

BEHIND THE SCENES: SCIENCE THAT DRIVES ILLUMINA'S SEQUENCING CHEMISTRY

Molly He Ph.D. Illumina Inc
Molly.He@foresitecapital.com

Key Words: NGS, Illumina, DNA polymerase, Library Preparation, Transposase

DNA polymerase is the engine of Illumina's Sequencing by Synthesis (SBS) technology. In the past few years, we have invented and adopted an array of cross-disciplinary approaches to understand the fundamental mechanics of the polymerase and how it interacts with the rest of the sequencing system. This work has led to several generations of polymerase variants that enabled significant improvements of the sequencing metrics, including turnaround time, read length and accuracy. This will be the first time we share some of the fundamental science behind the chemistry improvements with the scientific community.

We present structural, biophysical and kinetic studies to understand the relationship between the polymerase's molecular properties and the sequencing metrics. Based on the understanding of the mechanism, high throughput solution assays are developed to predict the mutant performances on sequencers. By a combination of screening methods, random and targeted mutant libraries are made and assayed to discover faster and better polymerases that drive the ever improving Illumina sequencing chemistry.

We use a similar scientific approach to understand and evolve the library prep enzyme transposase that is the core of the Nextera® library preparation kits. We present a short overview of how protein engineering and machine learning approaches are utilized to improve the insertion bias of the Nextera® transposase. We end with future directions to further advance Illumina's sequencing technology by protein engineering technologies. We also discuss the possibilities of using Illumina sequencers as a novel high throughput imaging tool to advance biological research for a wider scientific community.