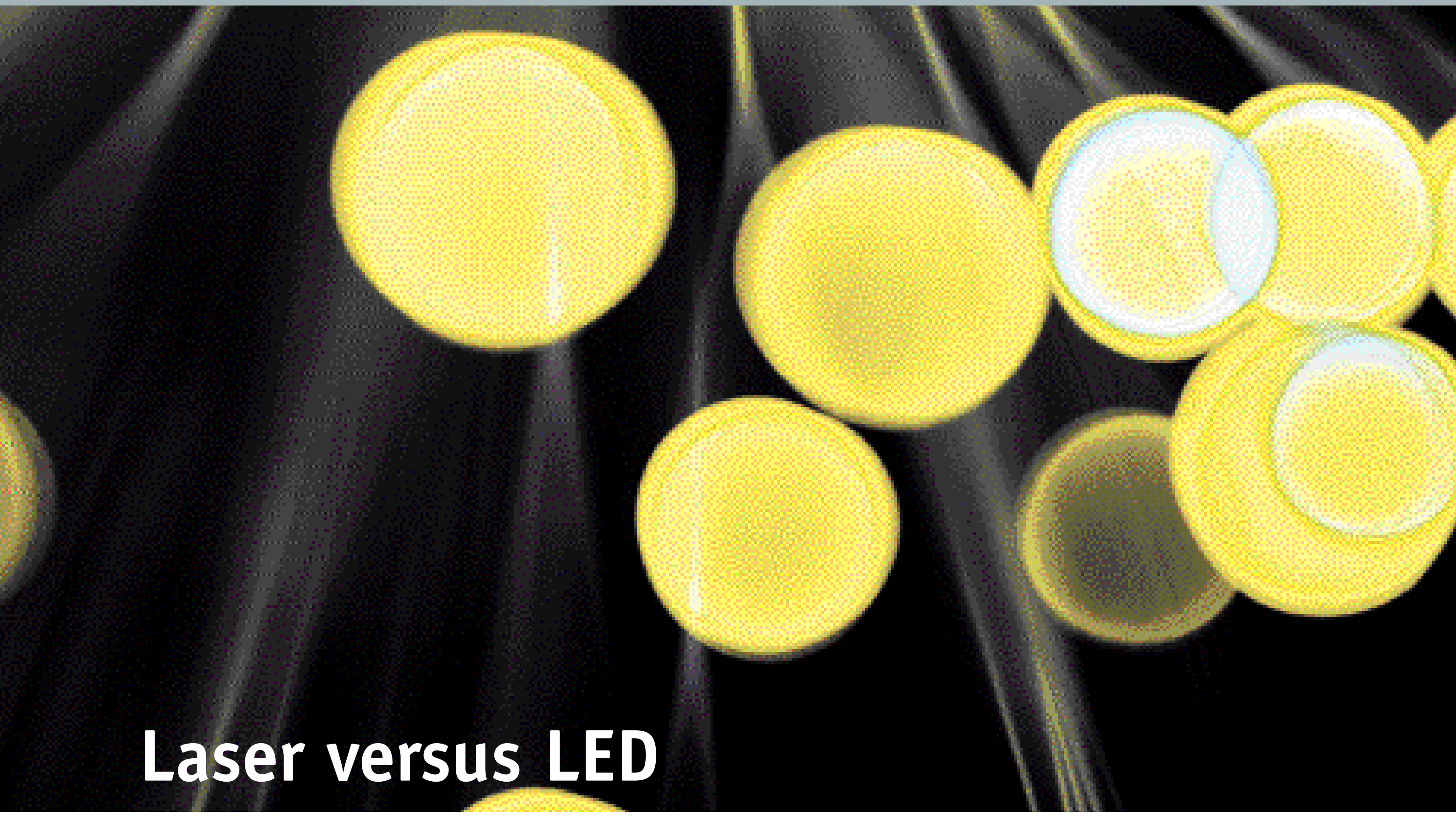

Laser versus LED

OPTIMIZING LASERS FOR COST-SENSITIVE BIO APPLICATIONS

A new generation of compact, OEM lasers provides the performance and economy needed for important bioinstrumentation sectors, such as gene sequencers and desktop analytical instruments intended for point of care.

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Biotech instrumentation manufacturers are currently developing products that feature increased miniaturization and lower costs per use, mainly due to worldwide trends in healthcare. For instruments based on laser-excited fluorescence, this has created demand for laser modules that emphasize low cost, compact packaging and reliability, rather than cutting edge performance. This article reviews why and how these market needs are being met, and also explores the advantages of laser sources over LEDs for these applications.

Fluorescence-Based Analyzers

Many instruments that analyze biochemical reactions and properties utilize fluorescent probes which are tagged to specific cells, antigens or sub-cellular components (or which are expressed by genetic modification of the cells themselves). Examples include cytometry, genetic sequencing, hematology, polymerase chain reaction (PCR), high-throughput drug screening, and microarray scanners. The advantages of fluorescence detection over chemical interrogation are fast, non-contact measurements with superb spatial discrimination. Plus, these techniques lend themselves to miniaturization, automation and simultaneous parallel processing.

Nearly all these instruments use one or more lasers to excite the fluorescence, where the laser is focused to a small area or spot size (typical spot sizes are given in **Table A**). By using several laser wavelengths to excite multiple fluorophores, some of these instruments can analyze multiple cell types in the same data run.

Application	Focused Spot Size
Gene Sequencing/Medical Diagnostics	1 to 10 x 1 to 10 mm
Medical Diagnostics	100's x 100's µm
Cytometry	30 x 30 µm

A Typical spot sizes for floureszenze applications

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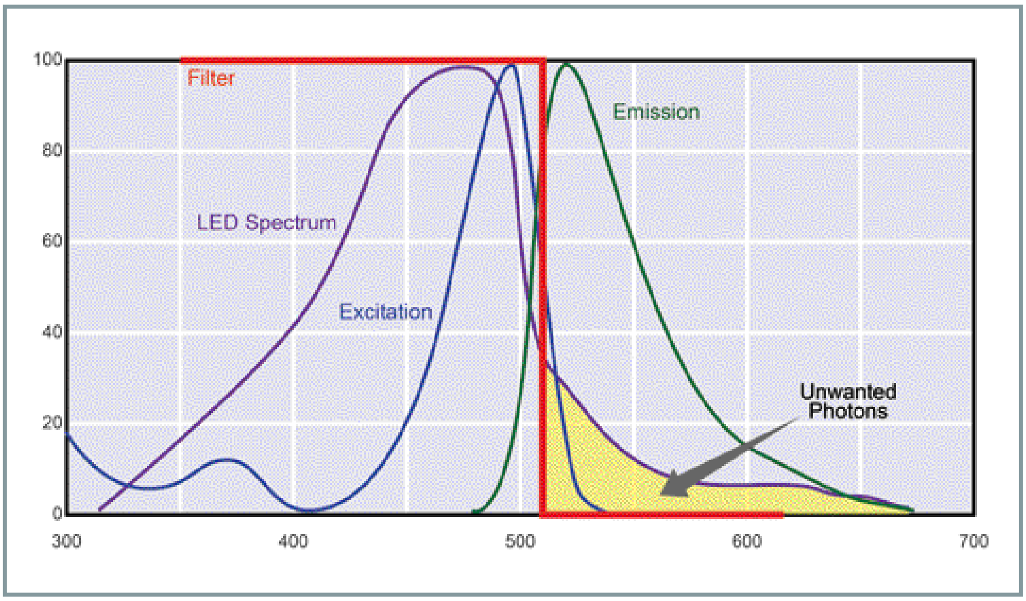


1 Every fluorophore is characterized by an excitation spectrum and a long wavelength emission spectrum. With a single wavelength laser, it is easy to separate scattered excitation light from the emission spectrum using a long-wave cutoff filter. But with a typical LED, the long wavelength tail of its output overlaps the fluorescence emission and must be somehow eliminated. Plus the size and shape of this tail can vary significantly between different batches of LEDs

Microfluidics and miniaturization lower costs

In many applications, there is shift from the research laboratory to the clinical laboratory, and, thence, to the point of care. In the West, the goals are personalized medicine and lower costs. Personalized medicine means genetic profiling of the patient and/or the specific disease to determine what drugs will yield an optimum result. In the fast growing Chinese market, the aim is to enable more testing through lower costs, bringing the standard of healthcare closer to that of the West.

In fluorescence-enabled diagnostics, this trend manifests itself in greater streamlining and automation. While in research and clinical laboratories the users may possess expertise in fluorophore chemistry, this is not the case in a doctor's office. As a result, the market needs instruments configured for simplified and repetitive use in common tests, rather than the multifaceted flexibility of a typical flow cytometer. This trend dovetails with the increasing use of microfluidic instruments, often called ›lab on a chip‹, which also enable much smaller instruments than are possible with legacy flow technology

Lasers vs. LEDs

High end instruments can easily cost several hundred thousand Euros, so the use of one or more lasers to enable high performance is easily justified. But, the development of miniaturized, lower cost instruments is causing manufacturers to ask whether it is cost effective to even use a laser at all. Can some of these applications instead be serviced with a lower-cost LED or super-luminescent LED (SLED) as the fluorescence excitation source?

Many applications don't need the extreme monochromaticity and spatial brightness of a laser, and a few instruments that use very wide-field illumination may be able to economize by using LEDs. But blood analyzers and lab on a chip instruments require a focused spot of light with a narrow, well-defined and consistently reproducible spectral bandwidth and intensity profile. This is actually quite difficult and highly inefficient to achieve with LEDs, and requires extra optics and careful LED screening (selection). These steps can push the real cost of implementing LEDs above that of using ›entry-level‹ lasers.

As one example of the advantages of lasers, note that a 1 W laser can easily be focused to a diffraction-limited spot containing over 0.9 W, while the focused spot from a 1 W LED might contain only 100 µW of useable photons. Part of the problem is that LEDs are rated by their power consumption, not their optical output. So, a 1 W-rated LED might only generate a total of 90 mW. Moreover, the LED emits into a large solid angle, and high numerical aperture (i.e., high cost) optics are required to capture just a part of this output. Plus, the LED is not a true point source, as is a laser, so there is an inescapable optical trade-off (called ›etendue‹) between collection efficiency and final spot size.

In addition, LEDs output a broad spectrum that usually must be wavelength filtered to avoid cross-talk between different fluorophore signals, as well as to minimize background noise due to scattered excitation light (Figure 1). All this adds cost and complexity to the instrument, while reducing the amount of light reaching the interaction zone (which can further reduce instrument signal-to-noise ratio).

Lastly, LEDs are volume manufactured on a massive scale. The instrument manufacturer, and even the LED reseller, has no control over the unit-to-unit variations in LED output spectrum and spatial illumination distribution. This presents a serious challenge to achieving instrument consistency and serviceability.

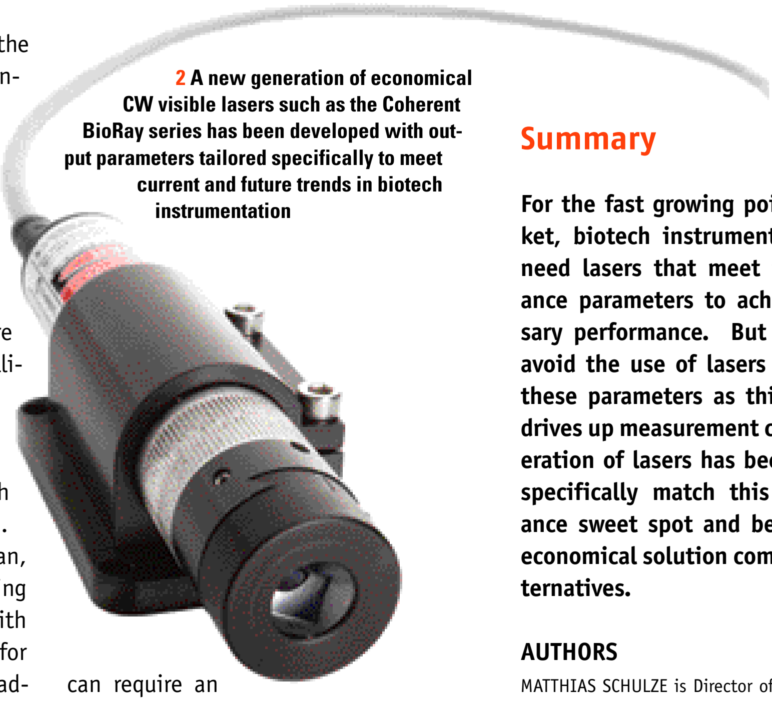
Optimized Lasers

Of course, the choice of a laser as the light source in an analyzer is also critically impacted by the cost/performance ratio of the available laser products. It is vitally important that the laser offers only the functions and performance parameters needed for optimum instrument operation. Higher laser specifications will increase cost without delivering any tangible benefit to the application. To meet this need, laser manufacturers have introduced ›entry level‹ products, such as the new Coherent BioRay series (Figure 2), that are optimized specifically for this new generation of analyzers.

These lasers deliver a few tens of milliwatts, and are available at several visible wavelengths which match the optimum excitation of common fluorescent probes and genetically encoded markers (typically 405, 450, 488, 520 and 640 nm). These products are based on ▶

laser diode technology, as that is the simplest and lowest cost method of generating CW laser output at these wavelengths and in this power range. Laser diodes also offer the highest efficiency, lowering the required power budget for the final instrument. Since edge emitting laser diodes emit a highly divergent and asymmetric (elliptical) beam, optics are used in the laser head to produce a collimated, elliptical beam. To reduce the complexity of downstream beam delivery optics, each head has an adjustable output lens to enable smooth adjustment of the beam waist location.

These lasers produce a clean Gaussian, TEM00 beam ($M^2 < 1.5$) enabling focusing to a small spot. In comparison lasers with higher order modes are not well-suited for use in biotech instrumentation where additional spatial filtering would be required. Another important feature for instrument manufacturers is direct analog modulation up to 500 kHz, in constant power mode, which supports fast cell counting and other applications. (Earlier diode-based lasers only enable modulation in constant diode current mode which can require an extra level of signal normalization.) Two other advantages are a simple, common electronic interface offering both RS 232 and GUI control, and a common mechanical platform irrespective of output power or wavelength. This enables simple field replacement or upgrading in the field, often called ›hot-swapping‹.



2 A new generation of economical CW visible lasers such as the Coherent BioRay series has been developed with output parameters tailored specifically to meet current and future trends in biotech instrumentation

Summary

For the fast growing point of care market, biotech instrument manufacturers need lasers that meet target performance parameters to achieve the necessary performance. But they must also avoid the use of lasers that far exceed these parameters as this unnecessarily drives up measurement cost. A new generation of lasers has been developed to specifically match this price/performance sweet spot and become the more economical solution compared to LED alternatives.

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