Reprinted from *American Biotechnology Laboratory* August 2006

# Impact of HTS on Multidetection Microplate Readers and Benefits For Life Science Research Laboratories

**by Xavier Amouretti**

The basic concept behind high-throughput screening (HTS) is a numbers game: If one has the technical ability to test thousands upon thousands of potential drug compounds against a specific target, it is likely that some compounds will interact with the target in a positive manner. Playing this numbers game quickly and efficiently is vital as our aging population faces increased incidences of heart disease, cancer, and respiratory disease. Drug discovery researchers have responded by increasing their efforts and placing more demand on HTS reagents, instrumentation, and software providers: more information, more sample processing, and more options. Detectors and related detection technologies, including microplate readers, have evolved at the same frenzied pace as the field of HTS to provide faster turnaround, higher accuracy and precision, and more efficiency for screening volumes of drug candidates.

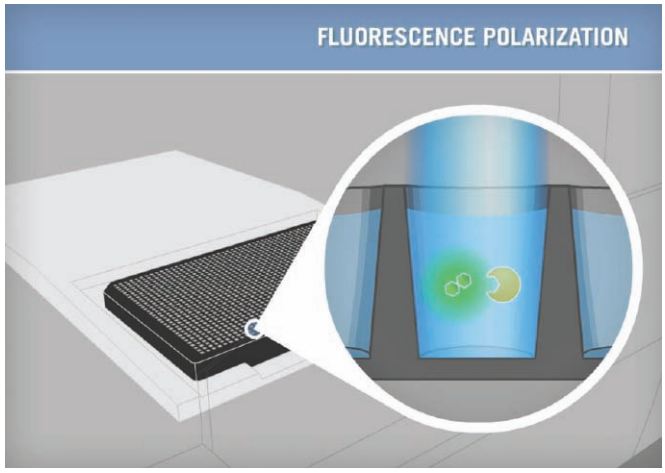


*Figure 1 Fluorescence polarization can provide information on changes in molecular mobility found, for example, in receptor–ligand interactions, protein–DNA interactions, or membrane fluidity.*

As the number of drug compounds has increased, assay miniaturization has developed to counter rising reagent, drug candidate, and drug target costs. Miniaturization to 384-well and 1536-well microplate formats has reduced the cost per test, although this miniaturization is not without its limitations. Common and robust assays such as enzyme-linked immunosorbent assays (ELISAs) are difficult to miniaturize beyond a certain volume due to a separation, or washing, step. This has led to a new generation of "mix and read" or "homogeneous" assay platforms, where separation is not required. Some of the most common homogeneous screening assay technologies are fluorescence polarization (FP), based on molecular rotation with a single fluorescent label (*Figure 1*); fluorescence resonance energy transfer (FRET), measuring the distance-dependent interaction of two fluorescent labels; and time-resolved FRET (TR-FRET), using a principle similar to FRET with a delay after the excitation light pulse to reduce background fluorescence. These fluorescence-based techniques achieve good sensitivity while using a very simple assay protocol, and are easy to automate and miniaturize. They are implemented using HTS microplate readers with rapid analysis times, advanced detection systems, and compatibility with various microplate formats. Detection technologies available on these readers are typically fluorescence polarization, fluorescence intensity (to enable FRET detection), time-resolved fluorescence (to enable TR-FRET detection), luminescence (commonly used for

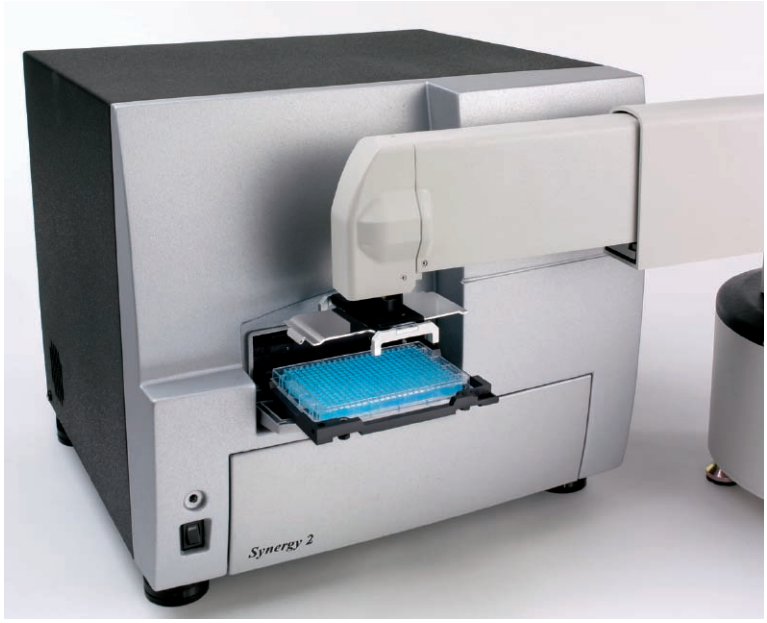


*Figure 2 Synergy 2 multidetection microplate reader shown with the Bio-Stack™ Twister 2.*

luciferase gene expression assays), and absorbance. Prices typically range from about $60,000 to well over $100,000.

Within life science research laboratories, popular multimode, or multidetection, microplate readers have developed because of their versatility. These differ from HTS readers in that there is no need to support high-density plates (1536-well plates), speed is less important, and homogeneous assay detection is not critical. Flexibility is the focus, with various features including kinetic reading, well scanning, reagent injection, monochromators, temperature control, and shaking. These features are not usually considered necessary in HTS instrumentation but can be critical for life science research applications. Prices typically range from $15,000 to about $60,000.

Although requirements from HTS and life science research differ, there has been convergence over time. On one hand, the limited success of massive screening campaigns thus far has prompted pharmaceutical laboratories and biotechnology companies to adopt a more thoughtful approach to screening; the all-speed, all-performance approach is giving way to more modular and targeted strategies, where flexibility and pricing become more important factors. On the other hand, new research applications for detection technologies such as FP and FRET have pushed researchers to look for instrumentation with high levels of performance in these modes of operation. The Synergy™ 2 (**BioTek Instruments, Inc.,** Winooski, VT) (*Figure 2*) is one of the first of a new generation of multidetection microplate readers that reflect this convergence. It has been designed with screening applications in mind but has retained the need for greater flexibility found in life science research laboratories. The system is fast, compatible with 1536-well plates, and has very high performance in polarization and time-resolved modes. At the same time, it is equipped with an extremely precise temperature control system, a built-in shaker, a monochromator-based spectrophotometer, and an optional reagent injection system for applications more traditionally found in research laboratories. Each of its detection technologies is available as a module so that researchers can tailor the instrument to their specific application and budget, while retaining the ability to upgrade whenever necessary. This new type of reader provides the combined benefit of bringing to research laboratories a level of performance and technologies usually found on high-end HTS instrumentation, while at the same time delivering efficient cost control to screening laboratories.

The HTS revolution has had a broad impact on instrumentation, software, and assay technologies. Multidetection microplate readers have benefited greatly from these evolutions, and now offer life science research laboratories technologies and performance previously found only on high-cost HTS instrumentation. In return, HTS screening laboratories can now access high-performance instrumentation at a cost significantly lower than traditional HTS readers.

*Mr. Amouretti is Product Manager,* ***BioTek Instruments, Inc.,*** *Highland Park, P.O. Box 998, Winooski, VT 05404-0998, U.S.A.; tel.: 888-451-5171; fax: 802-655-7941; e-mail: amourettix@biotek.com.*