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Perspective: Robotics and Smart Instruments for Translating Endomicroscopy for *In situ, In vivo* Applications

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Optical microscopy, with development dating back to the pioneers of experimental optics in the sixteenth century, is a well-established technique in the life sciences community. One of its key contributions to modern medicine is through histopathology, where biopsied tissue is sectioned, stained and studied under the microscope in order to aid diagnosis of a wide range of diseases.

While histology is undoubtedly a vital diagnostic tool, the process of obtaining the diagnosis is certainly not 'real-time'. There are many circumstances in which a more immediate and less invasive analysis would be beneficial. One example is in cancer surgery, where accurate delineation of tumour margins is needed in order to guide tissue excision. In this case, post-operative histology is clearly not ideal - one would prefer to obtain the micrographs immediately and so reduce the potential need for re-excision. Even in purely diagnostic procedures it may be advantageous to obtain continuous, real-time microscopic images at any location, rather than relying solely on a retrospective analysis of a finite number of discrete biopsy samples.

Despite these apparent clinical benefits, only relatively recently has serious attention been paid to the idea of conducting *in vivo* microscopy, most likely due to the array of technical challenges that must be overcome. For the examination of the skin, or other easily accessible organs such as the mouth or eye, the degree of miniaturisation needed is not particularly troublesome. The main requirement is that the device is sufficiently portable and manoeuvrable. But for imaging internal structures such as the gastro-intestinal tract, the microscope must be miniaturised much further, to a point where it is comparable to a conventional endoscope. Ideally, the microscope probe would be small enough to pass through the working channel of an endoscope, limiting its diameter to a few millimetres.

A further complication is that in order to produce images of an acceptable quality from thick tissue, the microscope must operate in the confocal regime. This allows blurred light from out-of-focus layers of the tissue to be rejected, leaving a well-resolved optical section; in conventional histology, the same effect is obtained by physical slicing of the tissue. Unfortunately, a confocal microscope is considerably more complex to miniaturise, not least because it requires that images are built up via point-by-point scanning. This *in vivo* optical scanning can be done in one of two ways. The first involves the complete miniaturisation of a scanning head using, for example, MEMS scanning mirrors or some form of piezo-electric cantilever. A second option is to use a fibre imaging bundle to transfer a scanning pattern from the proximal to the distal tip of the probe, allowing conventional scanning mirrors to be used. The latter approach offers the potential for high speed imaging using comparatively low-cost, disposable probes, and is the method employed, for example,

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by the Cellvizio endomicroscope (Mauna Kea Technologies). However, such fibre bundle devices are difficult to operate in reflectance mode and so require the application of fluorescent labels to the tissue, introducing further regulatory and safety barriers to clinical translation.

Regardless of the scanning method employed, a significant limitation of endomicroscopy is that the field of view is generally constrained to be less than 1 mm in diameter. Although a small field of view is an unavoidable feature of microscopic imaging, it makes operation of these devices somewhat troublesome, as it is necessary to hold the probe in position with an accuracy on the order of tens of microns. The real-time micrograph bears little apparent resemblance to conventional endoscopy and so is, in itself, insufficient for navigation. The large jump in scale between microscopic and macroscopic views makes synthesis of these information channels difficult, either on the display screen or in the mind of the operator.

Mosaicking has been proposed as a partial solution to these problems. By stitching together a number of images, either in real-time or through post-processing, a larger field of view is obtained. But mosaicking techniques relying solely on the information contained within the microscope image are easily corrupted by rapid movements of the probe and may struggle to cope with tissue motion and deformation. Clinical evaluations of endomicroscopy do not appear to suggest that mosaicking is currently a reliable tool, and there is clearly scope for further improvements in this area.

Transversal positioning, however, is not the only difficulty. Since the depth of focus is on the order of a few microns, there is also a requirement to maintain a constant working distance between the probe and the tissue. To simplify this, probes are usually designed so that the correct working distance is achieved when the tip of the probe is in contact with the tissue. Nevertheless, it is still necessary to maintain an approximately constant pressure: if the pressure is increased, tissue deformation occurs, whilst if it is decreased and contact is lost then the image may disappear entirely. In principle this problem can be solved using a closed-loop axial positioning system combined with a force sensor, although this has not yet been demonstrated for a flexible endomicroscope system *in vivo*. Optical range-finding using, for example, low coherence interferometry may provide a viable alternative to incorporating a distal force sensor.

Similar requirements for dexterity and accurate positioning in minimally invasive surgery led to the development of robotic surgical systems. It is little surprise that attention has been turned to the possibility of using similar technologies with *in vivo* microscopy. Indeed, two distinct strands of development have emerged. The first is the inclusion of microscopic imaging as an ‘add-on’ tool to existing robotic surgery platforms - a task that is likely to fall mainly to the manufacturers of those platforms. Of more interest to the general research community is the potential for robotics and smart instruments to assist with endomicroscopy in a way that is of lower cost and applicable to a wider range of diagnostic and interventional procedures.

One of the more obvious applications is to use ‘steady-hand’ systems to assist with obtaining images with reduced motion blur and increased positional stability. As well as improving the appearance of video sequences and allowing small features to be more readily identified, this stability could also allow for an increase in the frame integration time, or perhaps sequential acquisition using different wavelength bands.

The ability to scan over a significant area with consistent instrument-tissue contact and force control is another potential opportunity. Precise control over the position of the probe would simplify integration with the macroscopic endoscopic view, raising the possibility of a ‘smart’ instrument that integrates multiple imaging modalities together with repeatable and stable positioning. In this case it is clear that the challenge is not one simply of mechatronics, but of

combining mechatronics with optics and computer vision techniques to generate a single, unified imaging platform.

While these possibilities are certainly attractive, the integration of robotic technologies into to what is otherwise a relatively simple optical probe has significant implications both in terms of the cost and the complexity of imaging procedures. Clear clinical benefits will need to be identified in order to justify these additional burdens if robotic assisted imaging is to find truly mainstream applications. The challenge will be to ensure that technological developments are targeted at solving the real practical problems faced during *in vivo* microscopy. In this regard, the CMIG community is ideally positioned to tackle these challenges.