ARIMA GENOMICS

The Arima-HiC Kit for Reproducible 3D Genome Conformation Analyses

PRODUCT DATASHEET

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Introduction

The three-dimensional (3D) genome conformation has a profound impact on gene regulation, DNA replication, and DNA damage repair. Recent years have seen a rapid expansion of conformation capture techniques, including Hi-C[1,2], a sequencing-based assay that interrogates the 3D organization of the genome at unprecedented resolution. Despite its utility, broad adoption of Hi-C has been plagued by labor-intensive complex protocols, prolonged workflow durations, inconsistent experimental results, and high sequencing requirements.

The Arima-HiC Kit overcomes these technical and economical limitations with the development of a highly simplified and robust protocol that streamlines Hi-C to a 6-hour, 8-step procedure followed by library prep and NGS. Importantly, the Arima-HiC Kit enables researchers to quickly and reliably generate Hi-C libraries enriched in conformation signal, with reduced sequencing, for reproducible analyses of chromatin loops and TADs.

Fast, User-friendly Workflow

The Arima-HiC workflow was optimized to enable first time Hi-C users to generate high-quality data with ease (Figure 1). The rapid 6 hour protocol limits exposure of chromatin to external agents, leading to significant reduction of experimental noise. The use of a unique combination of multiple 4-base cutting restriction enzymes for chromatin digestion results in greater genome coverage uniformity.

Highlights

Fast and User-friendly Workflow

- Gain research insights quickly with rapid 6 hour protocol and reproducible results
- Scale projects with a single-tube, automation friendly workflow
- Assured library quality with quantitative and predictive QC steps

Low Input Support

- Analyze previously inaccessible low-input samples using robust Arima-HiC chemistry
- Generate high-complexity libraries with low cell or tissue input
- Maximize sample recovery with single-tube chemistry

Proven Performance

- Improve resolution and genome coverage with innovative multiple restriction enzyme chemistry
- Save substantial sequencing costs via increased long-range signal

Demonstrated Utility for Capture-HiC and HiChIP

- Generate reliable HiChIP or PLAC-Seq data with user-supplied antibodies
- Enrich for regions of interest and increase resolution with Arima Capture-HiC

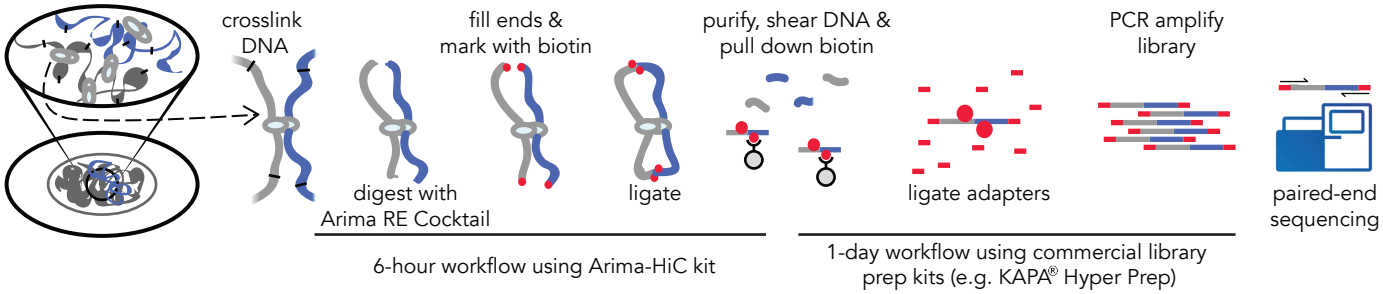

Figure 1: The Arima-HiC workflow results in ligated and biotinylated DNA that is prepared as a library and amplified using pre-validated library prep kits, and then subject to paired-end Illumina sequencing.

Proven Performance

Rigorous external and internal testing resulted in an Arima-HiC Kit with robust performance. When key opinion leaders compared Arima-HiC libraries with traditional Hi-C libraries, the Arima-HiC libraries manifested higher long-range (interactions >15Kb) conformation signal of up to 60%, and with high-complexity of 5nM with 4-7 PCR cycles. Importantly, while ~30% of the genome is often challenging to access when using a single 4-base RE in typical Hi-C[2], Arima-HiC enables uniform genome-wide accessibility via usage of multiple REs to capture conformation signal of all genes and regulatory elements alike (Table 1).

Subsequent sequencing of such high-quality Arima-HiC libraries generated reproducible conformation analyses – specifically, Arima-HiC data recovered known chromatin loops and TADs and identified a significant number of novel looping elements at half the sequencing depth of a previously published data set[2] (Figure 2). Altogether, Arima-HiC provides substantial technical and economic benefits to the user.

"The Arima-HiC protocol is days quicker than our previous lab's protocol. All together, better quality data for less effort."

- Eileen Furlong PhD, Head of EMBL Genome Biology Unit

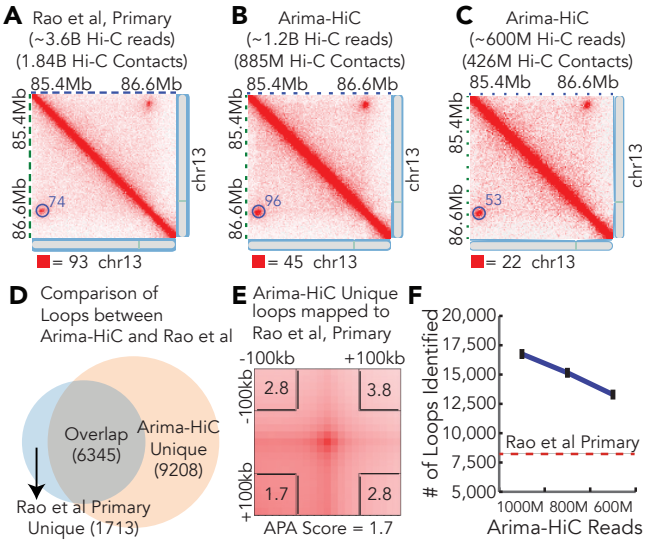

Figure 2: Comparison of Arima-HiC data with previously published Hi-C data (Rao et al) demonstrates the ability of Arima-HiC to recover known chromatin loops and identify novel loops and TAD structures at reduced sequencing depth. (A) Example of a chromatin loop detected in the Rao et al Primary GM12878 dataset generated from 1.84B valid Hi-C contacts using 2x100bp sequencing. (B,C) Example of the same chromatin loop detected in GM12878 Arima-HiC dataset generated from (B) 885M valid Hi-C contacts or (C) 426M valid Hi-C contacts, using 2x150bp sequencing. For all Hi-C snapshots, the red Hi-C signal maximum threshold is scaled linearly relative to the total number of valid Hi-C contacts in the map. (D) Comparison of Arima-HiC data (885M Hi-C Contacts) with Rao et al Primary dataset (1.84B Hi-C Contacts) showed significant recall of previously identified loops in addition to thousands of previously unidentified loops ("Arima-HiC unique loops"). (E) These Arima-HiC unique loops showed a moderate signal in Rao et al Primary, illustrating that these are likely true loops missed by Rao et al. (F) Analysis of the total number of loops identified in Arima-HiC data when sub-sampled down to 600M raw reads, indicating excellent loop calling sensitivity of Arima-HiC data.

Demonstrated Utility for Capture-HiC and HiChIP

The ease-of-use and proven performance of the Arima-HiC Kit extends to targeted approaches like Capture-HiC (where targeted sets of genes or regulatory elements are captured via probes) and HiChIP (also known as PLAC-Seq).

The motivation in HiChIP is to generate proximally ligated chromatin via Arima-HiC then immunoprecipitate DNA that is bound by a specific transcription factor or histone modification (e.g. Cohesin, H3K27Ac). Capture-HiC uses biotinylated probes to enrich for custom regions of interest.

Both methods are used to increase Arima-HiC resolution while significantly decreasing sequencing requirements.

"The ability of Arima-HiC kits to deliver greater insight with less sequencing cost will be critical in leveraging Hi-C technology for understanding gene regulation within the three-dimensional context of the genome."

- Changhoon Kim PhD, Chief Technology Officer, Macrogen, Inc.

"Still very impressed by the super rapid protocol!"

- Romain Koszul PhD, Group Leader of Pasteur Institute Spatial Regulation Group

"When we tested Arima-HiC kit in our hands, we consistently got very high-quality libraries. Particularly the fraction of inter-chromosomal reads is reduced."

- Daan Noordermeer PhD, Group Leader of CNRS Chromatin Dynamics Group

Additional Details

Please refer to the Genome Conformation and Low Input Application Notes, available by contacting info@arimagenomics.com.
Learn more online at arimagenomics.com

Table 1: Arima-HiC Assay Specifications

Total Time	6 hours
Hands-on Time	1 hour
Number of Steps	8
Automation Capability	Single-tube, 96-well plate compatible
Restriction Enzymes (RE)	RE cutting at GATC and GANTC
Genome Uniformity (fraction of genome with average sequencing depth)	~90% of the genome (8-10% of the genome inaccessible due to repetitive regions)
Sample Types	Tissue, blood, cell lines, whole insects
Sample Storage Conditions	Fresh/frozen, Cross-linked, Ethanol
Input Quantity	Standard Input: 750ng-5ug DNA Low Input: less than 750ng DNA
Species	Plants, Invertebrates, Vertebrates
Library Prep Compatibility	KAPA HyperPrep, Swift Accel-NGS, NEBNExt Ultra II, Illumina TruSeq, others
NGS Compatibility	Illumina NGS
Library Complexity	1 reaction, 600M reads
Recommended Sequencing Depth	Compartments: >50M reads, TADS: >200M reads, Loops: >600M reads
Data Analysis	References 3,4 and other open source tools

References

1. Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, Sandstrom R, Bernstein B, Bender MA, Groudine M, Gnirke A, Stamatoyannopoulos J, Mirny LA, Lander ES, Dekker J "Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome" Science 326, 289-293 (2009)
2. Rao SP, Huntley MH, Durand NC, Stamenova EK, Bochkov ID, Robinson JT, Sanborn AL, Machol I, Omer AD, Lander ES, Lieberman-Aiden E "A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping" Cell 159, 1665-1680 (2014)
3. Arima Genomics Mapping Pipeline. https://github.com/ArimaGenomics/mapping_pipeline
4. Juicer. https://github.com/theaidenlab/juicer

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