extension of the method described above, with a new score-function, allowing the integration of data derived from Hi-C, ChIP-Seq and RNA-Seq experiments. Hi-C experiments provide information on contact frequencies between portions of the chromatin fibre, ChIP-seq data provide additional information as factors affecting the steric hindrance of DNA. RNA-seq data reveal differential gene expression along DNA: because gene expression is correlated with the presence of a large number of proteins and other factors that affect the compaction of DNA in the transcribed portions, this can be introduced in the score function as volume information. The conformations generated by this extension of ChromStruct are expected to be more plausible from a biological point of view, as they account for specific information derived from different experimental methods.

Info

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Figure

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Availability	-

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