Integration of small animal SPECT and PET with other imaging modalities

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Abstract

Vaissier PEB, Wu C, Beekman FJ. Integration of small animal SPECT and PET with other imaging modalities. Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging of small experimental animals is used to quantitatively and visually assess the distribution of radioactive biological markers (tracers) *in vivo* in order to e.g. study animal models of disease and test new pharmaceuticals. While SPECT and PET provide information about molecular mechanisms through detection of gamma-rays that are emitted when the tracer decays, other imaging modalities use radio-waves (Magnetic Resonance Imaging; MRI), near-infrared/visible light (Optical Imaging; OI) or X-rays (X-ray Computed Tomography; CT) to obtain anatomical and/or functional information of living subjects. Since each modality has unique qualities, e.g. in terms of spatial- and temporal resolutions and abilities to measure structure and function, they are often combined: e.g. CT or MRI images can be used as an anatomical reference for locating tracer uptake, or can be used for attenuation correction of emission tomography images. An increasing effort is being spent on hardware integration of different imaging modalities. In this work we discuss the methods, limitations and challenges of multimodality integration in the development of preclinical dual- triple- and quadruple modality systems that include SPECT and/or PET.
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Introduction

In preclinical research, *in vivo* imaging techniques are used for non-invasive assessment of structure and function in small animals in e.g. studies of disease and to test new pharmaceuticals. Each imaging modality that is currently available has its strengths and weaknesses in terms of e.g. spatial- and temporal resolutions, sensitivity, abilities to measure structure and function and the availability of suitable contrast agents or tracers for the task at hand (1). Combining images from different imaging modalities can be very useful, as different modalities often provide highly complementary information. For instance, spatially registered SPECT and CT or PET and CT images enable anatomical localization and accurate quantification of uptake of radioactive tracer molecules, particles or cells. To achieve good spatial registration, much effort is being spent on integrating different modalities. Nice review papers about multimodality imaging include the ones from Cherry, Townsend and Beyer (2-6). These papers mostly focus on clinical dual-modality imaging, however in this work we only focus on preclinical multimodality imaging, including systems that integrate more than two modalities. The integration of preclinical imaging modalities can be as simple as a click-over bed that can be taken from one scanner to the other. This *side-by-side* integration of imaging modalities requires suitable mechanical interfaces to smoothly disconnect the bed from one scanner and (preferably) reproducibly mount the bed to another scanner. Multimodal fiducial markers attached to the bed or a pre-measured transformation matrix can then be used to automatically fuse the images (7-9). This approach allows for different systems to be used at the same time and allows for replacement or addition of individual modalities. A drawback that comes with *side-by-side* integration is that an animal may shift on the bed during (manual) transportation between scanners if the animal is not properly fixed to the bed, which may introduce image registration errors. Moreover, the animal must be kept under controlled anaesthesia in between scans, which might become problematic if the animal bed is disconnected to be moved between scanners. To overcome these issues, systems have been developed that integrate multiple modalities on a single platform (figure 1a).

Most of these systems achieve integration by placing the modalities in a *back-to-back (in line)* configuration, which is also commonly applied in clinical hybrid imaging instruments. In this configuration, modalities are placed in close proximity of each other and the animal is automatically transferred on a bed from one subsystem to the other along the common axis of the subsystems. The main advantage of *in line* integration is that the animal can be scanned without having to be manually transferred from one system to the other, thereby reducing the chance of animal movement and making it easier to keep the animal under controlled anaesthesia. Moreover, these solutions mostly offer a single control interface, which makes operating the scanners easier, rather than having to learn how to operate several separate scanners.

A clear disadvantage can be that the throughput on individual scanners is suboptimal since only one modality can be used at each given point in time. In addition, SPECT and PET systems

usually have detectors with photomultiplier tubes (PMTs) that are highly sensitive to magnetic fields. These systems can therefore only be safely combined *in line* with lower-field MRI systems which may result in long MRI acquisition times. MR-compatible SPECT hardware will likely overcome these issues in the future.

Instead of *in line* integration, imaging systems can also be integrated on a single gantry. An example of a preclinical system where both SPECT and CT are integrated on the same gantry is the Siemens Inveon SPECT/CT scanner (figure 1b). Drawback of such a system is that the number of (SPECT) detectors that can be integrated is limited by the space required for the CT's X-ray source and detector. In attempts to perform simultaneous SPECT-MRI and PET-MRI, SPECT and PET inserts for MRI scanners have been developed (10-14).

Full integration of modalities is achieved when the detectors of a system are optimized such that they can detect radiation signals from different modalities. The images that are obtained with such systems are inherently aligned in space and time. An example of such integration is the VECTor$^+$ system which can perform simultaneous SPECT and PET imaging (see the next section on the integration of SPECT with PET). Table 1 gives an overview of some commercially available preclinical multimodality imaging systems.

Integrating SPECT with PET

Preclinical SPECT systems are most times based on the use of pinholes that magnify projections of the radionuclide distribution on detectors that would otherwise not have been able to resolve the small details within such animals: reconstructed spatial resolutions of these systems can reach

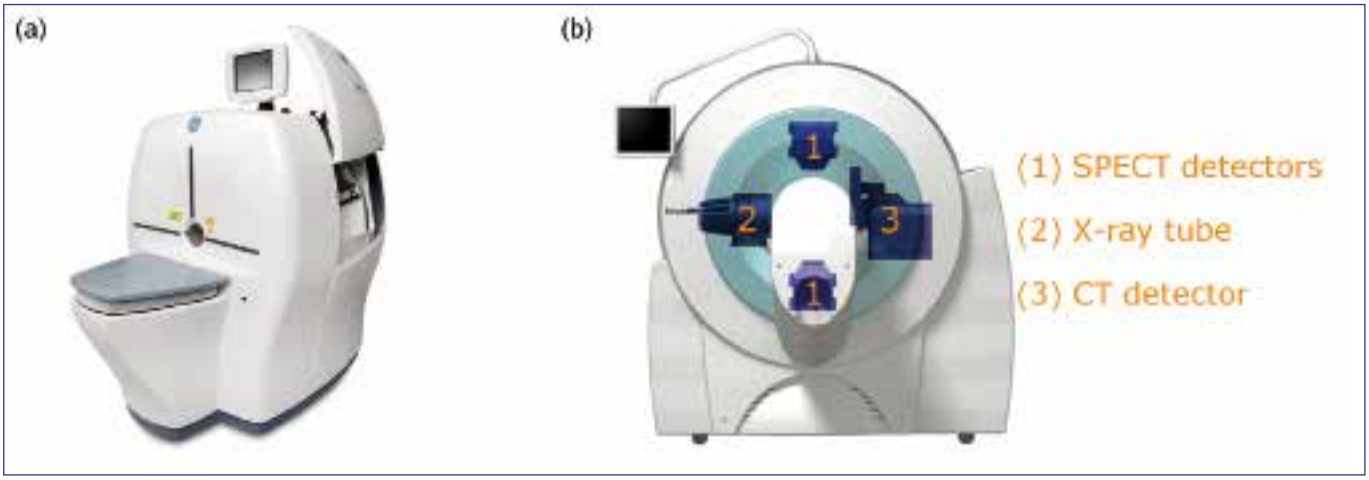

Figure 1. (a) The Triumph system is the world's first preclinical tri-modality imaging system as it combines SPECT, PET and CT on a single platform. Image courtesy of TriFoil Imaging. (b) Integrated SPECT/CT system with SPECT and CT subsystems attached to same gantry. Image courtesy of Siemens Healthcare.

Table 1. Overview of some commercially available multimodality systems

	MRI	OI	CT	SPECT	PET
Bruker Albira	no	no	yes	yes	yes
Mediso nanoSPECT/CT	no	no	yes	yes	no
Mediso nanoPET/CT	no	no	yes	no	yes
Mediso nanoSPECT/MRI	yes	no	no	yes	no
Mediso nanoPET/MRI	yes	no	no	no	yes
MILabs USPECT$^+$/CT/MRI/OI	yes	yes	yes	yes	no
MILabs VECTor$^+$/CT/MRI/OI	yes	yes	yes	yes*	yes*
Siemens Inveon	no	no	yes	yes	yes
TriFoil Triumph II	no	no	yes	yes	yes

**simultaneous SPECT/PET imaging possible*

well below half a millimetre (15, 16). Some commercial multimodality systems that can perform SPECT use a number of rotating gamma detectors and collimators to acquire complete sampling of the subject, which is required for image reconstruction, while other systems use a stationary setup and a focussing multi-pinhole geometry to readily obtain a high sensitivity and complete data within the focal region that is seen by all pinholes. For this reason, stationary SPECT allows for fast dynamic imaging (17).

Coincidence PET systems apply electronic collimation to reconstruct a line-of-response from each detected pair of anti-parallel 511 keV photons that are formed when a positron (emitted by the radioactive tracer) annihilates with an electron in the tissue. From these lines-of-response images of the tracer distribution can be reconstructed. The absence of physical collimators is a major reason why coincidence PET has a higher sensitivity than SPECT. State-of-the-art preclinical coincidence PET can achieve spatial resolutions of about 1 mm.

Imaging platforms that can perform both SPECT and PET can take advantage of the entire complement of available SPECT and PET tracers. Most commercial systems that are capable of SPECT-PET imaging have an in line configuration of a pinhole SPECT subsystem with a coincidence PET subsystem and can therefore only perform sequential SPECT-PET imaging. Another recent approach to combined SPECT-PET is to physically collimate the 511 keV annihilation (PET) photons by clusters of focussed pinholes on a SPECT platform (pinhole PET (18, 19)). This form of collimation can offer sub-mm spatial resolution (figure 2a) but relatively low sensitivity compared to coincidence PET. However, resolution and image quality in coincidence PET are limited by a number of physical factors (table 2) that are not prominent in pinhole PET and in a number of imaging situations pinhole PET imaging results in better resolution than coincidence PET.
A major difference between a pinhole SPECT/PET system over an *in line* combination of a (pinhole) SPECT subsystem with a coincidence PET subsystem is that a pinhole SPECT/PET system allows for simultaneous SPECT-PET imaging which may open up new possibilities for multiple functional studies (figure 2b).

Integrating SPECT and PET with CT

Combining SPECT and PET with CT can provide an anatomical context of biological processes (e.g. figure 3 (20)) and can

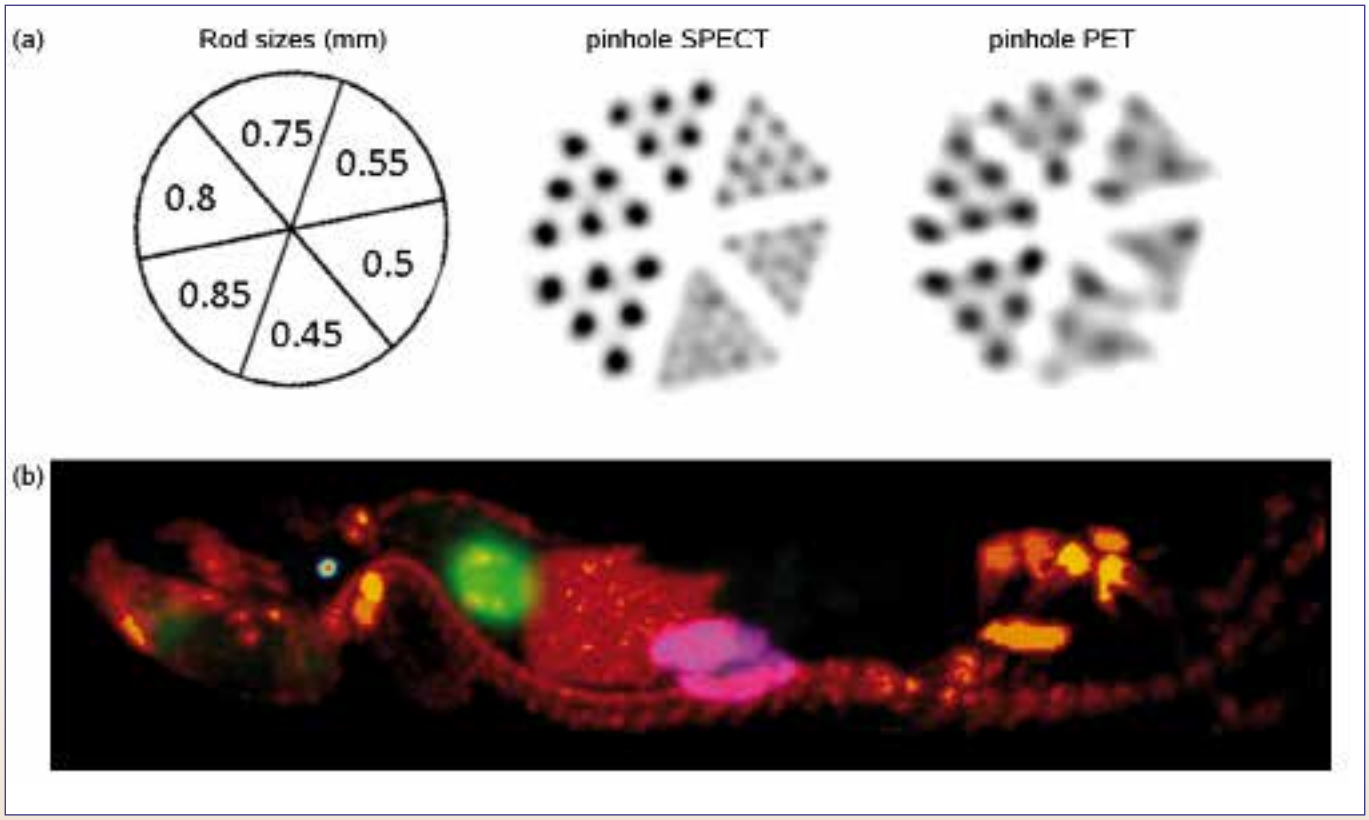

Figure 2. Simultaneous PET and SPECT isotope imaging with VECTor⁺: (a) SPECT and PET reconstructions of a Jaszczak phantom containing 16 MBq ^{99m}Tc and 24 MBq ^{18}F at the start of the scan (scan time was 60 min). For SPECT the 0.5 mm rods can still be distinguished, for PET the 0.75 mm rods. (b) Quadruple SPECT and PET isotope imaging showing a maximum-intensity-projection of a 60 minute total body mouse scan with 100 MBq ^{99m}Tc-HDP (red), 35 MBq ^{18}F-FDG (green), 19 MBq ^{111}In-pentetreotide (magenta) and 5 MBq ^{123}I-NaI (rainbow). Images courtesy of MILabs B.V.

Table 2. Differences in imaging physics between coincidence PET and pinhole PET.

	coincidence PET	pinhole PET
detector resolution and DOI	issue	small issue
non-collinearity	issue	no issue
random coincidences	issue	no issue
coincidence losses	issue	no issue
positron range	issue	issue

also improve the quantitative accuracy of SPECT and PET data through improved attenuation correction that is enabled by CT. CT systems used in small-animal imaging usually consist of a microfocus X-ray tube. The typical focal-spot size is less than 50 µm and reaches down to only a few µm in some systems. Reconstruction resolutions of well below 100 µm are achievable with such X-ray tubes in combination with accurate design of mechanics. The maximum voltage of the X-ray tubes in preclinical CT systems varies among vendors, but usually the actual working voltage for imaging small animals is less than 80 kVp (i.e. 80 keV maximum X-ray energy). In contrast, the energy of photons used in PET is much higher (511 keV). This has enabled the design of PET/CT systems that can perform simultaneous PET and CT scanning in order to prevent image registration errors due to changes in the position of the animal which may occur in the case of sequential scanning: e.g. a system that consists of a single-gantry with separate PET and CT detectors (21) or even with the same detectors (22). In some commercial preclinical multimodality systems that incorporate CT, the CT subsystem is integrated *in line* with the other modalities, while in other systems the SPECT and CT subsystems are mounted on the same rotating gantry (e.g. figure 1b).

Since CT measures radiodensity of the scanned object, CT data can be converted into attenuation maps which can be used for attenuation correction of SPECT or PET images (23-26). This undoubtedly strengthens the power of emission tomography since applications such as pharmacokinetic investigations can benefit from the accurate quantification of tracer distributions.

Integrating SPECT and PET with MRI

Since CT imaging uses ionizing radiation which may influence animal welfare and study outcome (27,28), a development towards integrating SPECT and PET with MRI, which offers a high-resolution, non-ionizing method for anatomical imaging of small animals with excellent soft tissue contrast, has commenced. To illustrate the use of CT and MRI images as an anatomical reference for locating tracer uptake in emission tomography images, figure 4a shows fused SPECT, CT and MRI images.

Initial MRI-compatible PET inserts were developed in the mid-1990s (10, 14). These systems used long optical fibre

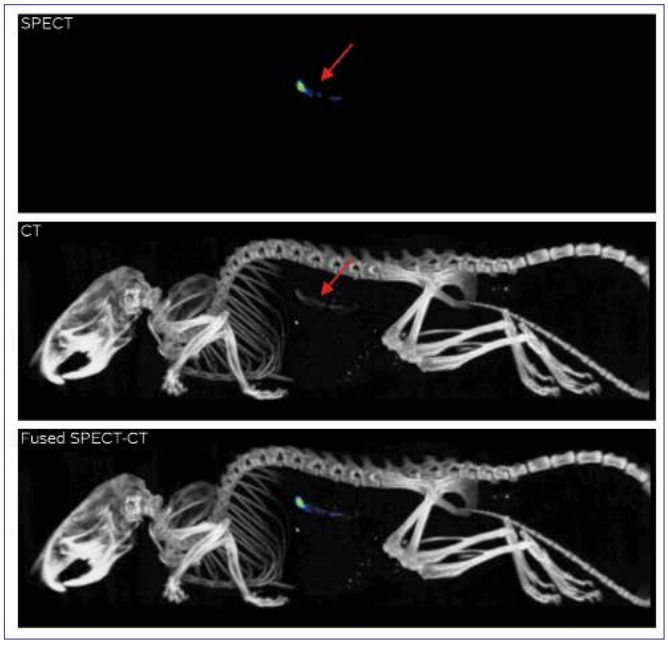

Figure 3. Example of SPECT/CT imaging: holmium-166 acetylacetonate microspheres (^{166}HoAcAcMS) are used for treatment of kidney tumours (for details see reference 20). ^{166}Ho emits high-energy beta particles suitable for anticancer therapy and the simultaneously emitted gamma rays (81 keV) allow for SPECT imaging. Moreover, nonradioactive holmium-165 can be visualised by CT. Arrows indicate the presence of the microspheres in the kidney area in the SPECT and CT images. The fused SPECT/CT image clearly shows agreement between the SPECT and CT signals. Images courtesy of W. Bult, University Medical Centre Utrecht, the Netherlands.

connections between the scintillator elements inside the MRI and the PMTs that were placed outside the MRI to effectively eliminate the interference of the magnetic field with the PMTs. More recently, MR-compatible PET inserts that are based on solid-state detectors have been developed and applied for *in vivo* studies (29, 30).

The development of SPECT/MRI systems started much later: the first combined SPECT/MRI platform was proposed in 2007. In this set-up a single pinhole SPECT system was used next to a 0.1T magnet (31). Similar *in line* set-ups are proposed by Mediso in which the SPECT or PET subsystem is combined with a 1T MRI subsystem. Other *side-by-side* solutions are provided by MILabs (figure 4b,c). Figure 4c shows a solution with a robotic rotation/translation stage that automatically transfers the animal between the MRI (available with field strengths of 1.5T or 3T) and up to three other modalities (SPECT/PET/CT). This set-up functions as if the MRI system is integrated *in line* with the other modalities, while preventing interference between the MRI and the other modalities. In attempts to perform simultaneous SPECT/MRI, SPECT inserts for MRI systems have been developed by using a stationary detector configuration and MRI-compatible

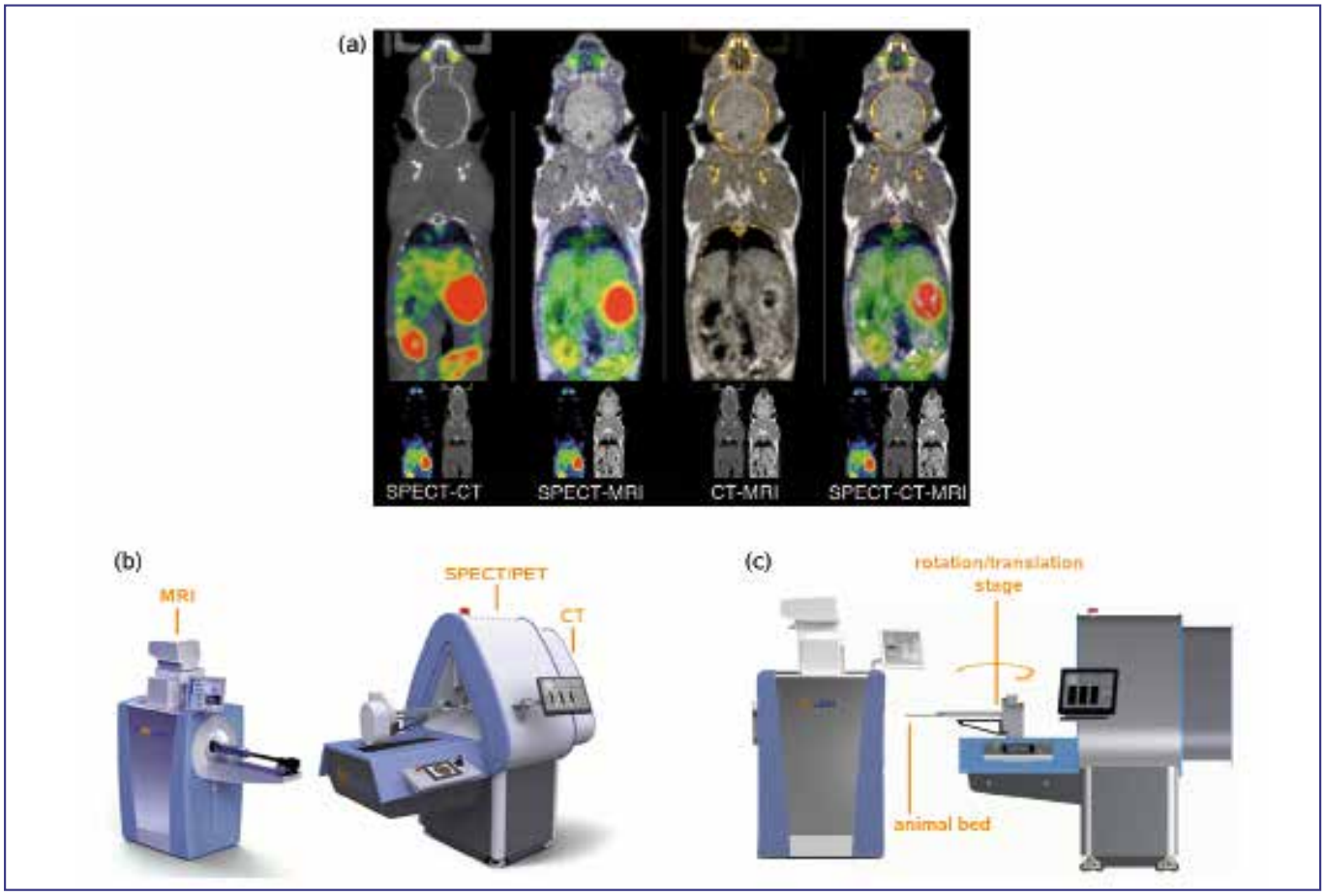

Figure 4. (a) Fusion display of an in vivo *mouse multimodality study, combining SPECT, CT and MRI. Image (a) reprinted from (4), Copyright (2013), with permission from Elsevier. (b)* Side-by-side *solution to imaging with MRI and other modalities. (c) Another solution uses a stage that automatically transfers the animal between the MRI and other modalities thereby preventing interference between the MRI and the other modalities. Images (b,c) courtesy of MILabs B.V.*

collimators and detectors (11, 13). The number of pinholes that can be integrated is relatively low compared to modern stand-alone multi-pinhole SPECT systems, which results in relatively low sensitivity. Due to the limited bore-size of MRI systems, pinhole magnification is also relatively low, which results in compromised image resolution. Very high-resolution MR-compatible detectors are required to enable performance comparable to that of modern stand-alone SPECT with traditional detectors and high pinhole magnification factors (32). However, today these detectors are costly and hard to acquire at an industrial-quality-level.

In contrast to CT, a potential limitation of MRI is that it does not readily provide adequate information for attenuation correction of SPECT and PET images, since it is a challenge to e.g. distinguish between bone and air. However, since the non-uniformity of attenuation or the high accuracy of attenuation maps do not play a critical role in small-animal emission tomography (33), MRI-derived attenuation maps may be sufficient for some studies.

Integrating SPECT and PET with OI

Optical techniques allow for in vivo imaging of cellular and molecular processes. OI systems generally consist of a black box in which a bioluminescent or fluorescent small animal is placed and images of the optical signal are acquired by a (CCD) camera. A number of prototype instruments for small animal PET/OI have been developed (34, 35). Furthermore, an OI system that can be docked in line to a SPECT/PET/CT platform is currently being developed (figure 5). This set-up allows for all combinations of SPECT/PET/CT/OI on a single platform.

Conclusions and perspectives

Preclinical multimodality imaging can be very useful, as different modalities can provide highly complementary or enhanced information for scientific researchers. Today, most commercial systems that can perform SPECT/PET imaging can only acquire the SPECT and PET data sequentially. However, a recently developed high-energy pinhole collimation technique enables simultaneous SPECT/PET

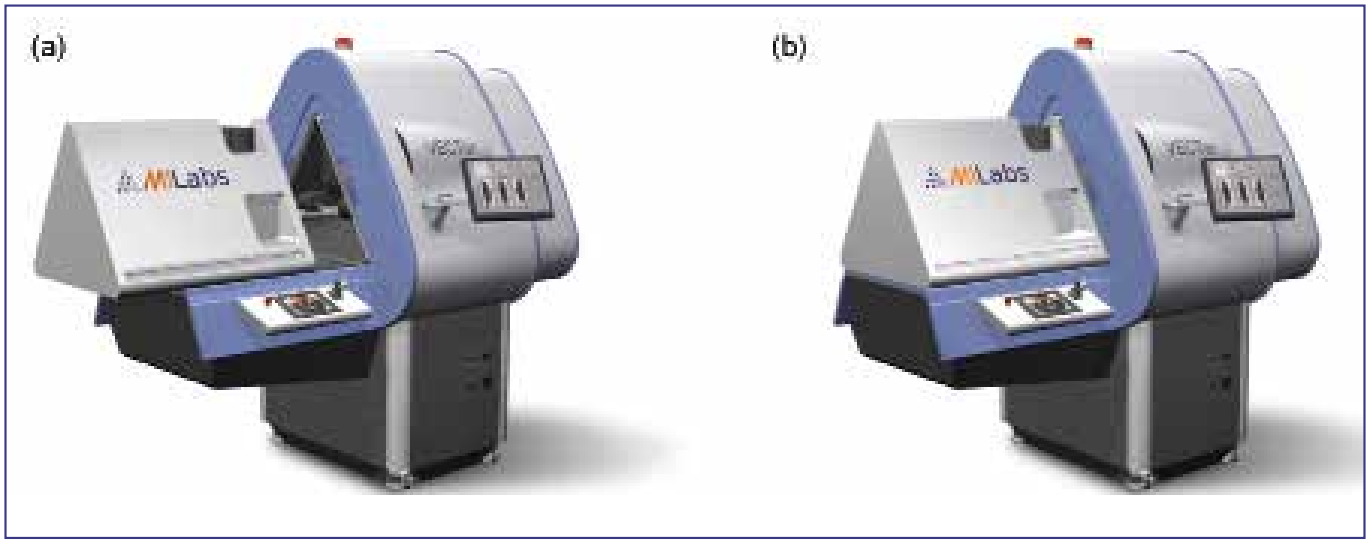

Figure 5. Conceptual impression of an optical imaging system that is docked to a SPECT/PET/CT system. In (a) the optical imaging box is open and the rodent can be prepared for scanning. In (b) the box is closed (i.e. light-tight) and SPECT/PET/CT/OI can be performed. Image courtesy of MILabs B.V.

imaging with sub-half-mm SPECT and sub-mm PET resolution. This enables to exploit the entire complement of SPECT and PET tracers in a single scan and may therefore open up new possibilities for multiple functional studies. CT mostly provides anatomical reference images for SPECT and PET images but can also be used for attenuation correction of SPECT and PET data. However, CT uses ionizing radiation which may influence animal welfare or even study results, although new developments in small animal CT (e.g. better reconstruction software (36-38) and improved scan protocols (28)) should lead to higher image quality at lower doses. MRI does not use ionizing radiation and can offer detailed anatomical images of soft tissues, which is compatible with longitudinal multimodality studies. Since stand-alone use of MRI and SPECT or PET systems gives rise to challenges regarding e.g. image registration and prolonged anaesthesia, highly integrated SPECT/MRI and PET/MRI systems are desirable. However, these systems are still in a very early stage of development and the feasibility of highly integrated SPECT/MRI and PET/MRI strongly depends on technologies that enable minimal compromises to the performance of the individual modalities.

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