Emerging Technologies with Emphasis on Phontonics

Report of Working Group 5
Medical Imaging Technology Roadmap

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PREFACE

This report of the Emerging Technologies with Emphasis on Photonics Working Group is one of five that comprise the Medical Imaging Technology Roadmap. This Roadmap is intended to provide a market-driven forecast of technologies needed to improve patient care and enhance the global competitiveness of the Canadian medical imaging sector. The Roadmap is expected to strengthen technology development, diffusion and adaptation, and help to guide public and private sector decision making with respect to product development, investment, human resources and other policy areas.

The 14-person Medical Imaging Technology Roadmap Steering Committee provides overall direction and guidance for this project (see Appendix A for the membership list). Steering Committee members represent companies, researchers, clinicians and government organizations involved with the Canadian medical imaging sector. Industry Canada is the catalyst and facilitator of the roadmapping process. A total of 75 people representing more than 50 organizations have participated in the project, creating opportunities for potential alliances and information sharing.

Visit the project Web site at http://strategis.ic.gc/medimage to view the following reports:

- WG1: Future Needs for Medical Imaging in Health Care (2000);
- WG2: Image Generation and Capture (2001);
- WG3: Transmission and Connectivity (2001);
- WG4: Image Analysis and Visualization (2000); and
- ORTECH: Medical Imaging: Discussion Paper (1999).

These reports are available in French at http://strategis.ic.gc/imagemed.

TABLE OF CONTENTS

INTRODUCTION

SCOPE

The scope of the Emerging Technologies with Emphasis on Photonics Working Group was to identify and describe enabling technologies not covered by the other Working Groups that need to be developed in order to fulfil future patient and market needs.

MEMBERSHIP

The Emerging Technologies with Emphasis on Photonics Working Group comprises clinicians and representatives of the corporate sector and the research community. Appendix B contains the complete membership list.

OUTLINE

This report identifies and describes emerging technologies with particular emphasis on photonics. The principal topics covered are photonics-based *in vivo* clinical technologies and laboratory-based technologies.

The working group used a critical technology template (see appendix C) to bring consistency to its work. Group members agreed that they would omit a heading from the template or add a new one at the end when the need was compelling; however, they would use existing headings to the extent possible.

PREAMBLE

Changes in radiological science may, on the one hand, originate from innovations in the tools used to image disease. The introduction of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) since the 1960s reflect such an imperative. On the other hand, radiology is not undertaken in isolation, and changes in medical practice provide a second imperative that is driving change in the radiological sciences, one that is likely to become dominant in this new century. This will be particularly true as the physical energies used to interrogate the body are nearly all explored.

It has been observed that "medicine will change more in the next twenty years than in the past two thousand."[1] In the light of this, it is relevant to reflect on what factors will drive such change. With the definition of the human genome and advances in molecular medicine, humankind is poised for the first time in history to understand the causes of illness and human disease at a fundamental biomolecular level, rather than at the cell or bedside level But there has to be a reconciliation of molecular medicine and the treatment of people, of the submicroscopic and the macroscopic, which can only be brought about through imaging methods of sufficient sophistication and power.

It is necessary here to pause and consider the short history of the radiological sciences, dating from Röntgen's discovery of X-rays in 1895 - barely more than a century ago. Many of the techniques that have since evolved provide sophisticated means of diagnosing anatomical abnormalities, be they fractures of long bones or stones in the gall bladder. More recently, techniques such as functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy, PET and optical imaging have begun to show how the body works rather than simply how it is constructed. The respective sensitivities of these techniques to metabolic events have been explored.[2] The ability to reconcile molecular medicine with clinical bedside care will only be possible when emphasis comes to be placed on measuring and imaging bulk biochemical and molecular events *in vivo.*[3-5] Recognition of the importance of this is implicit in the plans in the United States to spend US$180 million over the next five years on molecular imaging.[6]

Thus, a new field is emerging, often not represented in the traditional radiological literature, with the risk of a dichotomy developing between radiological practice and imaging research. Examples of emerging techniques in biochemical imaging include the following:

- imaging of gene and transgene expression;[7-10]
- *in vivo* detection of tumour angiogenesis, matched by the growing importance of anti-angiogenesis modulation in the treatment of cancer;[11-12]
- early detection of disease before phenotypic change;[13]
- advances in cancer management beyond imaging tumor burden extent (size) to examine tumor kinetics and gene expression, among other things;[13-15]
- functional imaging to accelerate the process of drug development and evaluation; thus, it is

no coincidence that several drug companies maintain or support imaging centres;[13] and
- fusion imaging, in which anatomical and functional images are overlaid.

At the same time, PET, fMRI, and magnetoencephalography are being used to explore brain metabolism, function and plasticity, thereby leading to insights about human behaviour and neurological and psychiatric disease.[7-16]

While reflecting on the future, it is important to consider the limitations of, and constraints upon, radiological science. At present, the practice of much of radiology, like that of much of medicine, lacks a clearly defined evidentiary basis. This needs to be remedied. Likewise, no amount of technical virtuosity seems likely to overcome, on a global scale, the social determinants of much human disease. Society needs to establish a balance between spending on technology and on the resources used in efforts to eliminate hunger and poverty. Indeed, the International Society of Radiology has concluded that two thirds of the world s population does not have access to any but the most rudimentary radiological services. These are all challenges enough for the foreseeable future.

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OVERVIEW

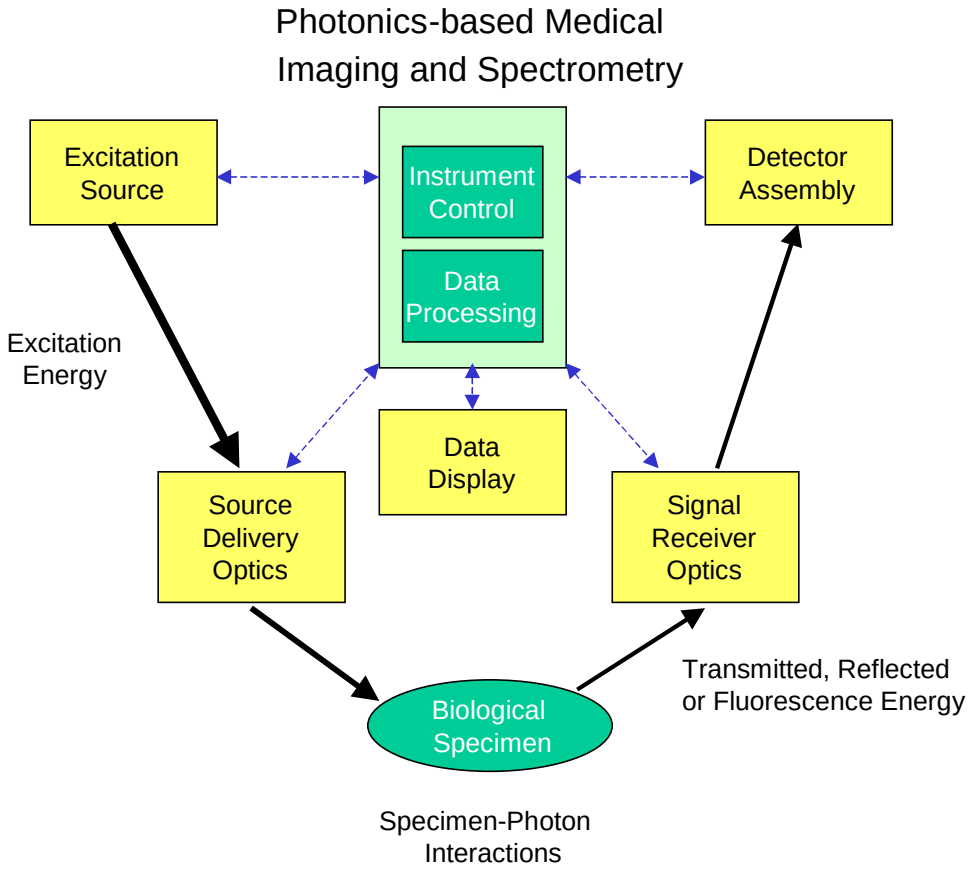
Medical imaging was divided traditionally between two major streams: anatomical imaging (usually within the realm of the radiologist) and microscopic imaging (often the role of clinical pathologists). While the family physician or general surgeon relied heavily on clinical observation for diagnosis, much of the medical imaging was left to other specialists. There were many reasons for these divisions aside from the obvious specialist training requirements. Radiology involved high capital costs for major equipment installations, along with high operating costs for maintenance and service. Centralized facilities and dedicated staff made economic sense. Microscopic imaging, in turn, often involved extensive sample preparation procedures and did not lend itself to real-time examinations. Consequently, medical imaging for the practicing clinician was often limited to endoscopic examinations - invasive procedures that would augment conventional clinical observations. The challenge, then, is to identify affordable, easy-to-use imaging methods that could provide useful diagnostic information at a doctor's office or a patient's bedside.

Table 1 introduces the basic characteristics and differences between the traditional methods and suggests some of the needs and benefits of emerging technologies.

	Traditional Medical Imaging		**Emerging Technologies**
Imaging Mode	Anatomical imaging (performed by radiologists)	Microscopic imaging (performed by clinical pathologists)	Spectroscopic imaging (performed by clinicians)
Features of interest	Anatomical changes	Cellular or molecular changes	Molecular changes of macroscopic areas
Image display	Most images displayed as 2-D slices or 3-D reconstructions with a possibility for time or phase-resolved additional dimension	Usually a 2-D image with 3-D image reconstruction based upon serial sections from microtome tissue samples	Most images displayed as 2-D or 3-D reconstructions of spectral (chemical) concentration gradients
Spatial resolution	Macroscopic areas of interest often greater than 1.0 mm in size	Microscopic areas of interest usually less than 1.0 mm in size	Macroscopic or microscopic depending upon technology applied
Sampling mode	Non-invasive, usually involves *in vivo* measurements of the patient	Invasive, often based upon tissue biopsy specimens	Often involves non-invasive, *in vivo* measurements
Period from collection of image until medical diagnosis	Often hours or days	Hours or days	Real time to minutes
Typical imaging modalities	X ray, ultrasound, CT or MRI	Electron or light microscopic methods	Refer to subsequent tables

Spectroscopic imaging is illustrated in its most general sense in Figure 1. Variations in the type of spectroscopic imaging depend on the type of excitation source, the physics of tissue-source interaction, and the subsequent method of detection.

Figure 1



Choices in the type of biological specimen under investigation along with the subsequent contrast mechanism give rise to a number of laboratory imaging methods, as set out in the chart below:

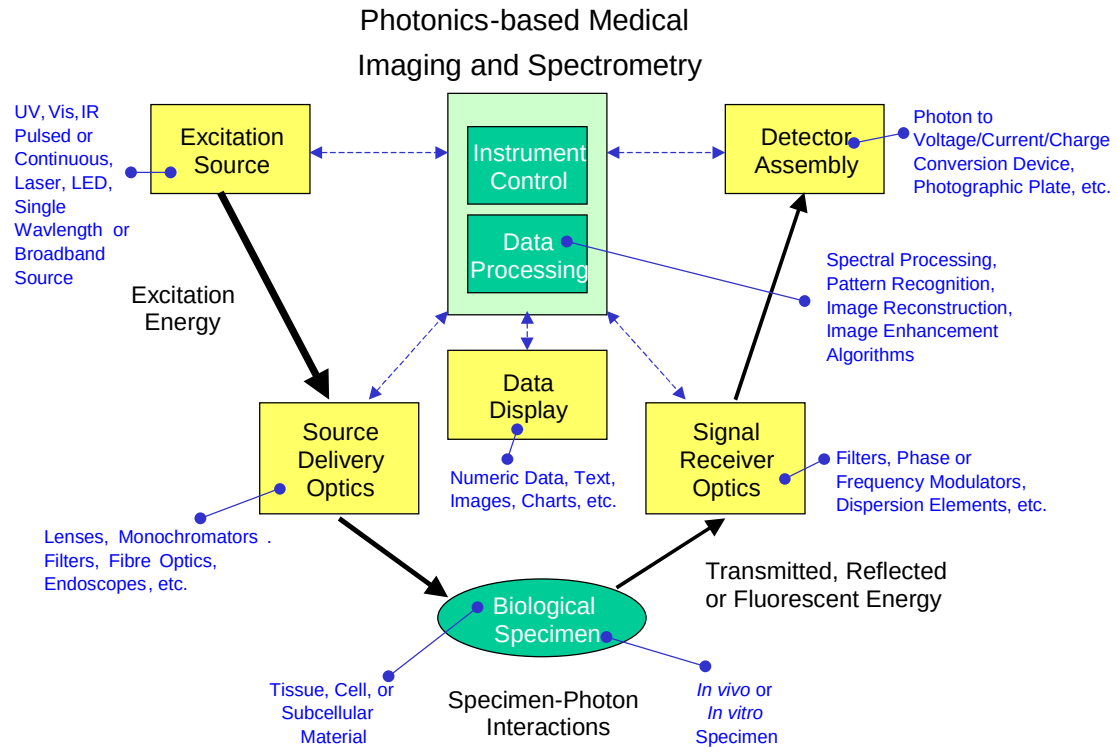
		Fluorescence					
Technology	Reflection and transmission	Intensity	n-Photon	Lifetime	Raman	IR and NIR	Interference
Microscopy	++	++	+	+	+	++	+
Macroscopy	+	+				+	
Genetic microarray		++					
Spectral mapping	+	+				+	+

Microendoscopy	+	+					
Assay array scanning	++	++					

+ some demonstration to date
++ strong indication

Figure 2 shows some of the options for the components of spectroscopic imaging when developing a new imaging device.

Figure 2



Many of the advances in new medical imaging methods are based on enabling photonic technologies for the spectrometer's optical elements such as those listed below.

Sources

- Ultrafast pulsed lasers provide high power excitations for time-resolved spectroscopic measurement.
- Rapidly tunable sources can facilitate spectral fluorescence.
- Multiple discrete sources (and detectors) can facilitate physiological measurements in the visible through infrared regions of the spectrum.

Detectors

- High spatial and/or spectral resolution.
- High sensitivity.
- High dynamic range based on charge-coupled device arrays.

Other optical and mechanical components

- Compact high-quality dispersive elements (gratings and prisms).
- Improved fibre-optic probe design and construction (for source delivery and/or emitted signal collection).
- Micromechanical components for routing optical paths

At the same time, optically labelled tracers are being developed to facilitate imaging of pharmacological and/or functional pathways.

Reduced hardware costs for embedded computers or computer workstations have meant faster mathematical processing, inexpensive memory (RAM) and abundant data storage for the massive data arrays associated with digital imaging. This has led to better "chemometric" software that manifests itself in faster, better algorithms for the collection and manipulation of images, for feature recognition and extraction, image compression and correlation of spectral images with physiological phenomena. (For more information, see past issues of the *Journal of Chemometrics* or *Chemometrics and Intelligent Laboratory Systems*.)

In the critical technology templates that follow, the spectroscopic imaging methods are classified on the basis of either photonics-based *in vivo* clinical techniques or laboratory-based technologies. The references provided within these sections can be used to explore this emerging field in greater detail.

PHOTONICS-BASED *IN VIVO* CLINICAL TECHNOLOGIES

1. GOALS AND OPPORTUNITIES

There is an evolving capability for novel non-invasive or minimally invasive clinical imaging methods based on optical (photonic) technologies. The clinical information arises from changes in the characteristics of light (ultraviolet, visible or infrared) when it interacts with tissue. While a number of optical imaging techniques such as endoscopy and ophthalmoscopy are well established, new photonic technologies and increased understanding of light-tissue interactions have recently expanded the opportunities for *in vivo* optical imaging considerably. Many of the new techniques are still at the developmental stage, although penetration into clinical practice has started to occur and is expected to accelerate. The potential of this field is still largely unexplored, as evidenced by the recent emergence of methods and instruments based on radically new approaches to optical interrogation of tissue (e.g. optical coherence tomography, photon migration imaging and elastic scattering imaging).

The potential roles of optical imaging include diagnosis (e.g. detection of disease, particularly early detection), staging, disease localization for therapeutic guidance, monitoring of therapeutic response, and monitoring of metabolic and physiological functions.

Optical imaging may be combined with other imaging modalities, such as radiological imaging, since there is minimal “interference” among the technologies. Components such as optical fibres are compatible with, for example, the magnetic field environment of magnetic resonance imaging.

Optical probing of tissues may be carried out as a non-imaging method, using fibre-optic point spectroscopy. In this case, the instrumentation is usually simpler and cheaper, and the spectral information content can be very high, since wavelength scanning can be performed. These methods may be either stand-alone, as in the case of non-invasive optical monitoring of glucose and other analytes, or may be combined with optical imaging, such as when complete spectra are measured at discrete points in tissue under optical image guidance.

2. DESCRIPTION

Optical imaging of tissue falls into three main categories: surface, subsurface and volume imaging. In the first two categories, accessible body surfaces are imaged. With fibre-optic light delivery and/or collection, this includes the surfaces of internal hollow organs (the oral cavity, bronchus, gastrointestinal tract, bladder and female reproductive tract) and of surgically exposed tissues. The optical transparency of the eye gives an obvious “window” to posterior structures such as the retina. Volume imaging of the breast or brain, for example, may be achieved by methods that are somewhat analogous to X-ray tomography, using multiple (fibre-optic coupled) light sources and detectors placed around the head, breast or limbs.

Optical imaging depends on measuring changes to one or more properties of light as a result of its interaction with tissues. The following are the main changes:

- **spectral**: the spectrum of detected light is altered by absorption, with or without subsequent emission of fluorescence or by inelastic (Raman) scattering;
- **spatial**: the distribution of light is altered by local absorption and/or scattering; and
- **temporal**: the propagation time of light through tissue is altered by reflection, absorption and/or elastic scattering, or by delayed emission of fluorescence.

In addition, properties such as the polarization and phase of light may be exploited in the future. The established and evolving optical modalities include those described below.

Endoscopy: White-light endoscopy is a well-established and widely used modality. There are two main types of endoscopes: fibrescopes that use a fibre-optic bundle to transfer the image of an internal tissue surface to an external detector, and videoscopes in which the detector array is at the distal end of the endoscope and the signal is transferred electronically. The image is a white-light display of the tissue surface. Evolving extensions of this technology include magnification chromoendoscopy using high-magnification optics and spray staining with vital dyes, and fluorescence endoscopy based on either the intrinsic fluorescence of tissues (autofluorescence) or administered fluorescent dyes. Optical coherence tomography devices and confocal microscopy also can be used endoscopically (see below). Spectroscopic fibre-optic point probes placed through the instrument channel of the endoscope may be used as an adjuvant to standard white-light endoscopy.

Opthalmoscopy: There are many established optical devices for imaging both the anterior and posterior parts of the eye, based on direct viewing by the operator or photographic, digital or video recording. This may include the use of fluorescent dyes, such as in fluorescein angiography to image the retinal blood vessels. More recent advances include laser doppler retinal blood-flow instruments and confocal laser scanning ophthalmoscopy (CLSO). In CLSO, a laser beam is scanned in a raster fashion and the optics are arranged with a single-element photodetector to build up an image of thin slices of very high resolution within the retina. Optical coherence tomography is also used to make high subsurface cross-sectional scans of the anterior or posterior structures. CLSO instruments are commercially available and are used for specialized examinations.

Fluorescence imaging: This is based on imaging either the tissue autofluorescence or that of administered dyes (fluorophores). The technology may be relatively simple in the case of dye-enhanced fluorescence imaging of skin, the oral cavity or surgical fields, or may be more complex in the case of fluorescence endoscopy. This is an evolving technology, both in terms of the devices and the fluorophores. A laser or high-powered filtered lamp source is required to

excite the fluorescence and high-sensitivity array detectors, such as intensified charge-coupled devices, to capture the image in one or more wavelength channels. An autofluorescence-based endoscopy system for use in the lung has become commercially available within the last few years. Fluorescence techniques may involve both devices and "drugs," in the form of administered fluorescent dyes.

***In Vivo* Confocal Microscopy**: This is an evolving technology that is the *in vivo* equivalent of confocal laser scanning microscopy applied to accessible tissue surfaces. This can operate either by reflected light or fluorescence. Very high subsurface resolution can be achieved in planes parallel to the tissue surface. Large-area scanning (macroscopy), up to millimetres or centimetres across, is under development, using special laser-scan lenses. Prototype endoscopic confocal instruments have been demonstrated.

Optical Coherence Tomography (OCT): OCT was first introduced in the early 1990s. It is the optical analogue of high-frequency ultrasound imaging, since it involves depth profiling of light backscattered from tissue microstructures. Since the speed of light is so high, measuring direct time-of-flight is not feasible for achieving the required depth resolution (~10 μm). Instead, an interferometric technique is employed, using a short-coherence-length light source (superluminescence diode or femtosecond [fs] laser). Two-dimensional images are generated, usually by lateral scanning, as in B-mode ultrasound. Unlike ultrasound, this does not require contact or water coupling to the tissue and can also be used for hard tissues such as bone and teeth. With fibre-optic light delivery and collection, endoscopic OCT is possible, although it is still at the experimental stage. Very high resolution (~μm) has been demonstrated under special conditions. An ophthalmic OCT system is commercially available.

Optical Tomography and Volume Mapping: Achieving the optical analogue of X-ray, PET or MRI imaging is difficult because of the limited penetration of light in tissue and its very high scattering. However, in the near-infrared spectral region (~700-1200 nm) there is an "optical window" that allows imaging through many centimetres of tissue. For example, transmission spectroscopy (non-imaging) is in routine clinical use for neonatal brain oxygen monitoring. Initial attempts to exploit this for breast cancer detection (diaphanography) based on imaging continuous wave light transmission yielded insufficient tissue contrast. In the past decade, imaging exploiting the photon time-of-flight in tissue (~0.2 mm per picosecond) has become possible. This is done either with a picosecond laser source and directly timing the light with an ultrafast detector (time-correlated photomultiplier tube or streak camera), or by imposing a high-frequency (~100 MHz) modulation on a laser source and using phase-locked detection of the phase shift and intensity demodulation of the diffusely transmitted or reflected light. Non-invasive imaging of the female breast and below the surface of the brain have been demonstrated, and there are numerous experimental systems currently undergoing clinical trials for various applications. In addition to mapping of endogenous tissue chromophores (particularly hemoglobin and oxyhemoglobin), absorbing or fluorescent contrast agents are under

development. For the latter, the fluorescence lifetime provides the contrast mechanism, as it adds to the photon time delay due to migration through the tissue.

Elastic Scattering: It has recently been demonstrated that, by cross-polarization suppression or numerical subtraction of the diffusely reflected (multiply scattered) light from tissue, the fine spectral structure from the superficial layers can be measured. This is due to light that has undergone few elastic scatters and so carries information on the size distribution of scattering "particles," primarily cell nuclei. This method has been demonstrated in point-spectroscopy mode for mucosal structures, such as those in the gastrointestinal tract, to detect pre-malignant changes. Imaging instruments are at an early stage of development. Very high spectral resolution (~nm) is required across a wide visible wavelength range.

The enabling technologies required for these optical imaging systems include some or all of the following:

- lasers and other light sources with specific spectral (wavelength) features;
- optical fibres and fibre bundles to deliver the excitation light to the tissue and to collect the light emerging from the tissue;
- high-sensitivity point or array light detectors with appropriate spectral and, in some cases, temporal response;
- fast electronics to convert and capture the detector output; and
- high-speed computers to analyze the optical images.

3. IMPORTANCE

The fundamental advantage of *in vivo* optical imaging is that it can directly provide "molecular" information, because the photon energies are in the range of molecular energy levels. In addition, since the wavelength involved is small, light is sensitive to the tissue microstructure. Hence, optical imaging fits well with advances in molecular medicine and is likely to play a major role as new molecularly based diagnostic and therapeutic techniques are implemented. Optical imaging can also be performed with little or no hazard to the patient.

The major challenge is to extract the information from the response, given the limited penetration of light in tissue and the very high degree of scattering that occurs. Advances in light sources, and in detectors in particular, combined with optical fibres, are generating new paradigms for overcoming these limitations.

4. ALTERNATIVES

Optical imaging is largely complementary to other established and evolving imaging modalities. For high-resolution surface and subsurface imaging of skin, hollow organs and the eye, it is

unlikely to be surpassed generically. There may, however, be specific niche applications for which other methods are superior or comparable - high-frequency ultrasound imaging versus optical coherence tomography, for example. Light-based endoscopy will remain significantly cheaper than "virtual" endoscopy using, for example, high-resolution volume MRI or CT. Optical volume imaging of tissues will not achieve the spatial resolution of techniques such as MRI or CT but, using absorption- or fluorescence-based contrast agents, should become competitive in performance with radionuclide imaging for some applications.

5. MATURITY AND RISK

While some of these clinical technologies are very mature (e.g. white-light endoscopy), many are recent inventions and are still at the developmental stage or are just entering clinical practice. There is an explosive evolution of photonic technologies generally, driven primarily by the needs of fibre-optic-based telecommunications and other applications, such as displays. As a result, the enabling technologies are advancing daily, so that there is a high risk of obsolescence, as well as opportunities for completely novel techniques. For example, OCT is based on short-coherence light sources (superluminescence diodes or fs lasers) and fibre-fibre couplers that have only become available in the last decade and, in the case of fs lasers, represent a technology that is still immature. Similarly, autofluorescence endoscopy requires very-high-sensitivity charge-coupled device array detectors, the performance and cost of which are still changing significantly.

6. AVAILABILITY

There are a number of long-established international endoscopy and ophthalmoscopy companies, whose range of products is expanding to include the novel optical technologies described above. In addition, there is a rapidly expanding number of small companies focussing on either specific market sectors and/or specific technologies. The modalities for which devices are currently available commercially are indicated in the descriptions above. The availability of these technologies will for some time continue to be heavily dependent on the development and commercialization of the component-enabling technologies.

7. BREADTH OF APPLICATION

These optical technologies have a wide variety of clinical applications. They may be used for many medical conditions and at several points along the detection, diagnosis, staging, treatment monitoring and follow-up path.

Since the enabling optical technologies are driven largely by high-volume consumer markets such as telecommunications, optical imaging should show an increasing cost advantage for many applications. Compactness, low weight and robustness are other intrinsic advantages of optical technology. Hence, these instruments should become more widely distributed, to point of care, for example, than imaging modalities based on large and expensive technologies. For the same

reasons, optical imaging is likely to be dominated by many application-specific devices, rather than by generic, all-purpose systems.

8. REFERENCES

The following scientific publications specifically cover biomedical optics:

Journal of Biomedical Optics: http://www.spie.org
SPIE Progress in Biomedical Optics (conference proceedings): http://www.spie.org

In addition, the following specialist optical science and technology journals commonly discuss biomedical optics:

Applied Optics: http://ww.osa.org
Optical Engineering: http://www.spie.org
Applied Spectroscopy: http://www.s-a-s.org

The following specialized clinical journals focus on biophotonics applications:

Lasers in Surgery and Medicine: http://www.interscience.wiley.com
Lasers in Medical Science: http:/www.hbuk.co.uk
Journal of Clinical Laser Medicine & Surgery: http://www.liebertpub.com

The following trade journals cover photonics, including biomedical applications:

Biophotonics International: http://www.biophotonics-mag.com
Photonics Spectra: http://www.photonicsspectra.com
Laser Focus World: http://www.laser-focus-world.com

9. CONTACTS

Industrial Contacts
The above trade journals and their Web sites are an excellent point of entry for industry contacts.

Academic and Clinical Contacts
The members of specialized medical laser societies are useful contacts for clinicians (and scientists) using biophotonic techniques:

American Society for Laser Surgery and Medicine: http://www.aslms.org
European Medical Laser Association: http://www.emla.net

In addition, the Society of Photo-Optical Instrumentation Engineers (SPIE: http://www.spie.org) and the Optical Society of America (http://www.osa.org) run many general and topical conferences on biomedical optics.

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LABORATORY-BASED TECHNOLOGIES

1. GOALS AND OPPORTUNITIES

There is a need to provide and extend for the analysis of patient specimens laboratory instrumentation that utilizes increased molecular information content. The opportunity and ability to do so has been made possible by the development of molecular probes of high specificity, the ability to extract and amplify specific genes from biological specimens, and the development of high-sensitivity and rapid optical imaging instrumentation. The first two enabling technologies are the result of advances in modern molecular biology and biotechnology, while the associated instrumentation results from advances in photonics technologies.

These technologies have the potential to improve the accuracy of pathological diagnosis based on tissue and cell imaging. The development of genetic microarrays enables rapid, low-cost genetic fingerprinting of individual patients, pathologies and pathogens.

2. DESCRIPTION

There are two main categories of technology - optical microscopies and genetic microarray imaging.

2.1 Optical microscopy

This is an old, established technology. However new enabling technologies - lasers, high-sensitivity digital light detectors and detector arrays, and high-efficiency spectral scanning and computing - have significantly extended both the classes and capabilities of microscopes now available. Examples include the following:

- confocal laser scanning microscopy, which provides very high resolution 3-D imaging in reflection, transmission and fluorescence modes;
- confocal laser scanning macroscopy, which extends the capabilities to large-area specimens, including tissue imaging and microarrays (see below);
- Raman microscopy, which provides images based on biochemical characteristics of the sample;
- infrared microscopy, which is complementary to Raman microscopy;
- hyperspectral microscopy, in which a “data cube” of images is produced at many separate optical wavelengths; and
- digital microscopes, which use digital array detectors along with conventional optics.

These instrument capabilities are complemented by the availability of an increasing range of optical contrast agents of high diagnostic specificity.

A Canadian company, Biomedical Photometrics Inc., holds several patents in confocal macroscopy and spectrally resolved confocal microscopy.

2.2 Genetic microarrays

These are a recent development in which DNA is extracted from a specimen of interest and exposed to a series of known DNA probes arranged as a 2-D array. By labelling the unknown material with, for example, a fluorescent tag, an optically readable array is generated by its selective binding to the array template. This allows the expression level of individual gene sequences to be determined for subsequent bioinformatics analysis (i.e. for matching with genetic sequence libraries). The imaging instrumentation may be of several types, including laser scanning and charge-coupled device array imaging.

3. IMPORTANCE

The new optical microscopies provide greatly enhanced spatial and molecular information on the tissue or cell specimen being imaged. For example, tissues may be stained with several molecular markers at the same time, each intended to image different targeted pathological features, so that the spatial relationships of these features can be determined. This procedure can markedly enhance the diagnostic information obtainable. Similar multispectral information may be obtained at the cytogenetic level to increase the information content of karyotyping. In addition, some of these microscopies, confocal laser scanning instruments, for example, may be used to image *in vivo*, non-invasively and at high resolution.

Genetic microarrays provide a technology for massively parallel measurements of the content and expression of DNA in a specimen. Although currently used almost entirely in research, this technology is expected to move into clinical diagnostics, including detecting microorganisms and disease-related genetic transformations (e.g. cancer), and monitoring the effect of treatment and disease progression. The technology will revolutionize drug discovery by monitoring the expression of genes shortly after a drug is administered, instead of waiting to see the effect of the drug on pathology or symptoms. Microarrays are analyzed using a high-resolution image of the array, usually formed using multispectral fluorescence. Genetic microarrays are expected to be a major component of a huge diagnostic and testing industry based on genomics, one that is currently in a very early stage of development.

4. ALTERNATIVES

For some applications, it may be possible to perform *in situ* high-resolution imaging without having to take a tissue sample. This includes both optical technologies such as optical coherence tomography, and high-resolution radiological technologies such as high-field MRI or high-frequency ultrasound.

For some applications, genetic microarrays are replacing a number of established technologies, such as gel electrophoresis and antibody-based assays.

5. MATURITY AND RISK

Optical microscopy is based on well-established optical principles and elements. However, critical technologies needed to enhance the capabilities of the newer forms of microscopy are still emerging,including the following:

- ultrafast pulsed lasers for multiphoton microscopy;
- compact light sources with a wide range of available wavelengths at lower cost;
- computer-designed linear and non-linear optical elements;
- detectors that feature high-sensitivity focal plane arrays and fast response time;
- fast electronics for data capture; and
- powerful image analysis algorithms and associated software.

To a large extent, the development of these technologies is being driven by fields other than medical imaging, particularly telecommunications and military applications.

Genetic microarrays are embryonic technology, appearing only in the last five years and experiencing rapid development and change. There are several alternative solutions that are actively being pursued, such as arrays based on robotic spotting on a glass substrate and arrays produced by microlithography. The corresponding optical “readers” also vary, with both laser canning and detector-array technologies as alternatives. There are also competing labelling technologies, including fluorescence and chemiluminescence, as well as non-optical solutions such as electrochemical detection.

6. AVAILABILITY

There are a number of long-established international microscope companies whose range of products is expanding to include the novel optical microscope technologies described above. In addition, there is a multiplicity of small companies focussing on either specific market sectors and/or on specific technologies. In the genetic microarray marketplace, there are a number of companies that are growing very rapidly, and new companies are appearing almost daily. It is not clear who the winners will be, or indeed how this field will be divided among the various companies. In addition, this technology is creating its own market, the ultimate size and extent of which is unknown, but which has the potential to be extremely large.

7. BREADTH OF APPLICATION

Microscopy and genetic microarray technologies are applicable to all diseases and all organ systems. They are relevant not only to diseases with a specific genetic basis but also can be applied to monitoring response to therapies.

8. REFERENCES

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9. CONTACTS

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SUMMARY STATEMENT

The future of photonics-based medical imaging and diagnostics is particularly difficult to predict. Many of the techniques in this field were developed relatively recently, and the enabling technologies are progressing at an explosive rate, due to powerful economic drivers such as telecommunications.

Laboratory-based imaging of tissues, cells and genetic materials *ex vivo* is penetrating biomedical science more rapidly than *in vivo* techniques are being adopted in clinical medicine. In part, this is due to the normal time delay involved in proving safety and efficacy of new clinical procedures. However, the rate of adoption should accelerate as techniques and instruments are approved, since this will establish a growing body of precedent technology.

It remains to be seen how these photonic imaging methods will displace, complement, or supplement established radiological imaging modalities. The low cost of the former will certainly be an important factor, as will the fact that photonic imaging methods offer the opportunity to probe and reveal new signals, particularly molecular signals, thus opening new domains for clinical imaging. This will involve not only hardware and software but also consumables, such as optical fibre probes, and optical tracers, such as fluorescently labelled targeting agents. As a result, there are opportunities for new commercial ventures, growing either through start-up companies specializing in optical systems or as new products within established medical imaging companies.

APPENDIX A

Medical Imaging Technology Roadmap Steering Committee

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APPENDIX B

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APPENDIX C

Critical Technology Template

1. **TECHNOLOGY WORKING GROUP**
WG name.

2. **CRITICAL TECHNOLOGY**
Technology name.

3. **RANKING**
Rank of this technology among the technologies investigated by the WG (i.e. 3/5).

4. **GOALS**
The performance goals of the technology:

- *are driven by customer requirements;*
- *should be defined in quantitative and qualitative terms (without disclosing proprietary information);*
- *include economic (cost, etc.), time (cycle time improvements, etc.), and physical property considerations.*

5. **DESCRIPTION**
Brief technical description of the technology.

6. **IMPORTANCE**
Why is the technology critical (e.g. regulatory requirements, customer demands, financial and other competitiveness issues)? When is the technology required? To whom is the technology critical? What happens if the technology is not available or implemented?.

7. **CLINICAL REQUIREMENTS**
What clinical requirements must the technology satisfy?

8. **ALTERNATIVES**
Other technologies, non-technological solutions, product substitution, etc.

Each WG should be familiar with the technologies under investigation by the other WGs, so that linkages can be made among alternative or competing technologies.

9. **MATURITY AND RISK**
What can the technology do today?
What incremental capabilities are required to produce the products required for the 2001 through 2005 time period?
What risks are associated in obtaining these incremental capabilities?

10. **AVAILABILITY**
Where is the technology currently available? From whom and how? What are the cost considerations?

11. **BREADTH OF APPLICATION**
How broadly can the technology be applied: which areas of the medical imaging industry, what other industry sectors?

12. **COLLABORATORS**
Potential sources of help in developing or acquiring, and implementing the technology: Examples: NRC, primes working with suppliers, etc.

13. **COST-BENEFIT ANALYSIS**
Costs could include technology development or acquisition, and implementation. Benefits are based on an estimate of market usage of the enabling technology.

14. **REFERENCES**
List of pertinent documents.

15. **CONTACTS**
Resource persons for further information.