A quantitative analysis of CLIP methods for identifying binding sites of RNA-binding proteins

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Cross-linking and immunoprecipitation (CLIP) is increasingly used to map transcriptome-wide binding sites of RNA-binding proteins. We developed a method for CLIP data analysis, and applied it to compare CLIP with photoactivatable ribonucleoside-enhanced CLIP (PAR-CLIP) and to uncover how differences in cross-linking and ribonuclease digestion affect the identified sites. We found only small differences in accuracies of these methods in identifying binding sites of HuR, which binds low-complexity sequences, and Argonaute 2, which has a complex binding specificity. We found that cross-link-induced mutations led to single-nucleotide resolution for both PAR-CLIP and CLIP. Our results confirm the expectation from original CLIP publications that RNA-binding proteins do not protect their binding sites sufficiently under the denaturing conditions used during the CLIP procedure, and we show that extensive digestion with sequence-specific RNases strongly biases the recovered binding sites. This bias can be substantially reduced by milder nuclease digestion conditions.
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