Advances in Biophotonics

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Executive summary

Photonic technology is being applied more and more in biology and medicine. Photonics uses light rather like electronics uses electricity. Light can travel faster than electrons, so photonic devices will be faster.

Photonics and photons

The technology of generating, managing and understanding photons, predominantly in the visible and the near infrared spectrum, is known as photonics. Photons are units of light energy capable of electromagnetic phenomena. This report looks at photonics for biological and medical applications and is aimed at suppliers of photonic elements and products and suppliers of medical test, sensor, imaging and measurement instruments.

Photonics in biomedicine

Biophotonics is the use of photonics in biology and investigates how biological matter interacts with photons. Bioimaging is the application of microscopy to the study of cells and organisms. It is a crucial tool for improving human life. It helps in the visualisation of physiological cellular activity; in other words, it helps to detect diseased tissues. Biosensors are devices that convert a biological response into an electrical signal. The detector of the biosensor is usually coated with a very sensitive biologically responsive element.

Photonic materials and devices

Heterostructure lasers

A laser is an optical source that manipulates energised atoms to emit coherent photons. Heterostructure lasers are laser diodes where two different materials are used to make the diode junction. Two examples of their use are spectroscopic sensing and coherent control of chemical reactions. They are susceptible to catastrophic optical damage (COD) when run at higher power.

Light-emitting diodes

Light-emitting diodes (LEDs) are semiconductor materials that convert electrical energy into light energy. An LED produces a negligible amount of heat compared to an incandescent lamp. It can emit narrow-spectrum incoherent light when biased in a forward direction. The light emitted is monochromatic – a single colour. The colour of the emitted light depends on the composition and the condition of the semiconducting material. LEDs are capable of emitting light in the infrared (IR), visible or near ultraviolet (NUV) spectrum. LEDs are used as light sources for biosensors. High-power LEDs are susceptible to current crowding.

Micro- and nanophotonics

Nanophotonics is the study of light at the nanoscale. It is used to produce and manipulate light using ultrasmall engineered structures. Nanomedicine is the diagnosis, preservation and improvement of human health using nanotechnology, molecular tools and molecular knowledge of the human body. Nanomedicine using photonics offers the possibility to cure and detect diseases, perform cell and tissue repair, or identify and repair cell mutations such as cancer. Nanotechnology has helped reveal the workings of living tissues such as bone, muscle and nerve, which has led to better diagnostic tools, new structures for specific disease treatment, and methods for selective tissue repair. Development of nanotechnology and nanophotonics is mainly constrained by cost.

Nanotubes

Nanotubes confine electrons in two dimensions. Carbon nanotubes (CNTs) are made of carbon, usually shaped into a cylinder. CNTs have medical applications. CNTs are used to make organic light-emitting diodes (OLEDs) for mobile phones and televisions. Flexible OLEDs will also bring breakthroughs in medical science.

Optical fibres and waveguides

Endoscopy was the first medical application of optical fibres. It allows surgery to be a minimally invasive procedure that requires less hospitalisation and produces less post-operative pain. Surgical tools are inserted into the body through existing holes in the body or minor cuts created for the surgery. An endoscope delivers light into the patient's body, then optical bundles inserted as part of the endoscope or alongside the endoscope relay images to surgeons so they can investigate the cause of any illness. A channel alongside the endoscope allows surgeons to insert microsurgical tools to perform operations on the body, or to insert an optical fibre that delivers laser light to treat the patient. The rapid growth of fibre-optic sensing has matched the industrial availability of low-attenuation optical fibres. Other waveguides are based on photonic crystal fibres (PCFs), prisms and hollow tubes. Hollow waveguides can be tuned by changing the thickness of a dielectric layer.

Quantum dots

A quantum dot is a nanostructure, often made from metals and semiconductors, where the electrons are confined in all three spatial dimensions. They resemble an atom but they are bigger than an atom. Many important characteristics of atoms can be deduced from a quantum dot. Like an atom, quantum dots have a quantised energy spectrum. Illumination with laser light causes a quantum dot to glow. Quantum dots have recently been made out of carbon and have similar behaviour. Carbon quantum dots could be used as biological sensors, medical imaging devices and LEDs for medical purposes. Carbon quantum dots are probably less toxic and more environment-friendly than metal quantum dots and could be less expensive than metal quantum dots. Another possibility is cheap, disposable sensors that can detect hidden explosives and biological warfare agents such as anthrax.

Silicon-on-insulator

Silicon-on-insulator (SOI) is a semiconductor manufacturing technology in which thin films of single-crystalline silicon are grown over an electrically insulating substrate. SOI improves electrical performance by reducing parasitic capacitance, especially in high-speed and very dense circuits. By reducing the parasitic capacitance, it is possible to fit the device circuits into a smaller area, which can increase the speed of the device by 15–20%. It also reduces energy consumption by up to 30% over CMOS chips. A very common type is silicon-on-sapphire (SOS).

Surface plasmons

Surface plasmon resonance (SPR) can occur when plane-polarised light hits a metal film under total internal reflection (TIR) conditions. Incident light photons are absorbed and converted into surface plasmons – electron density waves. When, in a TIR situation, the quantum energy of the photons is right, the photons are converted to plasmons and this leaves a gap in the reflected light intensity. Surface plasmons are used in surface-enhanced Raman spectroscopy and biochemists use SPR to detect the presence of a molecule on a surface.

Solid-state lasers

Heterostructure wavelength-tunable lasers are receiving significant interest in the field of electron band structure engineering, where the flow of electrons can be tightly controlled. The quantum cascade laser is the first room temperature semiconductor laser to operate in the mid-IR and far-IR regions.

Manufacturing photonic devices

Polishing, patterning and lithography

Polishing is done to planarise non-planar substrates, as scattering losses are proportional to surface roughness. Planarisation improves the yield of photolithography, etching and metallisation. Lithography is printing or creating patterns on a substrate; it is the main method of making microchips, where it is known as photolithography or optical lithography. A pattern is transferred from a photomask or reticle to the substrate surface.

In situ process monitoring

In situ process monitoring is a way to monitor and control semiconductor fabrication techniques, such as chemical vapour deposition (CVD). There is a need to monitor the chemical kinetics of the fabrication processes.

Laser deposition and irradiation

Laser CVD (LCVD) is widely used to make small and complex metal, ceramic and composite parts. A laser is used to produce a vapour of the deposition material; this vapour then reacts with a substrate surface to deposit a solid layer. Materials prepared by this process have high purity, low porosity and high crystallinity.

Microdrilling and microcutting

In microdrilling and microcutting, an instrument drills a hole into the semiconductor material. The chips from the hole are removed using a thin fluid, generally air or an air–oil mist; the fluid is made to move over the hole to prevent it flowing into the hole. Air–oil mist is preferred to air because it has lower friction.

Plasmas and electron beams

A plasma is an ionised gas that consists of free electrons, ions and energised neutrals. Plasmas can be used to create high-flux beams of energetic ions and electrons for ion implantation, ion etching and micromachining. Reactive ion etching (RIE) is a plasma technique used in the microelectronics industry to etch material deposited on wafers. The main advantage of RIE is improved directionality. Directionality is important because smaller and smaller devices require deeper and deeper etching. Deep RIE (DRIE) is a highly anisotropic process that is used to fabricate microelectromechanical systems (MEMS) plus 2D and 3D photonic crystals.

Packaging and assembly

Photonic materials go through three stages of manufacturing and assembly: chip production, optical assembly and packaging. About 60–80% of manufacturing costs for photonic components go on assembly and packaging. Reduce these costs and manufacturing becomes much cheaper.

Emerging materials

Key emerging materials are indium, gallium, silicon, aluminium gallium arsenide, sapphire, arsenic and phosphorus. Active integrated devices are heterostructures, LEDs, quantum wells, surface plasmons, etc. Passive devices are waveguides, optical fibres, etc. These active and passive devices are building blocks for biosensors, microscopes, spectrometers, etc. For greater precision, some applications use polymers instead of inorganic materials.

Photonics in biomedical applications

Bioimaging

Bioimaging is the application of microscopy to study cells and organisms. It offers a way to see inside the human body and its cells. Three examples are high-resolution imaging, magnetic resonance imaging and lifetime fluorescence imaging. Bioimaging aims to provide consistent data for therapeutic diagnosis and analysis, reducing the requirement for biopsies and other procedures and improving premature detection and treatment of cancers and tumours, targeted drug remedies, and screening of joint, valve and organ surrogates.

Bioluminescence

Bioluminescence is the production and emission of light by biochemical reactions in a living organism. It occurs mostly in marine animals but also in plants and insects.

Bio-optical detection

Different tissues respond to light in different ways. The same tissue may respond to light differently depending on whether it is healthy or diseased. It is possible to detect diseased tissue by measuring its diffraction, absorption and scattering properties. This is bio-optical detection.

Biosensors

A biosensor converts a biological response into an electrical signal. Biomedical research often requires live cell monitoring. Well-designed biosensors can make non-destructive, real-time measurements of chemicals in living cells. They combine a biologically sensitive element with a physical or chemical transducer to detect specific biological compounds in a given external environment.

Image processing

Medical images are often complex and have poor visual quality; this makes their interpretation rather subjective. Machine vision can be used to help analyse images such as radiographs and magnetic resonance scans, giving experts more time to do tasks that cannot be automated.

Medical imaging

In vivo imaging allows animals to be imaged at any stage of their lives and it does not cause the animals to die. It can also help in the study of animal genomes. Medical researchers use animals to investigate the nature of disease and the stages of tumours but to obtain useful information, the investigations often cause these animals to die. The assays are usually time-consuming and can only provide a snapshot of the overall disease course, even when performed on large numbers of animals. Medical imaging offers a way to overcome these problems and helps scientists to research diseases and develop drugs.

Medical sensors

Medical sensors come in a wide variety. Many have changed from analogue devices to digital devices based on semiconductors.

Multiphoton microscopy

Multiphoton excitation microscopy combines optical scanning microscopy with multiphoton fluorescence to create high-resolution three-dimensional images of biomolecules. Multiphoton excitation of biomolecules yields more spectroscopic information than standard one-photon studies. It limits cell damage and permits greater penetration depths.

NIR spectroscopy

Spectroscopy is a way to study the properties of matter by investigating how light interacts with it. Spectroscopy illuminates a specimen with a spectrum of light and measures the number of photons at each wavelength after the light has interacted with the specimen. Near infrared (NIR) absorption spectroscopy illuminates a specimen with NIR light in the range 12,500cm^{-1} to 4,000cm^{-1} then looks to see which wavelengths show the greatest absorption in the specimen. The chemical bonds in the specimen vibrate at characteristic frequencies; when they are illuminated with light of the right wavelength, the energy in the light causes these bonds to vibrate. Then the absorption spectrum will show that light has been absorbed at this wavelength.

Photodynamic therapy

Photodynamic therapy uses light to produce localised oxidative damage that destroys tumours inside diseased tissue.

Protein separation

Gene sequence information alone is inadequate to identify targets for therapeutic interventions or treatments, as researchers are yet to elucidate the function of most of the human genome. But it may be helpful to study proteomics – the structure and function of proteins translated from the gene sequence. Consequently, recognition and separation of proteins from living cells has become a major focus of drug innovation.

Confocal microscopy

A confocal microscope creates very sharp images of a specimen which would appear very small or blurred using an ordinary microscope. It uses laser light to excite fluorescence in a specimen treated with a fluorescent dye. It eliminates out-of-focus light using a pinhole before the detector. The pinhole is conjugate to the focus of the microscope lens, hence the name confocal microscopy. The laser is scanned across the specimen and the detector builds up an image pixel by pixel. A three dimensional image can be created by scanning many thin sections.

Photonic crystals

Photonic crystals have a periodic variation in refractive index. This creates a band gap at optical frequencies. Spontaneous emissions can be controlled using photonic crystals and artificially introduced defect states in photonic crystals. They can also be used to bend light very sharply, which is useful in other photonic devices.

Optical coherence tomography

Optical coherence tomography (OCT) offers high-resolution cross-sectional tomographic imaging based on backscattered or back-reflected light. It has many uses, including biomedical applications.

Coated optical fibres

Coated optical fibres are cost-effective and reliable sensors for rapid detection and identification of chemical and biological agents. They withstand high temperatures and possess very high strength.

Polymer semiconductor hybrids

Polymer-based grating waveguide structures are fabricated by spin coating and holography. They have yielded narrow-bandwidth optical filtering, with 55% reflection efficiencies and 1nm bandwidth.

Introduction

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This report looks at photonics for biological and medical applications and is aimed at suppliers of photonic elements and products and suppliers of medical test, sensor, imaging and measurement instruments.

Scope

The report covers optoelectronic materials and devices, processing and manufacturing, imaging, sensing and optical microscopy. It looks at developments in biological and medical applications and profiles companies that use and supply biophotonic materials and devices. It focuses on current and emerging applications of photonics in biology and medicine.

Methodology

The report is based on secondary research using market reports, technical books, newsletters, journals, conference proceedings and company websites.

Definitions

- *Absolute luminance threshold*: the lower limit of luminance necessary for vision.
- *Absorption*: loss of light as it passes through a material due to its conversion into other forms of energy, usually heat.
- *Active layer*: the layer in a semiconductor injection laser or LED that provides optical gain.
- *Afterglow*: the luminosity in a rarefied gas after an electric discharge is passed through the gas.
- *Amplitude*: magnitude of the electric vector of a wave of light.
- *Band gap*: the least amount of energy required for an electron to transfer from the valence band into the conduction band, which allows it to move freely in a semiconductor material.
- *Biometrics*: a technology that analyses unique biological characteristics such as voice patterns, fingerprints, retina or iris patterns, and hand or face geometry to establish the identity of an individual.
- *Biophotonics*: a technology that exploits the relationship between biological matter and photons.
- *Catastrophic optical damage*: damage that occurs when a semiconductor melts and recrystallises in the emission region. The damage is rarely detectable using optical microscopy.
- *Confocal microscopy*: an imaging technique used to increase micrograph contrast and/or to reconstruct three-dimensional images by using a spatial pinhole to eliminate out-of-focus light or flare in specimens that are thicker than the focal plane.
- *Dichroism*: in certain anisotropic materials, the property of having different absorption coefficients for light polarised in different directions.
- *Dielectric*: displaying the features of materials that are electrical insulators or those which can maintain an electric field using minimal power. They display non-linear characteristics such as saturation and their conductivity is anisotropic.

- *Dipole polarisation*: the electric polarisation created by the orientation of molecules that have permanent dipole moments arising from an asymmetric charge distribution. Also known as orientation polarisation.
- *Doping*: the addition of impurities to a substance, usually solid, in a controlled manner to produce desired properties. Silicon is doped with semimetallic elements to increase the number of charge carriers.
- *Electric vector*: in a light wave, it specifies the direction and amplitude of the electric field.
- *Electro-optics*: science and technology concerned with the use of applied electrical fields to generate and control optical radiation; synonymous with optoelectronics.
- *Electron*: a stable subatomic particle with a unit negative charge. Its positive counterpart is a positron, which has a unit positive charge.
- *Heterojunction*: the boundary between two different semiconductor materials, usually with a negligible discontinuity in the crystal structure.
- *Heterostructure*: a structure of two different semiconductors in junction contact having useful electrical or electro-optical characteristics not achievable in either conductor separately; used in some types of lasers and solar cells.
- *Infrared*: electromagnetic radiation with a wavelength longer than visible light but shorter than radio waves.
- *In situ*: in the original place.
- *In vitro*: processes or reactions taking place in a test tube, culture dish or elsewhere outside a living organism.
- *In vivo*: taking place in a living organism.
- *Laser*: a device that generates an intense beam of coherent monochromatic light by stimulated emission of photons from excited atoms or molecules.
- *Lasing medium*: in a laser, the lasing medium is the source of the electrons and can keep the electrons in an excited state until stimulated; also called the active laser medium.
- *Luminescence*: light emission that cannot be attributed merely to the temperature of the emitting body.
- *Neutralisation*: combining two lenses having equal and opposite powers to produce a result having no power.
- *Organism*: an individual animal, plant or single-celled life form.
- *Photodynamic therapy*: a form of non-surgical cancer treatment that combines a photosensitising medication with exposure to a laser or other specific light wavelength to kill cancer cells.
- *Photon*: a particle representing a quantum (q.v.) of light or other electromagnetic radiation. A photon has energy proportional to the radiation frequency but has zero rest mass.
- *Population inversio*n: the condition in which a higher energy state in an atomic system is more heavily populated with electrons than a lower energy state of the

same system. Population inversion is needed to produce stimulated emission in a laser, but the concept is not as relevant for solid-state lasers.

- *Quantum*: a discrete quantity of energy proportional in magnitude to the frequency of the radiation it represents.
- *Semiconductor*: a material that has a conductivity which falls between the values for conductors and insulators. The conductivity of a semiconductor can be altered by doping (q.v.).
- *Semiconductor laser*: a laser that uses a semiconductor as its photon source. The two key types are laser diodes and LEDs.
- *Wavelength*: electromagnetic energy is transmitted in sinusoidal waves. It is the physical distance covered by one sinusoidal cycle and is inversely proportional to the wave's frequency.

Photonic materials and devices

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Photonic devices include optoelectronic devices such as lasers, LEDs, nanotubes, waveguides, optical fibres, photonic crystals and other passive optical elements. They act as media for transmitting light.

Heterostructure lasers

A laser is an optical source that manipulates energised atoms to emit coherent photons. Heterostructure lasers are laser diodes where two different materials are used to make the diode junction.

Operating principle

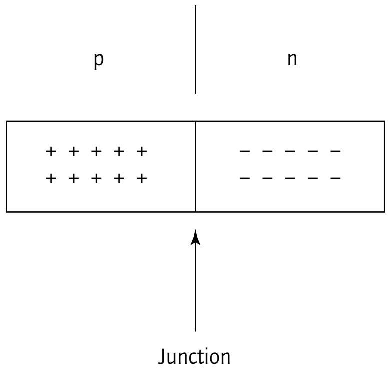
The laser consists of a lasing medium, which should be able to emit light when stimulated. The lasing medium can be a solid, liquid, gas or semiconductor material, which can be pumped to a higher energy state. Normally, the majority of electrons of the lasing medium are in their lowest energy state or ground state. A very small number of electrons are in their higher energy state. Here are the steps to excite electrons to higher energy states:

1. The lasing medium is pumped or excited through external means, usually by applying electric current or intense flashes of light.
2. This pumped energy is absorbed by some electrons of the lasing medium, which are already in higher energy states.
3. The excited electrons transfer energy to the other electrons in the lower energy state, so that they move to a higher energy state.
4. Eventually the number of excited electrons is greater than the number of unexcited electrons. This is a population inversion.
5. Some of the electrons in the higher energy state start to fall back to their ground state, emitting a single photon in a random direction. This is called spontaneous emission.
6. If an optical beam is passed through the medium, it stimulates more electrons to their higher energy state and there is more spontaneous emission. If an emitted photon encounters an excited electron in the right way, the electron drops down to its lower energy state and emits another photon with exactly the same wavelength, phase and direction as the photon it encountered. This process is stimulated emission.
7. If there is more stimulated emission than absorption, the laser will start emitting photons. These photons are monochromatic.

Construction

Doping a very thin layer on the surface of a crystal wafer forms a laser diode. Doping a semiconductor means deliberately putting impurities into the semiconductor material to improve its electrical properties. Doping produces a region containing a higher amount of electrons (n-type) and a region containing a higher amount of electron vacancies, or holes (p-type). The junction between the two regions is called a p–n junction (Figure 2.1).

FIGURE 2.1 A p–n junction



Source: Pira International Ltd

The n-type region contains electrons in a high energy state and the p-type region contains holes in a high energy state. These electrons and holes migrate towards the junction and combine with each other, emitting photons. The emitted photons generate more electrons and holes, and these electrons and holes also combine and emit more photons. If there is more emission than absorption, the diode starts lasing – it emits light coherently. Lasers can be separated into three main categories: continuous wave (CW), pulsed and ultrafast. A heterostructure laser is a solid-state CW laser. Solid-state lasers are lasers that use a crystal as the lasing medium. The atoms of these crystals are rigidly bonded to each other. The crystal produces laser light when light energy is used to excite the electrons. CW lasers produce a continuous and uninterrupted output.

A heterostructure laser generally employs two different types of semiconductors, one having a larger band gap than the other. When they are joined, potential barriers are formed that constrain the electrons and holes. In a double heterostructure laser, a layer of low band gap material is inserted between two or more high band gap materials. The low band gap layer has a higher refractive index than the high band gap layers, and this creates a waveguide effect similar to what happens in an optical fibre.

Applications

Heterostructure lasers have many applications. Here are some of their uses in biology and medicine: spectroscopic sensing, generation of radio frequency or terahertz waves, water purification using ultraviolet light, photodynamic therapy, sources for laser-induced breakdown spectroscopy, confocal microscopy, holography, medical imaging, tissue welding, blood cell analysis or haematology, plastic surgery, general surgery, cancer treatment, dermatology and neurosurgery.

Limitations

Hetrostructure lasers are susceptible to catastrophic optical damage (COD) when run at higher power. Short-wavelength lasers are more vulnerable to COD than long-wavelength lasers.

Light-emitting diodes

Light-emitting diodes (LEDs) are semiconductor materials that convert electrical energy into light energy. An LED produces a negligible amount of heat compared to an incandescent lamp. It can emit narrow-spectrum incoherent light when biased in a forward direction. The light emitted is monochromatic – a single colour. The colour of the emitted light depends on the composition and the condition of the semiconducting material. LEDs can emit light in the infrared (IR), visible or near ultraviolet (NUV) spectrum. Here are some advantages of LEDs:

- LEDs are small
- LEDs possess high radiance but consume less power
- LEDs have a small area of emission
- LEDs are highly reliable and have a very long life
- LEDs can withstand large shocks and vibrations
- LEDs can be modulated (switched off and on) at high speeds.

Operating principle

The most important part of an LED is a semiconductor chip. A diode is the simplest semiconductor device. It is doped with impurities to create a p–n-junction. The p–n-junction allows the electrons to flow easily from the p-type region to the n-type region when a sufficient voltage is applied. This means there is a surplus of electrons and holes near the junction. When these electrons meet the holes they fall to their lower energy level and release energy as photons with a frequency that is characteristic of the semiconductor material. The wavelength of the emitted light, hence its colour, depends on the band gap energy of the materials forming the p–n junction.

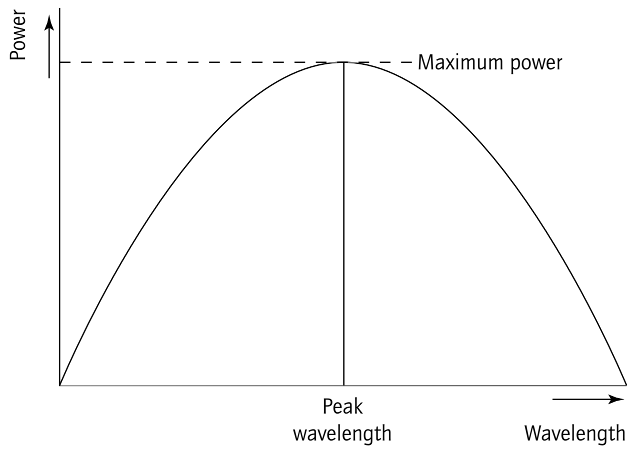
The electric energy is proportional to the voltage needed to cause electrons to flow across the p–n-junction. The shortest-wavelength LEDs exhibit the largest voltage drops. The voltage drop decreases as the wavelength increases. LEDs using gallium aluminium arsenide (GaAlAs) emit shorter wavelengths (red and infrared). LEDs using indium gallium arsenide phosphide (InGaAsP) emit longer wavelengths.

Key characteristics

- *Peak wavelength*: the wavelength at which the LED exhibits maximum power (Figure 2.2).
- *Spectral width*: the amount of the electromagnetic spectrum that an LED covers (Figure 2.3).
- *Forward voltage*: the voltage measured across the LED when it is drawing forward current.
- *Forward current*: the current flowing through the LED for normal operation.
- *Reverse voltage*: the maximum voltage that can be applied in reverse polarity across the LED.
- *Power dissipation*: the maximum power that the LED can dissipate without causing damage. It is the product of forward voltage and forward current.

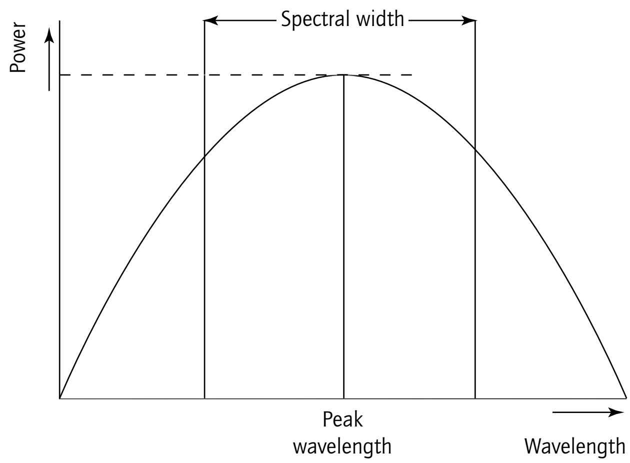
- *Linearity*: the degree to which the optical output is directly proportional to the current.

FIGURE 2.2 Peak wavelength



Source: Pira International Ltd

FIGURE 2.3 Spectral width



Source: Pira International Ltd

Edge emitters and surface emitters

Edge-emitting LEDs (Figure 2.4) are costly and more complicated devices. They give high output power densities and performance speeds. They have a narrow emission spectrum (small spectral width), hence their coherence length is greater, which means the light is more monochromatic; Figure 2.5 shows the emission pattern. Surface-emitting LEDs (Figure 2.6) have a simple structure and are comparatively cheaper. They offer low to

