Applied Biosystems

SOLiD™ System

The SOLID Generation Delivers

Revolutionary Technology
SOLID Platform

The Applied Biosystems SOLiD™ System sets the standard in next-generation sequence analysis. This technology, based on sequential ligation with dye-labeled oligonucleotides, enables massively parallel sequencing of clonally amplified DNA fragments. Mate-paired analysis and two base encoding enable the study of complex genomes with greater accuracy than any other next-generation technology. It is a complete system that contains the necessary computing power and software to perform base calling on such a large scale without the need for additional computing hardware.

The next generation is The SOLiD System:

- Gigabases of data
- Superior accuracy
- Flexibility for numerous applications
- Scalable throughput
- System robustness

Applied Biosystems

Applied Biosystems has been the leader in sequence analysis for more than 20 years and has revolutionized the industry by developing innovative chemistries and robust, automated instrumentation. These technologies have enabled groundbreaking science, including the first draft of the human genome as well as the genomes of more than 500 other organisms. With each generation of new technology, Applied Biosystems has redefined the speed, cost, and accuracy associated with sequence analysis. The SOLiD™ System is Applied Biosystems' latest revolutionary step forward in sequence analysis technology. The throughput capability and unrivaled accuracy inherent in the SOLiD System, coupled with broad application flexibility, provide a unique system for advancing your research like never before.

Imagine the scientific discoveries that can be achieved with the power of the SOLiD System:

- The throughput to sequence multiple bacterial strains at unprecedented levels of coverage for a fraction of the current cost and time
- The ability to accurately sequence complete genes involved in a particular disease or drug phenotype at a level sensitive enough to detect rare variants and somatic mutations
- The potential for unbiased, hypothesis-free assessment of chromatin immuno-precipitation experiments, not limited to known promoter regions
- The sensitivity to measure expression of genes detectable on standard microarrays, plus all the genes you could previously see only with real-time PCR methods
- The power to view global structural rearrangements and copy number variants (CNVs) with the unparalleled resolution that is enabled by mate-paired technology

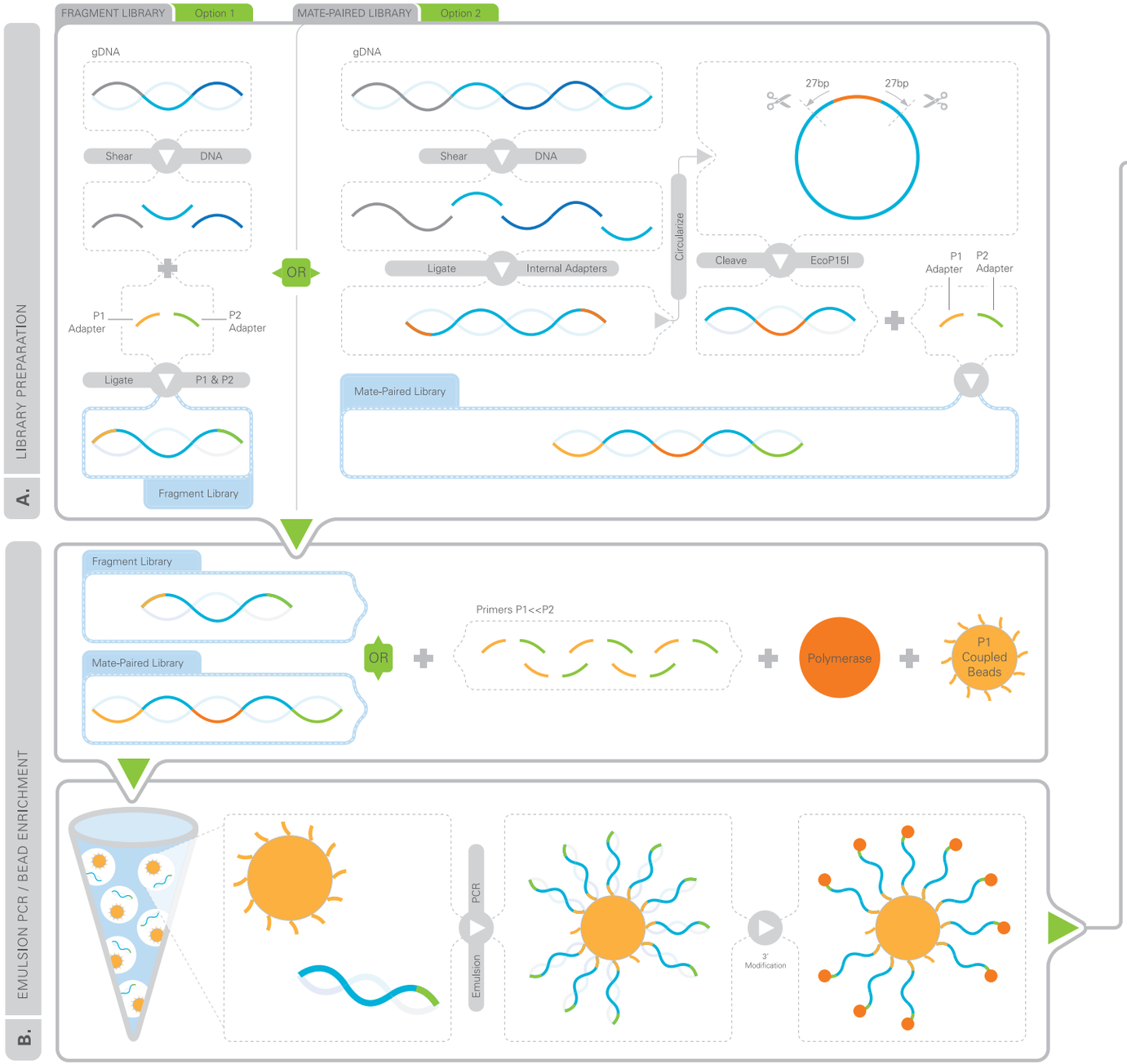
SOLiD™ System Chemistry | SOLID INSIDE AND OUT

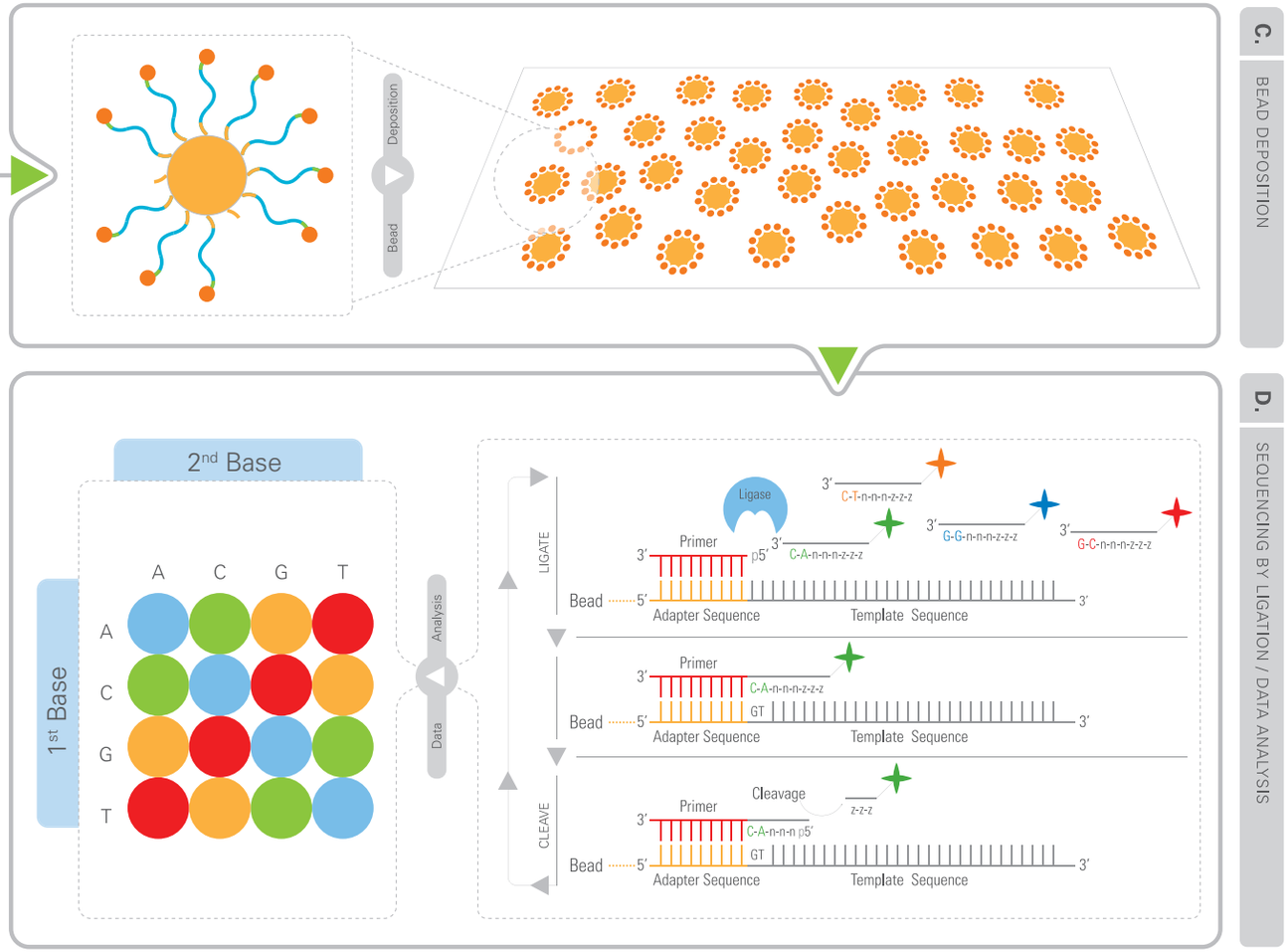
A. LIBRARY PREPARATION

The SOLiD System can use two types of libraries—fragment or mate-paired. The type of library used depends on the application and information needed.

B. EMULSION PCR/BEAD ENRICHMENT

Clonal bead populations are prepared in microreactors containing template, PCR reaction components, beads and primers. After PCR, the templates are denatured and bead enrichment is performed to separate beads with extended templates from undesired beads. The template on the selected beads undergoes a 3′ modification to allow covalent bonding to the slide.





C. BEAD DEPOSITION

3′ modified beads are deposited onto a glass slide. Deposition chambers offer the ability to segment a slide into one, four or eight chambers during the bead loading process. A key advantage of the system is the ability to accommodate increasing densities of beads per slide, which will result in a higher level of throughput from the same system.

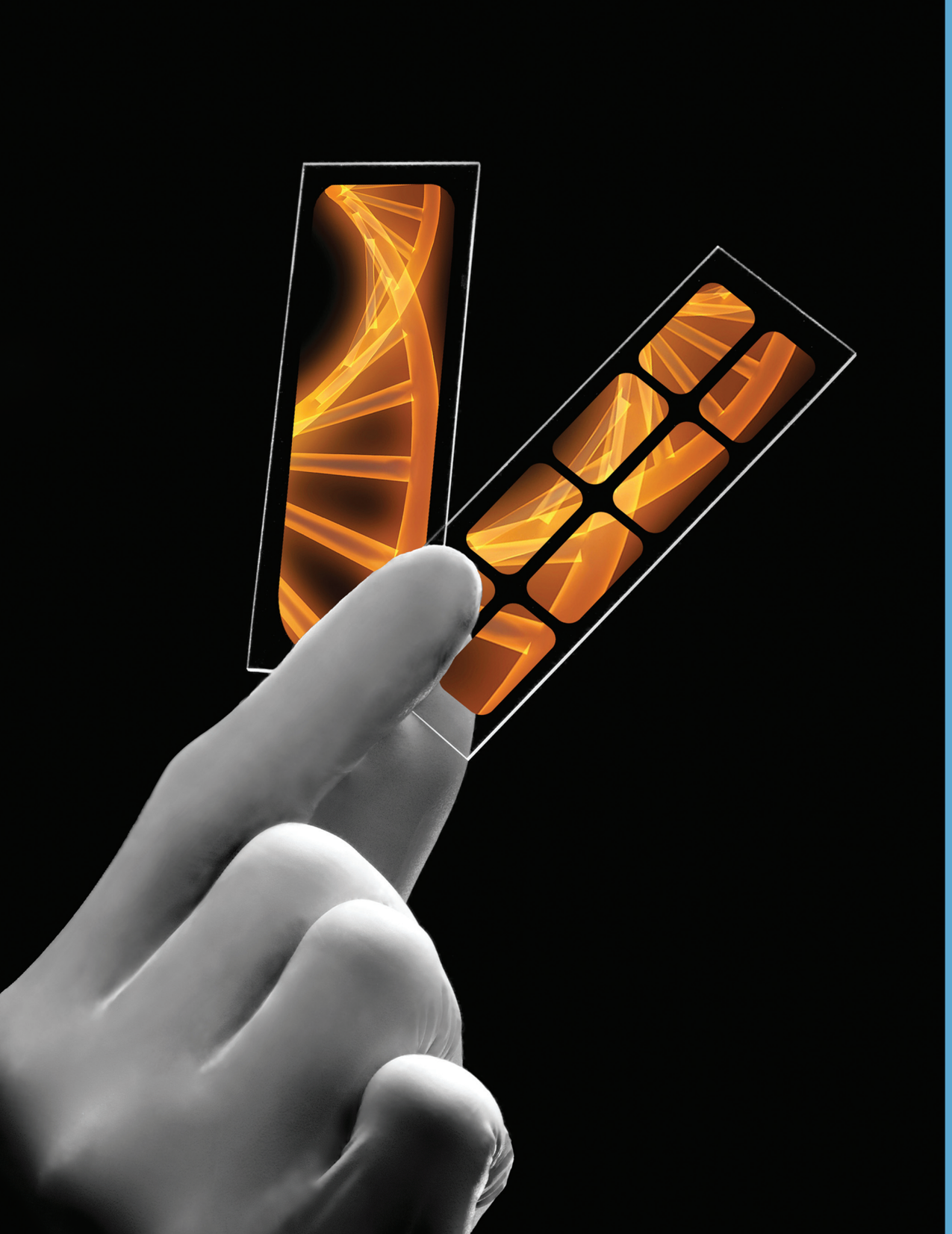
D. SEQUENCING BY LIGATION/DATA ANALYSIS

Primers hybridize to the P1 adapter sequence within the library template. A set of four fluorescently labeled di-base probes compete for ligation to the sequencing primer. Specificity of the di-base probe is achieved by interrogating every 1st and 2nd base in each ligation reaction. Multiple cycles of ligation, detection and cleavage are performed with the number of cycles determining the eventual read length. Following a series of ligation cycles, the extension product is removed and the template is reset with a primer complementary to the n-1 position for a second round of ligation cycles. Five rounds of primer reset are completed for each sequence tag. For mate-paired libraries, the entire process is repeated for the second tag with primers complementary to the internal adaptor. Data is analyzed in color space for rapid discrimination between system errors and true polymorphisms.

SOLID Delivers – Next Gen Now

The first draft of the human genome took millions of dollars and multiple years to complete.

To accomplish the same goal in a fraction of the time and cost, researchers have developed new methods, including clonal cluster sequencing. By leveraging this and other novel technologies, the SOLiD™ System performs highly parallel sequential ligation reactions, dramatically increasing throughput over conventional methods and other competing technologies. The SOLiD System is revolutionary in terms of throughput and differentiates itself from other next-generation platforms with unparalleled accuracy, system robustness and scalability.



Ultra High Throughput

Whole genome studies require the use of high throughput platforms. The SOLiD™ System can generate over six gigabases of mappable data and more than two hundred forty million tags per run, which is more usable data than any other next-generation system available today.

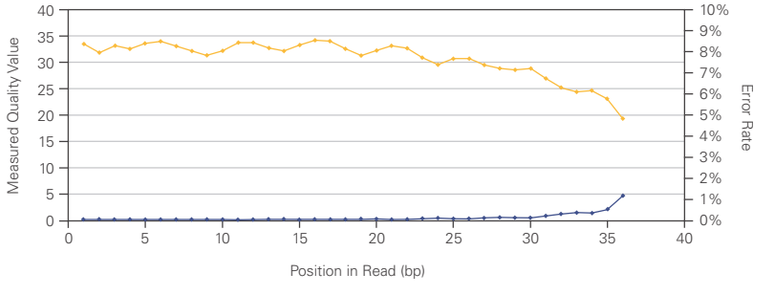
The massive throughput of the SOLiD System is attributed to the following three features: (1) single molecule amplification of DNA through emulsion PCR, which provides effective amplification of all molecules; (2) a thorough bead enrichment process that eliminates unhybridized beads and therefore maximizes slide space usage for productive beads, and; (3) high-density bead deposition onto a glass slide rather than constraining flow channels or microtiter plates.

Scalability

Applied Biosystems' world class Scientists have produced an extremely flexible chemistry and hardware set up, which allows for rapid progress in achieving increasing levels of throughput. The SOLiD System's open slide format and flexible bead densities enable increases in throughput on the current system with modest protocol and chemistry optimizations. While competitive technologies are already near, or have achieved maximum throughput, the SOLiD System has ample room for throughput advancements utilizing the same platform. The SOLiD System's performance today provides unparalleled throughput for higher levels of genomic coverage in sequencing experiments, and more reads for tag counting applications, such as gene expression or ChIP.

Unmatched Accuracy

Why waste an inordinate amount of time sifting through data to discern what is usable? With system accuracy greater than 99.94%, due to two base encoding, the SOLiD™ System distinguishes itself by providing data that is more accurate than alternative next-generation platforms for variation detection. This unrivaled accuracy is inherent in the system and results from properties that are unique to the chemistry and analysis of SOLiD System data: high fidelity ligation reactions, 2 base encoding technology, primer resets and mate-paired libraries.



Ligase enzymology provides significantly higher selectivity than polymerase-based approaches and dramatically reduces errors associated with mis-incorporated bases. Two base encoding interrogates each base twice during sequencing allowing for rare SNP detection with extremely high confidence. The built-in primer reset function automatically caps system noise at given intervals to yield lower background and error rates compared to polymerase-based chemistries. A mate-paired technology that allows for a tight distribution across a range of insert sizes enables the accurate analysis and assembly of complex genomes. It is ideal to utilize larger insert sizes for detection and fine resolution of *de novo* genomic aberrations, such as inversions, translocations and duplications. Smaller insert sizes do not allow the same level of resolution.

With the SOLiD System, you will be able to focus on the biological significance of your data rather than spending time identifying poor quality data.

System Robustness

Robustness can be defined as the sum of run success and system downtime. Scientists can be assured of the SOLiD System's robustness, and they will reap the benefits of the system's revolutionary technologies, run after run and project after project. The SOLiD System allows users to track run status in real time to help ensure that runs are completed successfully. Unlike competing systems, the SOLiD System offers users the ability to re-enter the workflow at multiple steps without the need to regenerate the sample or slide. Other "black box" technologies routinely result in lost data, time and money from failed or incomplete runs. To generate the desired data on these systems, one must restart the workflow from the beginning. After 25 years, Applied Biosystems continues to deliver instruments of the highest quality. The SOLiD System maintains that quality, which results in minimum downtime, maximum run success, and a robust system.

System Flexibility

The independent flow cell configuration enables users to run two completely independent experiments on a single SOLID Analyzer – providing 2 instruments in 1. Scientists can analyze both sequencing and expression experiments, or sequence multiple mate-paired libraries with different insert sizes in a single run. Implementation of barcoding protocols will allow for sample multiplexing, further increasing the flexibility of the system to support a variety of experimental designs. Sample multiplexing will also decrease the cost and time requirements for the upstream sample preparation. These advances will put your research, today and in the future, on the cutting-edge of what was once thought impossible.

SOLID Science
SOLID Applications

The SOLiD™ System not only possesses the capability to carry out sequencing in the traditional sense, but also enables or enhances many applications with its massive throughput and unparalleled accuracy by providing tremendous multiples of coverage and unequivocal sequence reads. The SOLiD System allows for large-scale projects to be imagined and executed; and all the while, scientists can be confident that sequence variations are discriminated from sequencing errors. All of these features have been woven together to create an instrument with Applied Biosystems' time-honored quality that is at the forefront of next-generation sequencing technology.

Application Flexibility

The breadth of applications enabled on the SOLiD™ System is a direct result of the flexible library preparation methods. Application-specific libraries are subjected to sequential ligation with dye-labeled oligonucleotides. The resulting data can be exported to application-specific analysis tools.

Applications Include:

Targeted Resequencing

The high accuracy inherent in the SOLiD System is required for targeted resequencing. The SOLiD System technology is amenable to region-specific pullout methods and barcoding, that when coupled with alignment against a known reference sequence, will yield a very flexible format for region-specific resequencing.

Gene Expression

The massive amount of sequence tags generated in a single run can be used to identify and quantify exon sequences associated with alternative splicing and promoter usage. Simple tag counting allows for digital readout of expression levels and the ability to detect lowly expressed genes with greater sensitivity.

MicroRNA Discovery

MicroRNAs (miRNAs) are highly conserved, small, RNA molecules encoded in the genomes of plants and animals. The SOLiD System technology enables the identification and quantification of large numbers of small RNAs from diverse species.

Chromatin Immuno-precipitation (ChIP)

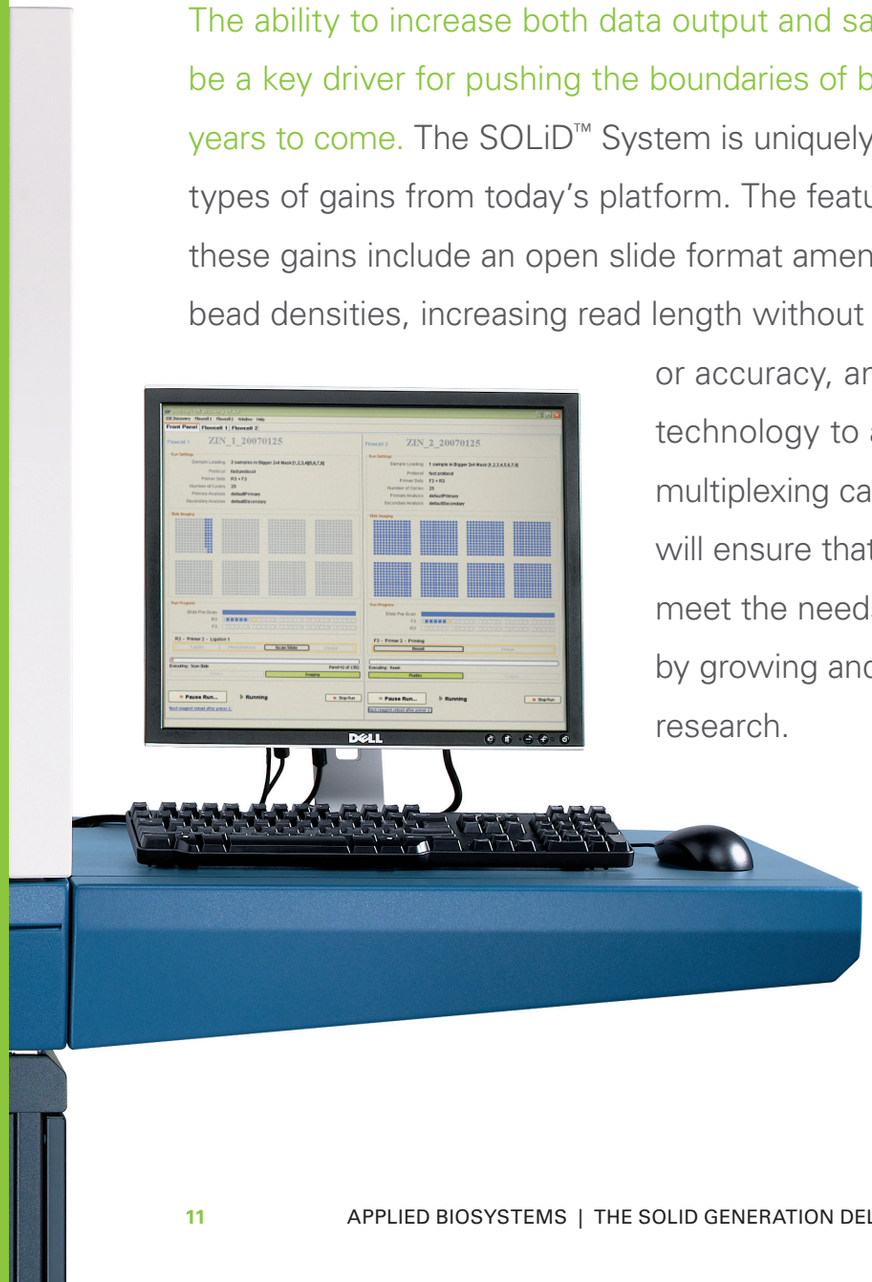
The vast number of sequencing reads generated by the system coupled with high accuracy and mate-paired technology enable a whole new way to study ChIP with unmatched specificity and accuracy.

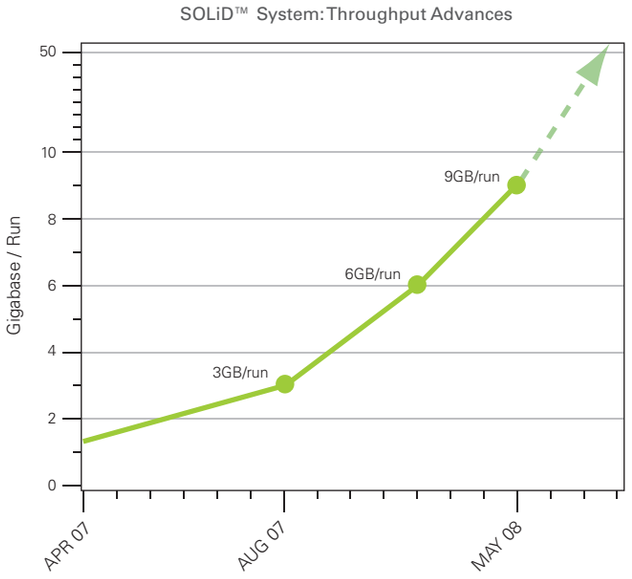
Whole Genome Sequencing

The SOLiD System enables a new level of whole genome sequencing with massive throughput and mate-paired technology. The system's throughput allows for high coverage levels and the ability to sequence multiple genomes in a single run. These and other features dramatically reduce the time and cost required by other technologies.

The Future Is SOLID

The ability to increase both data output and sample throughput will be a key driver for pushing the boundaries of biological analysis in the years to come. The SOLiD™ System is uniquely poised to deliver both types of gains from today's platform. The features that will enable these gains include an open slide format amenable to vastly increasing bead densities, increasing read length without sacrificing robustness or accuracy, and a novel barcoding technology to allow improved sample multiplexing capability. These features will ensure that today's system will meet the needs of future experiments by growing and expanding with your research.





In 2008, the SOLiD™ System demonstrated throughput of 9GB in a single run.

Increasing Future Data Output and Throughput

The SOLiD™ System's ability to dramatically increase data output from the same platform is a function of the flexible and modular nature of the technology. Achieving higher levels of increased data output is possible through these modest improvements:

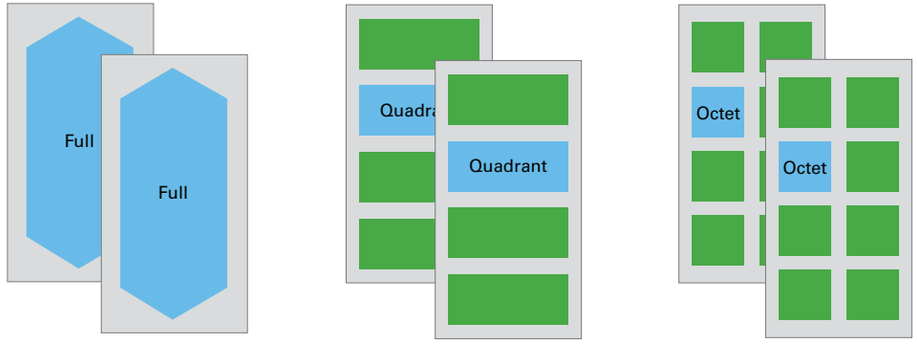
Bead Density—Amount of beads that are able to be deposited on a slide and analyzed. The unique open format of the SOLiD System allows more beads to be packed onto a single slide, without changing the system configuration, than with microtiter based technologies. Advancements in the algorithms for bead finding will also increase the number of beads able to be analyzed from a given slide. These combined improvements are anticipated to more than double the data output of the current system.

Read Length — Measure of the number of bases sequenced. Protocol and chemistry optimization will increase the read length of the current system, while maintaining strict accuracy and consistency standards.

	FRAGMENT LIBRARY Using two full slides/run			MATE-PAIRED LIBRARY Using two full slides/run		
	2007	2008	2009	2007	2008	2009
Read Length	35	35	50	25	35	50
Total Output*	~2.5 GB	~4 GB	~9 GB	~3.5 GB	~6 GB	~9 GB

* Mappable data from 2 slide run

Sample Multiplexing—Increase sample throughput per run. While the SOLiD System currently has the capability to segment slides into sections of one, four and eight, barcoding will provide even greater sample throughput. The assignment of a unique identifier to beads of a given library will allow for matching sequence information back to the source sample library.



Full Slide
16 samples/slide
32 samples/run

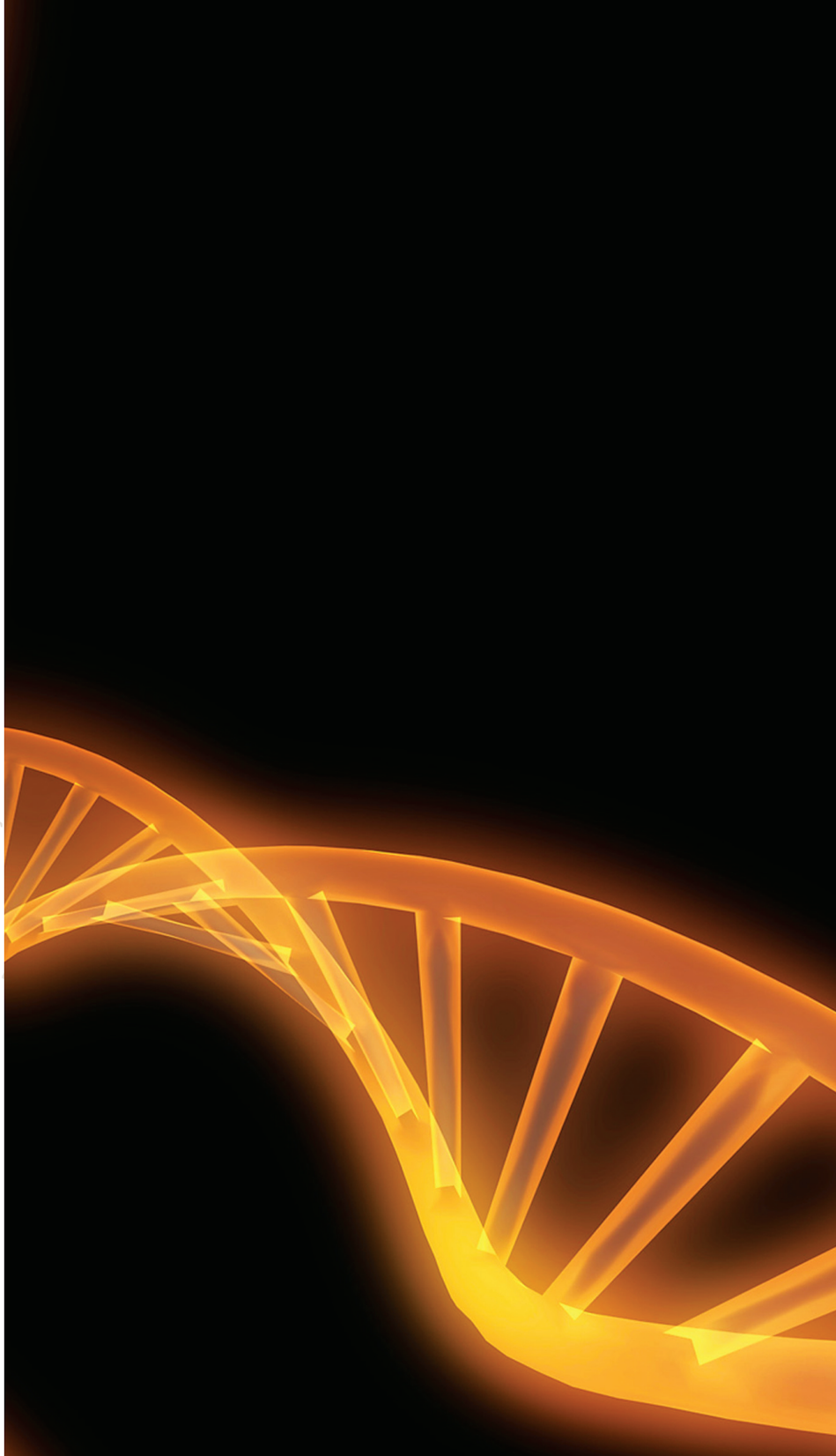
Quadrant Slide
64 samples/slide
128 samples/run

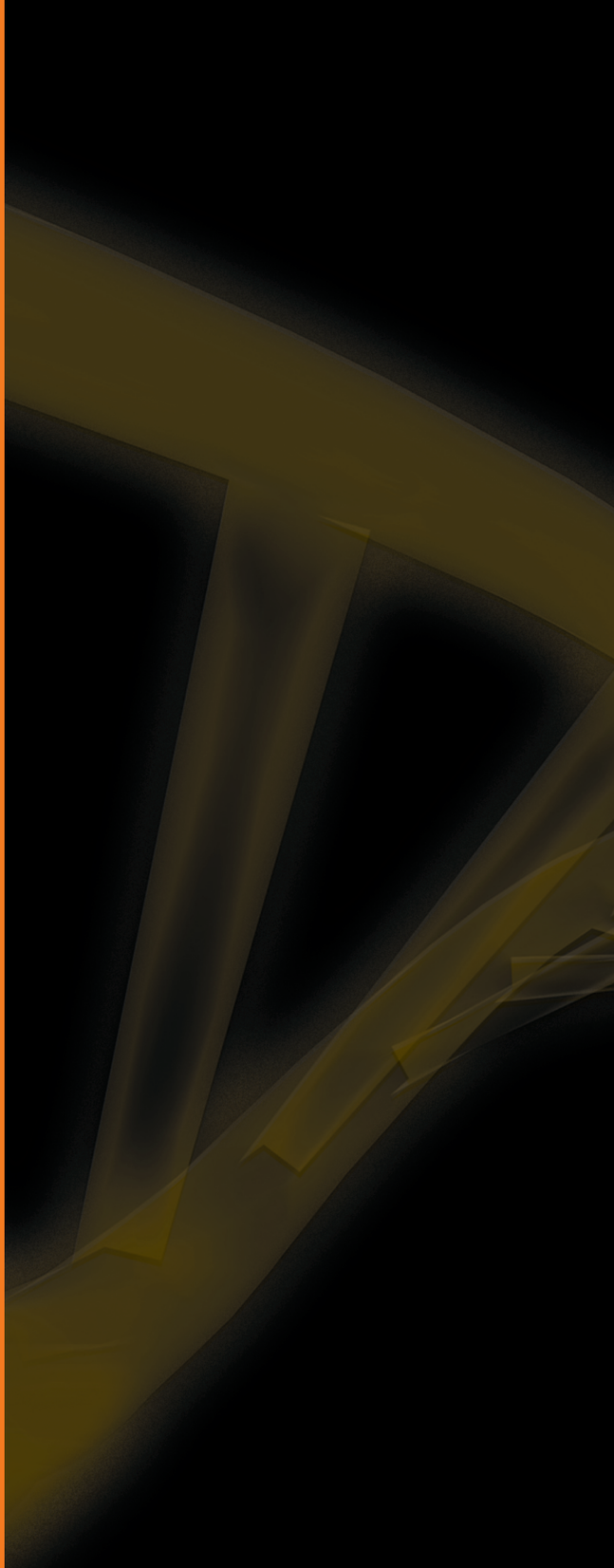
Octet Slide
128 samples/slide
256 samples/run

SOLID Support

Global Service & Support

With over 2,000 global service and sales personnel, Applied Biosystems has the most extensive network of dedicated Field Application Specialists (FAS) and Support Engineers to work with you. With Applied Biosystems, you can feel confident that we will be there when you and your science need us most.





Applied Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404
USA

Publication 139BR01-02