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EDITORIAL

Navigating beyond the 6th dimension: a challenge in the era of multi-parametric molecular imaging

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This is an exciting time for molecular imaging as we are witnessing a convergence and combination of various imaging modalities driven by an unprecedented multidisciplinary collaboration between scientists. A consequence of this growth is a paradigm shift in health care delivery that is now revolutionizing clinical practice. Within the spectrum of macroscopic medical imaging, sensitivity ranges from the detection of millimolar to submillimolar concentrations of contrast media with computed tomography (CT) and magnetic resonance imaging (MRI), respectively, to picomolar concentrations in positron emission tomography (PET): a 10^8–10^9 difference [1]. Despite the remarkable progress and outstanding scientific innovations achieved and the much worthwhile successful research carried out both in academic and corporate settings, there are still plenty of open research questions that offer ample opportunities for the new generation of molecular imaging scientists [2]. There is no shortage of challenges and opportunities nowadays for developing novel molecular imaging probes and technologies and for establishing their role through innovative applications in clinical and research settings. The only limit is the imagination and creativity of the investigators and the challenge is the ability of opinion leaders to attract the best scientists into this discipline.

It is the responsibility of scientists involved in today's molecular imaging research enterprise to debate about essential issues related to the relevance of novel technologies with the aim of focusing the limited resources available for the best benefit of our community. In this respect, the issue of whether the development of molecular imaging technologies should be driven by fundamental molecular biology or design engineering was raised recently [3] and is still a matter of debate [4]. What our community has learned and accepted as a fact dictated by the unremitting modernization of our profession is that medical physicists must either learn to include the biology of molecular imaging in their research programmes or prepare to become irrelevant to the future of this discipline [3]. Among many other issues, the important role of multimodality imaging is growing steadily and gaining acceptance both in the clinical setting [5] and experimental preclinical studies [6]. As diagnostic techniques transition from the systems to the molecular level, the role of multimodality imaging becomes ever more important.

Multimodality imaging with high spatial resolution and good sensitivity, allowing one to combine modalities and record either sequentially or simultaneously complementary information gathered from SPECT, PET, CT, MRI, ultrasound (US), optical imaging (OI), fluorescence and bioluminescence imaging, offers many advantages in certain research experiments. MRI, US and CT are favourably suited to assess perfusion, relative blood volume and vessel permeability and as such functional data derived from these imaging modalities may be combined with molecular information provided by SPECT and PET. Optical imaging is a very sensitive biological imaging technique to examine gene expression due to the very low background light levels [7]. Its capability to probe very small signals allows visualization of early expression and signal changes compared to PET imaging. However, PET is a quantitative modality that can provide measurements of metabolic function.

While virtually all commercially available clinical and hybrid imaging systems have been configured in the form of SPECT/CT [8] or PET/CT [9], combined PET/MR scanners [10, 11] allowing for simultaneous (as opposed to sequential

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scanning for the above-mentioned systems) clinical whole-body imaging following the successful design of a brain dedicated prototype [12] are being designed taking advantage of significant financial support from European and North American funding agencies targeting these particular technologies. In this respect, there are clear indications that several manufacturers are focusing their efforts on the development of various designs of MR-compatible whole-body PET systems. In parallel, potential applications of this technology are being explored in the scientific literature [13–16]. These technologies will allow exploitation of the full potential of anatomical MRI in terms of high soft tissue contrast sensitivity in addition to the many other possibilities offered by this modality including BOLD imaging, functional MRI (fMRI), diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), diffusion tensor imaging (DTI) and MR spectroscopy (MRS) [17].

Hardware-based multimodality imaging is not limited to the above combinations of techniques as several investigators proposed and in many cases have implemented and tested prototype dual-modality preclinical systems that combine various imaging technologies such as SPECT and PET [18], PET and OI [19] and MRI and OI [20]. Moreover, efforts are also underway to develop tri-modality preclinical systems integrated in a single gantry including PET/SPECT/CT [21, 22] and PET/SPECT/OI [23] as well as PET/SPECT/US.

Image fusion techniques have been very popular since the 1990s where the move from 3-D (space) to 5-D (space+time+function/metabolism) imaging driven by the development of software-based image registration techniques was pivotal to the clinical acceptance and triggered further the development of multimodality imaging [24]. With the highly sophisticated technologies available today, navigating beyond the fifth dimension in vivo is becoming feasible by incorporating cardiac or respiratory gating or both [25], CT or MR contrast agent dynamics or alternatively multitracer PET studies [26, 27] probing other biological or physiological processes (e.g. tumour hypoxia in oncological imaging). The latter can be achieved through the use of one of the above-referenced dual-modality SPECT/CT systems [8] by exploiting the capabilities offered by dual-tracer imaging where multiple energy windows can be used for simultaneous imaging of radiotracers having different energies in addition to the 5-D information provided by the CT following contrast enhancement and online tracking of contrast agent dynamics.

Typical examples of clinical studies involving signal extraction from simultaneous dual-tracer imaging through energy discrimination include stress and rest imaging in myocardial SPECT perfusion imaging using ^{99m}Tc-sestamibi (140 keV) and ^{201}Tl (75 keV/167 keV), respectively [28], and ^{99m}Tc (140 keV) perfusion and ^{123}I (159 keV) neuro-transmission brain imaging, respectively, which proved to be useful in the diagnosis of neurodegenerative diseases [29]. In this context, the use of simultaneous acquisition increases patients' throughput by reducing acquisition time and thus also patient discomfort as well as image artefacts due to patient motion. Another important benefit is that the images resulting from the different tracers are perfectly registered in space and time and as such allow true multiparametric imaging. The known complications associated with dual-tracer imaging including the presence of crosstalk between the multiple energy windows have been addressed in various ways in the peer-reviewed literature (see e.g. [30, 31]).

Alternatively, one would use a tri-modality PET/SPECT/CT imaging system where a positron-emitting radiotracer probing presynaptic dopaminergic function (e.g. ^{18}F-FDOPA) for instance and a single photon emitting radiotracer probing for example perfusion (e.g. ^{99m}Tc-HMPAO) are combined to record and differentiate through energy discrimination the two signals. Another more interesting and also more technically challenging approach would be to exploit recent developments in multitracer PET studies targeting different physiological or biological processes [26, 27], where two to three PET probes, e.g. ^{18}F-FDG and ^{18}F-EF5 [32], are injected either sequentially or simultaneously to allow imaging tumour glucose metabolism and tumour hypoxia, respectively. However, the latter approach is difficult to perform in PET imaging given that positron-emitting radiotracers produce the same energy following the annihilation process (511 keV).

While sequential dual-tracer PET imaging reflecting different biological features of disease (e.g. ^{18}F-FDG for glucose metabolism and ^{18}F-FLT for tumour cell proliferation) is already performed routinely in some centres [27], simultaneous dual-tracer imaging using PET is very complicated to achieve and still is an immature field. The possibility of fast scanning of multiple PET probes using a well-designed dynamic imaging protocol allowing one to extract the signal of each probe based upon inherent differentiation between radionuclides' half-lives, tracer kinetics and biodistribution has been reported recently [33, 34]. In these studies, the components of each probe are assessed using principal component analysis (PCA) as the most popular multivariate analysis tool available. The authors reported promising results in terms of overlapping signal recovery using the developed methodology combined with a dynamic dual-tracer scanning protocol with staggered injections. A follow-up study by the same group confirmed that quantification of blood flow using ^{13}N-ammonia can be accomplished by means of the fast dual-tracer technique in only 20 min allowing provision of blood flow estimates with accuracy very similar to the conventional extended single-injection standards [35]. One of the limitations of this study is the limited number of subjects

involved (six patients). The potential impact of this methodology on patient management also still needs to be defined. More recently, they come up with a more sophisticated algorithm allowing improved tracer separation where signal partitioning performance was assessed for imaging various combinations of ^{18}F-FDG (glucose metabolism) plus ^{62}Cu-PTSM (blood flow) and/or ^{62}Cu-ATSM (hypoxia) [36]. In a follow-up study, the same group performed sequential dynamic scanning using the above-mentioned radiotracers in four dogs with pre-existing tumours allowing combination of the acquired projection data to emulate dual- and triple-tracer imaging where the single-tracer data served as gold standard for performance evaluation of the algorithm [37]. They report an accurate recovery of static quantitative imaging measures (SUV) and partial recovery of rate parameters derived from compartment modelling (excellent agreement for k_1 and k_2 but large discrepancy for k_3). They concluded that the results obtained so far are promising; however, further refinement of the signal separation algorithms is essential for more accurate recovery of quantitative imaging measures for each radiotracer. This field is now an area of active research [37–39], and to be successful the approach deserves further research and development efforts and additional evaluation for potential clinical use. The next challenge would be to handle the enormous amount of data generated and to develop flexible display strategies allowing one to overlay and navigate through the multidimensional and multiparametric images in a visually compelling fashion.

It is worth noting that molecular imaging is also facing many challenges. For example, it appears that ultrasmall superparamagnetic iron oxide particles (USPIO) used for MRI studies have been or will be shortly removed from the clinical market by the pharmaceutical industry. Moreover, most companies have substantially reduced their commercial activities in contrast agent development, except for SPECT and PET, since the market potential appears to be too small and the production costs too high. Moreover, the enormous costs involved with implementing the sophisticated infrastructures needed to commercially produce and distribute PET tracers is also another obstacle to the widespread accessibility of molecular imaging.

The challenges faced by the molecular imaging community include the shortage of qualified personnel to carry out the various tasks associated with the use of this multifaceted technology. This is pertinent to the whole chain including running cyclotron facilities, synthesizing routine and new tracers and operating the multimodality imaging units. There is a great demand for premium physicians and scientists who are adequately trained to offer this type of service with high standards.

Despite the enormous challenges faced, the development and recognition of the potential of multi-parametric molecular imaging has been very rapid and exciting, and there is every reason to believe the field will move forward more rapidly in the near future with the advent of novel technologies and methodologies and the unlimited imagination of active researchers in the field. History demonstrated that today's research heads toward tomorrow's clinical practice. Thus, it is not farfetched to speculate that in the future multi-parametric molecular imaging will likely be the spotlight of medical practice where early and accurate diagnoses and individualized therapy planning will be made by appropriate imaging probes.

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