OpenPET offers in vivo dosimetry

A transformable scanner geometry improves in-beam PET verification of particle therapy.

PET has the potential to verify charged particle therapy in vivo, reducing uncertainty in particle range and improving treatment accuracy. However, biological washout and the short half-life of positron emitters generated by the treatment beam mean that scans must be performed during or shortly after treatment.

Researchers from the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, are developing the first open-geometry PET scanner that provides access to the patient for introduction of a treatment beam, for example, during imaging. They envisage that the potential applications of this OpenPET scanner will include in-beam PET imaging for monitoring dose distribution during particle therapy and real-time tumour tracking during radiotherapy.

In a new development, the NIRS researchers have demonstrated the feasibility of a unique transformable version of this PET system that images both during and after irradiation. The team, led by Taiga Yamaya, has created and evaluated a miniaturized transformable OpenPET prototype (Phys. Med. Biol. 61 1795).

Unique system

In “open” mode, the detector ring is sheared along the scanner axis, creating a field-of-view (FOV) centred in the ring that is accessible by the treatment beam. A simple hand-driven mechanism transforms the detectors into a conventional “closed” toroidal geometry that enables imaging immediately following treatment.

The detector ring comprises 16 detector units arranged in a 259 mm diameter circle. Each unit consists of two depth-of-interaction (DOI) detectors; each of these comprises a 16 × 16 array of zirconium-doped gadolinium oxyorthosilicate scintillators. In open mode, the detector units are staggered along the scanner axis.

While conventional PET detectors are attached to a fixed frame, OpenPET detectors are attached to their neighbours by guide rails. Using a rotating handle to drive them along the guides, it takes less than 10 seconds to switch between the two scan geometries. The structure supports a total detector mass of 16 kg.

“Designing a transformable mechanism for the heavy detectors was really challenging.” Yamaya told medicalphysicsweb.

Images of a Na-22 point source reconstructed with the 3D ordered subset expectation maximum (OSEM) algorithm revealed that open mode scans had lower sensitivity and resolution. Sensitivity was 30% lower than in closed mode, dropping from 7.3% to 5.1%. The drop was attributed to a greater detector-phantom distance that decreases the solid angle covered by the detectors.

Quantified using the full-width at half-maximum and the same source, the researchers also observed a lower spatial resolution in open mode (2.6 mm versus 2.1 mm). This difference arose from different detector orientations relative to the centre of the FOV. In closed mode, the scintillators point towards it, while in open mode, they point 45° away from the centre of the FOV, introducing a parallax error.

Based on the results, the researchers propose maximizing OpenPET’s performance by imaging patients in open mode during treatment, then in closed mode immediately following treatment.

In another experiment, the team delivered 2.5 Gy at the Bragg peak to a cuboid plastic phantom using a carbon-11 beam from NIRS’ HIMAC (Heavy Ion Medical Accelerator in Chiba). This revealed that sufficient count statistics for image reconstruction were achievable upon combining counts acquired during irradiation with less than a minute of acquisition following irradiation. In this way, the system improves upon previous OpenPET designs that could only be operated in open mode.

“It is hard to satisfy all imaging requirements at the same time with one mode,” said first author Hideaki Tashima. “Therefore the transform system works well – we can minimize the sensitivity loss in practical use by switching between the two modes.” The dual-mode scanner also saves space and is more economical than two separate PET systems.

Prototype success

The in-beam experiment showed that the prototype could successfully resolve a shift in Bragg peak depth when half the beam was fired through a 9 mm thick PMMA board. It also demonstrated agreement between the measured position of the Bragg peak and that predicted by the planning system within 2 mm, the uncertainty of the experiment.

Based on their findings, the researchers are developing a larger clinical system and plan to acquire the first patient images later this year. The journal continues to build on its reputation for publishing excellent research rapidly. Our 2015 impact factor stands at 2.811*.

*As selected in Freeman’s Medline 2016 Journal Citation Reports.

Team effort: Taiga Yamaya and colleagues at NIRS with a small prototype of their novel switchable PET system.
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### VMAT: does the dose rate matter?

Until recently, radiation treatments were mostly delivered at a constant dose rate. But this changed dramatically with the introduction of volumetric-modulated arc therapy (VMAT). VMAT delivers complex dose distributions by simultaneously modulating gantry position, monitor unit rate, jaws and collimator leaves. Beam planning is performed by dose optimization algorithms that use any dose rate/modulation available from the linac, resulting in a large range of dose rates. Human tissues, however, exhibit varying response to radiation depending upon the dose rate.

Several recent studies have shown that for low-LET radiation, there is little difference in response for dose rates between 1 and 12 Gy/min. “But everyone seems to have forgotten about the low dose rates,” explained Frank Verhaegen from MAASTRO Clinic, adding that dose rates below 1 Gy/min have a sparing effect and a differential response between tissues. “We noticed that VMAT results in a large fraction of the treatment being delivered with low dose rates. This is worrisome, since we know from brachytherapy that for low dose rates, a significant tumour sparing occurs.”

To investigate this further, Verhaegen and colleagues from MAASTRO Clinic and the British Columbia Cancer Agency have used time-resolved Monte Carlo simulations to quantify the distribution of dose rates for clinical VMAT treatments (Phys. Med. Biol. 41 4048).

#### Dose rate distributions

Current treatment planning systems do not enable dose rate to be included in planning goals, or even calculated for assessment. Hence, Verhaegen explained that by chemical engineering, we can develop formulations that are less invasive and biodegradable, thus allowing the material slowly to biodegrade, resulting in a large range of dose rates. Hence, Verhaegen said there is little difference in response for dose rates between 1 and 12 Gy/min.

### Clinical Impact

It remains to be seen whether low dose rates in external-beam therapy have a clinically relevant impact. However, the results demonstrated that VMAT plans produce the same total dose distribution but with very different dose rate distributions, with large contributions at dose rates below that known to exhibit sparing. Knowledge of dose rate distribution at the planning stage could enable low dose rate contributions to be minimized in the first place. Some organs, such as lungs, can be spared.

So, rather than looking at cumulative dose, clinicians can look at dose rate, which can be lower for VMAT than conventional therapy.

#### Liquid fiducials up the precision

Fiducial markers used in radiation therapy come in various shapes and sizes; but until now, all were solid structures. Danish start-up company Nanovi has now developed a liquid fiducial – BioXmark – that can be injected via thin needles directly into the tumour site. Following CE Mark approval in April, Nanovi commercially launched its novel liquid soft-tissue marker at the ESTRO 35 meeting in Turin, Italy.

“BioXmark is now indicated for radiographically marking soft tissue in or adjacent to malignant tissue in the thoracic region,” explained Torsten Jepsen, Nanovi’s Director for Value & Access. “The liquid is injected using standard syringes and needles, using a smaller needle size than needed for gold fiducials, and the marker size is controlled by the injected volume.”

Once injected into the body, the liquid’s viscosity increases and the drop transforms into a viscous gel-like marker. Jepsen noted that formed fiducials have no sharp edges and are very sticky, “gluing” themselves to the tissue to minimize the risk of migration over a treatment course. The material slowly biodegrades, with no significant change in size during the first three months after injection, and is cleared from the body in a few years.

“There have been a wide range of fiducials around, but we envisioned that by chemical engineering, we could create high-tech biomaterials that are less invasive and biodegradable,” explained Rasmus Jelck, Director for Development & Supply at Nanovi.

### Tami Freeman is editor of medicalphysicsweb.com

### Two clinical studies investigating BioXmark

A study in patients with locally-advanced non-small cell lung cancer showed that the fiducials were clearly visible in tumour tissue, lymph nodes and lung tissue, and were stable from the planning CT to the end of treatment. The study is now in a long term follow up phase. A second ongoing study in patients with oesophageal cancer reinforces the finding that the fiducials are well tolerated and do not migrate.

The company is now working with clinicians to investigate the clinical value of its liquid fiducials, and is planning studies in other indications. “There are lots of areas where gold markers aren’t performing well, such as within lymph nodes for example,” Jepsen told medicalphysicsweb.com. “There is also interest from clinicians in using BioXmark in breast treatments.”
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Radiotherapy of heterogeneous tumours containing regions of hypoxic or hypermetabolic cells can prove less than optimal due to the presence of radioresistant subvolumes. Non-uniform irradiation – or dose-painting – is under investigation as a more effective treatment for radiobiologically heterogeneous targets. The idea is to prescribe a non-uniform dose distribution to the tumour, based on image-guided identification of potentially radioresistant biological target volumes (BTVs).

Dose-painting is usually implemented by delivering increased dose to radioresistant regions. But according to Ala Yaromina from MAASTRO in the Netherlands, in some cases, the opposite may hold true. Speaking at the 3rd Symposium on Small Animal Precision Imaging-Guided Radiotherapy, held earlier this year in Ghent, Belgium, Yaromina described conventional dose painting and introduced a new approach: “inverse dose painting”.

**Defining the target**

The BTV in a tumour can be determined using molecular imaging; PET scanning with the tracer 18F-FDG, for example, can pinpoint regions of high metabolic activity. “Dose painting combines anatomic imaging with biological information to define radioresistant tumour subvolumes that would be good targets for dose escalation,” explained Yaromina. “Clinical data support FDG uptake as a promising target for dose escalation." To examine the feasibility of this approach, Yaromina and colleagues studied dose painting based on FDG uptake in a rat rhabdomyosarcoma tumour model. The animals were injected with FDG and PET/CT scanned two hours later. The image was processed to define the BTV, according to the tracer uptake, and used to create a volumetric-modulated arc therapy (VMAT) plan. Finally, the animals were positioned on a RapidArc treatment system using cone-beam CT and the treatment delivered.

The researchers first performed a targeted dose escalation study comparing hot and cold boost strategies. The BTV was defined as the 30% of gross tumour volume (GTV) with the highest (BTV_high) or lowest (BTV_low) FDG uptake. For the hot boost regime, BTV_low received a dose of 15 Gy while the rest of the GTV received 10.7 Gy. For the cold boost, BTV_cold received 13.5 Gy while the remaining GTV received 10.7 Gy. The mean dose to the GTV was 12 Gy in all cases.

Comparisons of the time taken to reach twice the starting tumour volume after treatment revealed no difference in tumour response between the hot and cold boost regimes. “Dose escalation to high- and low-FDG uptake subvolumes was equally effective,” said Yaromina, adding that the investigation demonstrated that high dosimetric accuracy dose painting studies are technically feasible in medium-sized animals on a clinical platform.

In parallel, they examined dose redistribution, comparing the hot boost regime with uniform 12 Gy irradiation to the entire GTV. In terms of tumour growth delay, the hot boost did not improve upon results from uniform irradiation. When the experiment was repeated at 8 Gy (10 Gy to BTV_low and 7.1 Gy to the rest of the GTV, versus uniform 8 Gy dose), the hot boost was actually detrimental to the outcome. Yaromina suggested that these data support the hypothesis that tumour response is dependent on the minimum intratumoral dose, rather than the highest BTV dose.

**The inverse approach**

Tumour hypoxia is another promising target for dose escalation, but hypoxic tumour cells are two to three times more radioresistant and such a dose escalation is difficult to achieve clinically, Yaromina told the audience. “So the idea is to target hypoxic cells with the hypoxia-activated prodrug TH-302 and to deliver a higher radiation dose to the regions with low drug accumulation, associated with the worse dose painting based on FDG uptake.”

In this inverse dose painting approach, the team targeted hypoxic tumour cells with TH-302, which is expected to make tumour regions more similar to the 18F-HX4 hypoxia tracer. The researchers performed a pilot study of rats with rhabdomyosarcoma tumours. They used HX4 PET to define tumour subvolumes of LDUV (low drug uptake volume), the 40% of the GTV with the lowest HX4 uptake and HDUV (high drug uptake volume), the 40% with the highest HX4 uptake.

The researchers examined several treatment arms: TH-302 or saline plus a 50% boost to the LDUV; TH-302 plus a 50% boost to the HDUV; and TH-302/saline with a uniform boost to the entire GTV. To assess tumour response, they evaluated the time taken to reach three times the starting tumour volume. The LDUV boost regime combined with TH-302—which delivered 18.4 Gy to the LDUV and 12.1 Gy to the remaining GTV —proved more effective than the HDUV boost (18.8 Gy to the HDUV and 12.3 Gy to the remaining volume). Tumours in the LDUV boost arm that received the saline instead of TH-302 exhibited a worse response, demonstrating that TH-302 kills hypoxic cells.

Preliminary results showed that a split dose boost of 18.5 Gy to the entire GTV provided a similar outcome to the LDUV boost. This suggests that the proposed inverse dose painting strategy is effective as a dose escalation to the entire tumour, but with a greater capacity to spare normal tissues. These results are currently being extended to the use of a larger tumour volume.

“Dose painting based on the uptake of labelled drugs may prove a promising strategy to pursue further,” said Yaromina.

Yaromina concluded her presentation by explaining that while these experiments were performed successfully using a commercial linac, moving to a precision small-animal irradiator such as the X-RAD SmART could increase flexibility. “This would also let us use smaller animals such as mice, decreasing the cost of experiments,” she said. “Dose-painting strategies could be performed using a commercial linac, but at a higher dose, we would also be able to use smaller animals such as mice, decreasing the cost of experiments.”
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Risk index accounts for body shape

A new cancer risk model based on body physique, rather than just weight, has been developed for paediatric patients undergoing nuclear medicine imaging. Developed by a US team using virtual phantoms, the model may help to minimize radiation doses while ensuring that adequate image quality is maintained (Phys. Med. Biol. 61 2319).

A fundamental aspect of nuclear imaging lies in the selection of an appropriate dose of radiopharmaceuticals – balancing the need for a high enough image quality against the risks of the patient developing cancer. This issue is particularly acute in paediatric patients, who are considerably more vulnerable to radiation-induced tumour growth.

At present, radiopharmaceutical dosing guidelines for paediatric patients are based on patient weight. “[This] involves the use of body mass scaling of adult administered activity to that for a smaller weight child,” comments lead author Wesley Bolch from the University of Florida. Instead, he counters, “…our studies indicate that body weight alone is not sufficient and that optimal administered activity should be based upon body shape and not just body weight.”

To demonstrate their point, Bolch and colleagues created a series of 48 computational paediatric phantoms – with varying ages, genders, heights and kidney masses – on which they simulated the effects of $^{99m}$Tc-DMSA, one of the most commonly employed radiopharmaceuticals for imaging paediatric patients. $^{99m}$Tc-DMSA is used typically for evaluation of pyelonephritis, an inflammation of the kidneys, and cortical scars.

Using the weight-based administering guidelines, the researchers calculated the effective dose for each phantom, along with a risk index – an expression showing the percentage likelihood that a patient would develop radiation-induced cancer (based on the modelling) compared with the risk of cancer occurring naturally. They reported that the effective doses calculated in their study were lower than those documented in the International Commission on Radiological Protection’s guidelines – a product, they propose, of their age-specific and more anatomically detailed models.

The researchers observed significant risk index variations – of up to 38% increased cancer risk – between similarly aged phantoms of different heights. While shorter, newborn patients are liable to receive higher absorbed doses, due to their organs being closer together – and therefore susceptible to greater levels of cross-dosing, taller patients in the 5, 10 and 15-year modelled ages were seen to receive greater doses than their shorter counterparts. These findings, the researchers say, highlight the need for revised dosing guidelines.

Furthermore, the team also noted dependence between the phantoms’ kidney size and risk of radiation-induced cancer, with newborns with smaller kidneys being at the greatest risk.

Calling the study “excellent”, Michael Lassmann – a medical physicist from the Universitätsklinikum Würzburg who was not involved in this study – commends the researchers for taking a first step away from the standard description of radiation risk following diagnostic exams. “This publication merits further attention as it might lead, on the long term, to a more realistic modification of administered activities to paediatric patients in nuclear medicine than today,” he said.

With this initial study complete, the researchers are now using their phantoms to simulate the nuclear imaging of kidneys, both with and without particular renal defects. From this study, Bolch explains, the team intends to calculate – for various patient types, kidney sizes and imaging protocols, the administered activity that will yield the best quality diagnostic image at the lowest potential risk to the patient.

A hybrid optical gamma imager

A portable hybrid molecular imaging system presented at the SNMMI Annual Meeting combines optical imaging at the surface level with scintigraphy to capture the physiological function of what lies beneath. The scintigraphy aspect of the scanner comprises a gamma camera that detects signals emitted from the body after injection of a radionuclide.

“This research covers the first patient results obtained with the hybrid optical–gamma camera developed in the UK at the universities of Leicester and Nottingham,” said Alan Perkins, from the University of Nottingham. “This scanner has hand-held potential and can be used in a variety of settings, including the outpatient clinic, patient bedside, operating theatre and intensive care unit.”

In a pilot clinical study, the investigators imaged subjects undergoing routine molecular imaging procedures such as bone scans or imaging of the thyroid, eye or lymphatic system. They optimized the image resolution and reduced acquisition time to less than 5 mins. Results showed that the optical–gamma camera was highly effective for imaging lymphatic and thyroid tissue, as well as drainage from the tear ducts. Successful absorption of the radionuclides in these targeted areas was clearly seen in tandem with optical images of surface anatomy. The authors note that this imaging system is still under development and needs further investigation before being made more widely available.

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A helmet-like PET scanner for brain imaging is being developed by a multi-institutional research team. Initial simulations showed that the ambulatory microdose PET (AMPET) device offers a greater than 400% increase in sensitivity and requires a much lower radiation dose than conventional whole-body PET scanners. Additional simulations using a scaled AMPET design confirmed the fourfold sensitivity increase and the ability of a helmet PET to resolve smaller features than existing cylindrical brain PET scanners (Phys. Med. Biol. 61 3681).

Improving PET sensitivity is important for brain imaging, both for diagnostic exams and as a potential screening tool – such as for the early prediction of Alzheimer’s disease. The objective of AMPET is to be able to evaluate normal and disordered human brains in an upright natural environment. Designs proposed are: a helmet suspended by an ecostucture support, a backpack support and a helmet that is worn whilst seated. The research team conducted simulations to assess a scaled AMPET design, examining different scanner configurations to determine which has the best performance. The geometries of an existing cylindrical brain PET scanner and a clinical whole-body scanner (Siemens’ mCT) were used for reference comparisons. Senior author Jinqi Qi, from University of California Davis, directed first author Kuang Gong, a PhD student who performed the study. Qi, Gong and colleagues examined the effect of a compact geometry on image quality, simulating four single-ring scanners with different ring diameters. Using the Cramer-Rao variance bound to compare the performance of these different scanner geometries, they proposed a helmet scanner design with three components: a top panel, a bottom panel and six ring sides with varying diameters that approximated a hemisphere. The researchers used various phantoms to compare photon detection efficiency among different scanners and to mimic a brain activity distribution. They evaluated three different AMPET configurations to assess the contribution from each component of the helmet. They determined that a more compact geometry improved photon detection sensitivity and reduced variance of region-of-interest (ROI) quantification at the centre of the field-of-view (FOV). When scanners were equipped with depth-of-interaction (DOI) detectors, they could outperform a larger scanner. These findings indicated that the weight and cost of materials of a prototype helmet scanner could be reduced.

The sensitivity of the full helmet scanner was 4.2 times that of the cylindrical brain PET scanner. However, a helmet PET configuration using only the six side rings had a sensitivity improvement of only 73%. The full helmet scanner also significantly outperformed the mCT scanner with respect to sensitivity, being 3.2 times greater.

Optimizing the design
The helmet design using top and bottom panel components reduced the scatter pattern more than the other design configurations. In assessing visual spatial sensitivity, the helmet scanner substantially increased the sensitivity in the upper FOV compared with the cylindrical brain PET scanner. The researchers determined that the maximum improvement was near the top FOV, with a maximum sensitivity ratio between the full helmet and the cylindrical brain PET scanner of 35.

Location of the panels also impacted sensitivity, with the top panel improving sensitivity significantly more than the lower FOV and the bottom panel in the lower FOV. The researchers suggested that configuring the helmet design based on the area of the brain being investigated would be possible. Data from a 3D Hoffman phantom, used to simulate brain activity, showed that the helmet detected 46 million events, compared with 18 million detected by the cylindrical brain PET scanner. The helmet also produced reconstructed images with higher contrast and lower noise, particularly in the top planes. Improving time-of-flight resolution from 400 to 200 ps resulted in noticeable improvement in image quality.

Reconstructed images from a Derenzo phantom showed that the helmet scanner again outperformed the cylindrical brain PET scanner, detecting 10.1 million true events, compared with 3.3 million. Comparisons for a centre and a top slice showed that the helmet PET had similar spatial resolution to the cylindrical brain PET but lower noise for the centre slice, and much better resolution for the top slice. DOI information improved the spatial resolution of both scanners, but the helmet scanner took full advantage of the higher resolution, producing images that were much clearer with far less noise. Qi told Medical Physics that the research team will continue to evaluate the performance of the helmet PET design for specific applications in brain imaging. They are talking with neuroscientists and clinicians to determine the specific requirements on the scanner performance and ergonomics. They plan to develop and test a prototype scanner, which they hope will be put into practical use to answer questions in neuroscience.

Cynthia E Keen is a freelance journalist specializing in medicine and healthcare-related innovations.
Radiotherapy’s future: physics or biology?

What is the best way to maximize tumour control? Should we “crank up the volume” or “turn off the switches”? That was the intriguing theme of a debate at this year’s ESTRO 35 conference. Pitting physicists against biologists, the ensuing discussion examined whether physics- or biology-based developments will better progress radiotherapy.

At the start of the debate, a show-of-hands vote revealed an audience preference for a biological approach. Could the speakers change the attendees’ minds?

Reimagine the future

First to the podium, Bradly Wouters from the Princess Margaret Cancer Centre, argued in favour of “turning off the switches” and exploiting knowledge of cell signalling, genetics and cell biology. He described three aspirations in radiation oncology-driven cancer treatment, the first being improvement of local tumour control. He pointed out that the progression of radiotherapy from 3D conformal to intensity-modulated, image-guided and adaptive treatments has certainly improved outcomes for patients, but that ongoing technical developments are now producing smaller gains.

While radiation is highly effective, the same can be said for cancer drugs, Wouters noted. “But even ‘near perfect’ drugs are limited by biology,” he explained. When melanoma patients relapse after therapy, a physician would say “give more drug, more conformal drug” — but the problem is not that the drug’s not effective, the problem is the biological diversity in tumours. The way to achieve significant gain, Wouters proposed, lies in targeting that diversity, using knowledge gained from biopsies and imaging to tailor individual therapies and increase cure rates.

A second aspiration is treatment of systemic disease. The problem here, says Wouters is “you can only treat what you can see — and patients inevitably have cells that you can’t see.” Biological approaches such as immunotherapies may help.

The third aspiration is reducing toxicity in cured patients. While normal tissue exposure will inevitably always be part of curative radiotherapy, there are new biological ways to approach this problem, via protection or regeneration of tissue. So why has biology not had a big impact in the field yet? “We’re in the middle now, aiming for transformational change,” said Wouters. “The question is, do we want more of the same, or to reimagine the future?”

Technology is key

“The past, the present and the future of radiation oncology is dominated by technological innovations,” declared Jan-Jakob Sonke from the Netherlands Cancer Institute. Stat-
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**GEM detectors eye proton QA**

Medical physicists in Indiana have worked for several years to develop prototypes of scintillation gas electron multiplier (GEM) detectors for use in clinical proton beam commissioning and quality assurance (QA). Their most recent dose-imaging prototype incorporates features that provide high spatial resolution and tissue-equivalent dose response in the Bragg peak region. The detector is intended for pretreatment dose verification, imaging of dose distribution in the transverse plane, and as a possible dosimeter for depth-dose measurements, particularly in small fields.

Scintillating GEM detectors are functionally comparable to state-of-the-art commercial 2D dosimeters, such as radiochromic films and scintillating screens, according to lead author Dmitri Nichiporov, currently lead physicist at McLaren Proton Therapy Center. However, the response of these detectors to absorbed dose is nonlinear and subject to various quenching effects. Ion chamber arrays, meanwhile, are limited to a spatial resolution of several millimeters, and are therefore not suitable for obtaining accurate dose distributions in radiation fields with small sizes and high dose gradients (Phys. Med. Biol. 61 2792).

A GEM detector’s response to proton radiation is dependent upon the properties of the gas mixture filling its sensitive volume. It is necessary to use a gas mixture with mass stopping properties similar to that of air and water. The researchers used 60% He and 40% C2H6 gas, as a compromise between the intensity of the detector’s scintillation light output and the expected tissue-equivalence of the gas mixture. This composition proved to be sufficient for dose imaging applications.

**Enhanced prototype**

The detector consists of an entrance window with a cathode mounted on it, a sensitive volume, a double-GEM amplification structure, a transparent exit window, a mirror and a CCD camera with a lens. Improvements to the beam’s latest prototype included an increased imaging area, repositioning of the cathode, a better lens, and a camera with a higher-resolution sensor and a spectral sensitivity that better matched the emission spectrum of the gas mixture. A number of design changes were also made to reduce light scatter inside the detector. These factors, combined with the use of the new water-equivalent He/CF4 gas mixture, resulted in a better spatial resolution (0.3 mm) and provided more accurate dose measurement at the Bragg peak.

The research team evaluated this GEM-based detector in a uniform scanning-beam delivery system at the Indiana University Health Proton Therapy Center. They measured transverse and depth-dose distributions of an unmodulated beam, and studied spatial response and dose-rate response. They also measured dose-rate response along a beam central axis with an acrylic phantom, to evaluate response in a clinically relevant range-modulated beam delivery scenario.

The authors reported that initial irradiation of the detector was needed to establish charge equilibrium and achieve further stable operation. During testing, the GEM detector showed good linearity of dose response intensity and the detector’s output, over a range of beam currents corresponding to typical average dose rates used in patient treatments with uniform scanning-beam delivery.

**Accurate detection**

The detector was able to detect dose variations on the level of less than 1%. The authors noted that “the observed good agreement between the GEM detector and the PinPoint ion chamber in a clinically relevant, range-modulated beam suggests that the GEM detector with the He/CF4 gas mixture can become a good alternative to a small-volume ion chamber in depth–dose and lateral profile measurements”.

Co-author Alexander V Klyachko, currently a senior research scientist at Phenix Medical, the company that intends to commercialize the prototype detector, told particlephysicsweb that the detector’s compact design is intended for easy use in a treatment room to obtain routine QA measurements. The GEM detector’s high data acquisition speed will allow accurate characterization of a treatment plan in a time period similar to that needed for the actual delivery of the dose fraction to a patient.
Injectable hydrogels verify proton range

The range uncertainty during proton therapy provides a strong driver for the development of in vivo range verification techniques. Currently, the only approach used clinically is PET imaging of positron emitters generated by the proton beam. This method, however, suffers from minimal activation of tissues near the beam’s distal end, activity washout and the short half-lives of activated isotopes.

To overcome these limitations, researchers at the University of Texas MD Anderson Cancer Center are investigating the use of implantable markers with a high proton interaction cross section to increase the PET signal intensity. Previously, the team identified 18O, 16O, 15N and 13C as suitable markers. In their latest work, they study the feasibility of using these materials to create syringe-injectable hydrogel markers for in vivo proton range verification (Phys. Med. Biol. 61 1421).

“Hydrogel markers can be injected using a very fine needle, get absorbed into the body in three months and show minimal in-tissue migration,” said first author Jongmin Cho, currently at Oklahoma State University. “Most importantly, hydrogels become proton-activated and can be imaged using PET for treatment and range verification.” With the right composition, hydrogel markers can also replace the CT-visible gold fiducials currently employed for treatment planning and beam set-up.

Testing the markers Cho and colleagues created the injectable markers from polyethylene glycol (PEG)-based hydrogels, which offer excellent biocompatibility and extremely low toxicity. They immersed the hydrogels in 18O-enriched or 60O water containing zinc powder, to create Zn18O-water and Zn60O-water hydrogels.

The researchers used tofu immersed in water as a tissue-equivalent material, and injected it at four depths with 0.9 ml of the hydrogels using a 18-gauge needle. As a reference, they placed samples of both hydrogels in Petro dishes to simulate a dry environment. The hydrogels in the wet phantom and dry Petri dishes were then CT scanned and the images used for treatment planning.

The plans were delivered to the phantoms using a passively scattered 150MeV proton beam. All phantoms were positioned at the proton distal edge with a dose of 2 Gy. Following irradiation, the phantoms were PET/CT scanned after delays of 1–1.5 hours. The Zn18O-water hydrogels injected into the tofu phantom were clearly visible on CT scans. These samples, however, exhibited no noticeable PET signals. The authors note that natural zinc does not seem to be a good candidate for a hydrogel marker, in terms of PET signal, partly because of its low 44Zn abundance. “Alternatively, we could just use 68Zn,” said Cho. “This will give the same CT contrast while providing approximately five times stronger PET signal.”

Proton CT could simplify planning

Proton therapy planning is currently performed based on X-ray CT (xCT) images of the clinical target. This approach introduces errors into the range calculation, however, due to uncertainties when converting CT Hounsfield units to the water equivalent length (WEL) needed for dose calculations. To mitigate this problem, researchers in Japan have constructed and measured the performance of a proton CT (pCT) imaging system (Phys. Med. Biol. 61 4156).

“Proton CT can provide the image of WEL directly,” explained first author Sodai Tanaka, a PhD student at the University of Tokyo. “A key characteristic of our detection system is the simple measurement system, which enables data acquisition of residual proton energy through an irradiated target within a short time, increasing the possibility of realization.”

The pCT system The proposed pCT imaging system is based on a 20 x 20 x 15 cm plastic kangaroo. The pCT camera consists of a 20 x 20 x 15 cm plastic kangaroo. The pCT camera consists of a large scintillator, made from almost water-equivalent material, and a CCD camera. During imaging, the proton beam passes through the object, generating a projection image of the beam path as it travels through the phantoms. The phantoms are then stoppered by the scintillator, which, in this system design, is thick enough to encompass the range of a 70MeV proton beam. The CCD camera photographs the generated scintillation light integrated along the beam direction and the measured light intensity is then converted to proton beam range using a light-to-range conversion table. Tanaka and colleagues prepared this table in advance of the pCT data acquisition, by irradiating polystyrene objects of various thicknesses.

In a pCT image, WEL is represented by the pixel value. By measuring the proton beam energy before and after the beam penetrates the object, the imaging system creates the sum of the WEL factor along the proton beam path. A pCT image showing WEL distribution can then be reconstructed using a standard method such as filtered back projection (FBP). The researchers tested the pCT system using a 70MeV proton beam, collimated to a field size of 10 x 10cm at NIRs. They first acquired pCT data of images in an acrylic cylinder. The 2D projection image of scintillation light clearly differentiated the container and the water from the surrounding air. WEL values calculated from the pCT image were higher than expected for the container and lower for the surrounding air, slightly blurring boundaries in the image – attributed to multiple Coulomb scattering of the proton beam in the object.

Phantom scans: (top to bottom) PET/CT images of the tofu phantom injected with Zn18O-water and Zn60O-water hydrogels and irradiated by a proton beam, PET and CT images (plus isodose curves on the left).

The researchers note that multiple Coulomb scattering is an unavoidable physical phenomenon. To correct for this in future, they plan to estimate the level of scattering from acquired pCT and xCT images and use these data as feedback to correct the pCT images.

To evaluate the achievable spatial resolution in pCT images of complex shaped objects, the researchers reconstructed an image of a 2 cm plastic kangaroo. The pCT image clearly showed a thin structure of approximately 1 mm, an inner cavity and a thin skin of approximately 1 mm. Comparison with an xCT image showed similar spatial resolution between the two. Finally, to determine pixel values of materials other than water, the researchers reconstructed images of air, 99.5% ethanol and 40% dipotassium hydrogen phosphate solution in the acrylic container. Evaluating the pCT image pixel values by comparing them with the xCT-to-WEL conversion table revealed a maximum error of 8.8%, seen for the dipotassium hydrogen phosphate solution.

Next, the researchers plan to investigate 200 MeV protons, using a thicker (about 63 mm) bismuth germanate (BGO) scintillator. “We are improving the detection system for high-energy pCT,” said Tanaka.

Ground breaking: Varian delivers the cyclotron to HollandPTC in Delft.

Proton centre begins installation

The Zn18O-water hydrogels in the tofu phantom also provided excellent CT visibility, despite containing less zinc. High PET signals were observed for Zn18O-water hydrogels in the Petro dish (attributed to the 18O-water rather than the zinc) and moderate signals for these hydrogels in the wet tofu environment. The researchers suggest that this weaker PET signal may be due to 60O-enriched water leaching out of the hydrogels into the surrounding water.

Investigation is now needed to determine the hydrogel composition or technique that allows injection via smaller-gauge needles. In addition, the low PET signals in the wet environment necessitate PET scans of 1.5 hours. The team’s current work on combining Zn into the hydrogel should help reduce the required scan duration. The researchers are also investigating the use of stronger water-binding polymers, which can hold 18O-water for longer and reduce leaching of 16O into the tissue. “Both projects will reduce the required volume of hydrogel that needs to be injected in patients to achieve acceptable PET signals with a scan time of about 10 minutes,” Cho told medicalphysicsweb.

As well as offering pencil-beam scanning, the most advanced form of proton therapy, HollandPTC will be a key research site feeding into a national program to study and improve the efficacy of protons. HollandPTC business director Rob Florijn adds: “The arrival of the cyclotron is an important milestone in the realization of HollandPTC. Varian has been a great partner in achieving this, as well as joining us in our research efforts towards a new generation of proton therapy.”

Varian’s ProBeam technology is used to treat patients at the Scripps Proton Therapy Center in San Diego, the Maryland Proton Therapy Center in Baltimore, the Rinecker Proton Therapy Center in Munich and the Paul Scherrer Institute in Switzerland. Varian also has contracts for installations at 10 other sites around the world.
An investigation into the implications of variable relative biological effectiveness (RBE) on proton dose across a pencil-beam-scanned spread-out Bragg peak (SOBP) has shown that the absorbed dose calculated using the generic RBE value of 1.1 underestimates the biological effective dose. This is particularly true in fractionation regimes with low doses per fraction. The study, by radiobiologists and medical physicists in the Czech Republic and the UK, has produced an RBE dataset that can be used to optimize fractionated proton therapy (Int J Radiat Oncol Biol Phys 95 70).

The lack of strong radiobiological datasets supported by accurate dosimetry, particularly under fractionation regimes, is one of the primary reasons that a fixed generic RBE (used to correct for differences in radiobiological effectiveness between protons and photons) of 1.1 is employed in proton therapy planning. However, uncertainty in the RBE translates to an uncertainty in the biological effective dose delivered to a patient.

Increasingly, the accuracy of a fixed RBE value is being questioned with respect to its efficacy and safety. With too low a delivered dose, there is risk of cancer recurrence, and with too high a dose, severe toxicities may occur. A fixed RBE during fractionated exposures disregards any effects due to the variation of dose per fraction and the total number of fractions delivered in relation to the linear energy transfer (LET). Utilization of a variable RBE on a fractionated regime may have significant deviations from current clinical assumptions.

The work was part of a collaboration between Queen’s University Belfast and the National Physical Laboratory, with experiments performed at the Proton Therapy Centre in Prague. The researchers investigated the cell killing RBE of various proton fractionation regimes in normal human skin fibroblast cells.

Cell monolayers were exposed with sub-millimetre precision at key positions on a clinical dose profile: at the entrance, proximal, central and distal regions of a SOBP generated by a scanned pencil-beam of maximum energy 219.65 MeV. This represented clinically relevant exposure conditions with a wide range of LET values. The cells received up to three fractions of the same dose per fraction, with an inter-fraction rest period of 24 hours.

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The researchers reported that cell survival curves became consistently steeper towards more distal positions and remained steeper than the X-ray curves for all fractionation regimes. Additionally, when fractionation increased, the level of cell sparing increased across all positions varied along the SOBP, with the most distal positions seeing the least amount of sparing. Cell survival curves effectively overlapped regardless of fractionation regime at the distal position. For all fraction sizes, fractionation of the proximal and central positions allowed significantly more cell sparing than the distal region, where survival curves were significantly steeper.

The authors note that their findings indicate a significant increase in RBE over the acute delivery of protons, where the same total physical doses are delivered in fractionated regimes. They note that exposure to low-LET regions of the SOBP appears to produce cell survival levels similar to that of X-rays.

“The investigation of various fraction sizes has given insight into the challenges in delivering iso-effective treatments when altering fractionation schedules for proton therapy, particularly since RBE varies along the particle path,” explained Prise. “By evaluating cell survival at different SOBP positions, we have further outlined this increase in RBE and its dependency on physical parameters. Our study has further outlined the impact of fractionation on this effect, beyond single exposures.”

The work also highlights the importance of research into biologically relevant dosimetry quantities to optimize radiotherapy by accounting for biological effectiveness in treatment plans. “We believe that our study provides an RBE dataset that can be used by the modelling community for the optimization of fractionated proton therapy,” Prise told multiphysicweb.
Adaptive treatments are increasingly applied in proton radiotherapy, with images acquired during the treat- ment cycle used to evaluate and replan the delivered dose distributions and compensate for any anato- mical changes. The same cannot be said for proton therapy, however. Instead, proton treatments tend to focus on sites where anatomical changes are not expected, such as within the skull, or are designed with beam paths tailored to avoid regions where changes are likely.

But according to Marco Schwarz, from Trento Proton Therapy Center and INFN-TIPPA, this may be about to change. Speaking at the ESTRO 35 conference in Turin, Italy, Schwarz said: “There is currently no framework for treatment adaptation during proton therapy. But we shouldn’t take the current level of adaptive therapy as indica- tive of what’s going to happen over the next few years,” Schwarz told the delegates.

Schwarz explained that treatment adapta- tions considered suitable for proton therapy increase, the need for adap- tive treatments will grow alongwith. Schwarz described an example of a large tumour covering a parallel- responding organs-at-risk. The tumour site exhibited little intrafrac- tion motion and seemed an ideal case for treatment adaptation. However, the lesion was not firmly attached to the bony anatomy and did change over the treatment course – necessi- tating adaptive approaches. Patient anatomy can then change on a scale of days or weeks, due to weight loss or gain, for example, or from day-to-day due to processes such as bladder filling. Tumours can also regress, progress or exhibit changes in functionality. Using imaging to glean new information during a treatment course enables treatment parameters to be modified to suit the latest anatomy. But what is the best way to assess the impact of anatomi- cal changes and determine whether adaptation is needed?

Schwarz first considered pho- ton-based irradiation where, he explained, “we ideally would like to assess the impact on TCP [tumour control probability] and NTCP [nor- mal tissue complication probability], but this is too complicated”. We then look for surrogates, he explained, such as the impact on the delivered dose, for example, but the required recontouring makes this too slow a process. “So instead, we typically determine the impact on the treat- ment geometry, which is feasible.”

The same chain of thought can be applied for proton therapy, but here it is not pos- sible to relate changes in geometry directly to the dose. The finite range of protons makes the dose distribu- tion sensitive to density changes in the beam path that would not affect photons. “The fact that the geometry is fine doesn’t tell you that the dose is fine,” Schwarz explained. “Things are already different in protons.” Ide- ally, he said, we should stop at the dose stage.

Can we borrow from photons? Looking at the imaging tools available in the treatment room, for photons, cone-beam CT (CBCT) represents a compromise between quality and speed, while the available methods of real-time MR guidance will provide clear visualization of anatomical changes during treatment. For proton ther- apy, CBCT is starting to be used, but is reserved for a specific approach. “Is the compromise between image quality and speed of intervention good enough?” Schwarz asked. 

Schwarz emphasized that many tools and techniques developed for adaptive photon therapy cannot simply be transferred to protons. For example, targeting the accuracy of anatomic movement in proton treatments would not work in the same way for protons, where changes in range rather than anat- omymay be important. Margins are also used in proton therapy to address range uncertainties due to CT cali- bration, currently set at 3% for all patients and disease sites. The use of CT-based dosimetry, for example, could help estimate the impact of CT calibration, dose calculation and/or anatomical changes on range for individual patients and treatments. In some instances, photons and protons can employ the same adap- tation approach, but this may need to be performed more often for protons. In other words, some stereo- nary data from a study performed in Aarhus by Ditte Møller and col- leagues, looking at proton therapy of the lung. Comparing the initial plan with plans recalculated at fractions 10 and 20 revealed that 95% cli- nical target volume (CTV) coverage was only maintained in nine of 23 patients studied. In seven patients, 80% or more of the CTV was covered, while seven exhibited CTV coverage of just 45% or more. Such findings clearly show the need for plan adap- tation during treatment, but “do we have technologies to react fast?” Schwarz asked.

Finally, there are adaptive approaches that protons can borrow from photon therapy, but this may be done with care. Schwarz described the use of weekly CBCT to perform adaptive proton therapy, citing a recent study from the University of Pennsylva- nia using on-board CBCT to scan patients prior to each treatment. The workflow involved calculating a fast, range-corrected dose distribu- tion based on a virtual CT generated from CBCT images. A second CT may then be acquired to fine-tune the setup; if not, a more accurate offline dose recalcula- tion was performed on the virtual CT, which can trigger a reacquired CT for replanning.

“Adaptive proton therapy is both a need, to broaden the spectrum of clinical applications, and an oppor- tunity; to fully take advantage of pro- tons,” Schwarz concluded. The big priority now is the development of imaging tools for volumetric image guidance. “The dose is fine, but there is still work to do to have adaptive therapy being routinely used at most proton therapy centres.”

PATENTS

A round up of recent international patent applications.

Rapid scanning conforms dose
US start up Phenis Medical has designed a device for delivering intensity- modulated ion-beam therapy doses that closely conform to tumours of arbitrary shape (WO/2016/019322). The approach uses a series of 2D continuous raster scans of a pencil beam, each taking no more than about 100 ms to complete. The device includes a fast scanning nozzle, coupled to a rastering control system, but the speed of each scan line, continuously vary the beam intensity along each scan line, and execute multiple rescan of a tumour depth layer within a single breathing cycle. The beam delivery system provides millimetre-scale position resolution and feedback to ensure treatment safety and efficacy.

Active phantom offers ion beam QA
Researchers from Brookhaven Science Associates and Phenis Medical have developed an active water phantom for rapid 3D (QA) of intensity-modulated ion beam therapy plans (WO/2016/018122). The detection medium is a tissue-equivalent water- based liquid scintillator (WbLS). The WbLS volume is viewed from three orthogonal sides, to provide simultaneous 2D projections of the scintillation light generated upon ion beam irradiation. A 3D pattern of scintillation light is reconstructed from the 3D profiles, which are read out by a single ion beam energy layer. This 3D information has a dose measurement accuracy of 1-2% and a spatial resolution of 1-2 mm.

Optimization creates robust plans
RaySearch Laboratories has detailed a method for generating treatment plans using scenario-based robust optimization (WO/2016/070938). The aim is to create robust plans for modalities such as particle radiotherapy, where planning using margins is not suitable. The approach considers a set of scenarios, where each represents the uncertainty in one or more treatment planning parameters, and determines mappings of the region-of-interest, including at least one mapping based on each scenario. The overlap of these scenario-specific is determined, and weights are calculated based on the energy overlap. The optimization function is then evaluated over scenarios using at least one of the weights.

Scanner tracks delivered dose
Decision Sciences has developed a charged particle tomography scanner that detects individual particles in an charged particle beam delivered to a patient during therapy (WO/2015/113170). The device includes one detector that detects the trajectory of charged particles entering the patient, and a second at the opposite side to detect the trajectory of particles passing through and exiting the patient. The detectors cover an area at least equivalent to the beam’s cross-section, and their movement is controlled via a motion control unit. A particle tracking algorithm calculates the energy loss of the charged particle beam and maps the radiation dose in the region of interest.
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Bimodal probe finds arterial plaque

Raman and fluorescence lifetime spectroscopy can be combined to form an effective bimodal probe for chemically imaging atherosclerotic plaques, reports a new study by researchers from Germany and the US. If developed clinically, the combined probe may complement existing imaging approaches, helping to inform patient treatment and the development of plaque-stabilizing agents (J. Biophotonics 10:1002/jbio.201500341).

Atherosclerosis is a chronic disease in which artery walls thicken and harden through the accumulation of white blood cells and lipids, forming a plaque. Unstable or “vulnerable” plaques have the potential to rupture, generating dangerous blood clots. “Plaques rich in lipids, or with large lipid pools and a thin fibrocartic cap are more likely to rupture,” explains paper author Laura Marcu, a biomedical engineer at the University of California Davis. “Sudden plaque rupture can result in acute cardiovascular events, and potentially death.”

Traditionally, two modalities are used for in vivo imaging of atherosclerotic plaques: intravascular optical coherence tomography (OCT), which can provide information on plaque morphology; and intravascular ultrasound (IVUS), which is used to determine the size of the plaque core. Information on the nature of plaques can inform therapeutic treatment or help optimize stenting procedures.

Both of these modalities, however, have their complications. While OCT is good for imaging fibrous caps, it has a high false positive rate in the identification of lipids. IVUS can clearly visualize the presence of calcium – which can be an indicator of plaque instability – but has a limited resolution. Together, these techniques are unable to distinguish between lipid and necrotic plaque cores, which is important for identifying unstable plaques and determining the risk of rupture.

In their new paper, Sebastian Dochow of the Friedrich-Schiller University Jena and his colleagues propose that OCT and IVUS might be complemented with a combined fluorescence lifetime imaging (FLIM) and Raman spectroscopy probe to provide specific chemical information on plaque components. To test the potential of these modalities, the researchers developed a dual probe comprising nine 300 µm-thick UV silica/silica fibres – two for FLIM excitation/ collection, and the rest for Raman spectroscopy. They then used the probe to take measurements on two excised human left anterior descending coronary artery specimens. The resulting images from this analysis were then compared with histological analyses of the two artery samples – sorting regions-of-interest into one of seven pathological groups – with reportedly promising results.

The researchers concluded that the significant separation between average cyst fluid and tumour attenuation suggests that it may be possible to distinguish cystic from solid lesions using FLIM – which works by measuring the different decay rates of a fluorescing sample – can quickly create maps of plaque surface composition, and can allow for measurements of lipid to collagen ratios, which can help determine plaque stability. Raman spectroscopy, meanwhile – which exploits the inelastic scattering of light – is more suitable for point measurements and can be used to distinguish between calcifications, caroteneoids, cholesterol and triglyceride deposits in plaques. Together, these techniques can identify features important to plaque characterization, such as the degree of white blood cell infiltration and the presence of necrotic cores, which are important for identifying vulnerable plaques.

With their initial study complete, the researchers are now exploring the application of fluorescence lifetime imaging to in vivo applications, with the aim of working toward a clinical application. At the same time, the team is also working to improve and develop the FLIM probe, which uses a large volume of fluid, to make the probe more flexible.

Commercial system: the Philips MicroDose SI mammography system.

Unenhanced spectral imaging is an emerging X-ray technique that can measure tissue properties without requiring a contrast agent. Unlike standard X-ray imaging – which cannot differentiate a thin, highly attenuating sample from a thicker, less attenuating material – spectral imaging can make this distinction by considering both the absolute attenuation and its energy dependence.

Spectral imaging could potentially be used to distinguish cysts from tumours during breast-cancer screening, helping to address the relatively low specificity of X-ray mammography and reduce recalls. However, the introduction of spectral techniques for this purpose has been hindered by a lack of tissue X-ray attenuation data.

A collaboration between Sweden and the UK has developed a method to measure the energy-dependent X-ray attenuation of tissue using photon-counting spectral mammography. In a previous study, the researchers used this technique to measure the attenuation of cyst fluid (Phys. Med. Biol. 58 8609). Now, they have applied the same approach to solid breast lesions, to establish whether the attenuation differs enough from that of cysts to distinguish the two lesion types (Phys. Med. Biol. 61 2395).

“A spectral mammography system, the MicroDose SI, is already commercially available from Philips and is used in many clinics worldwide,” said Erik Fredenberg, senior scientist at Philips Health Systems in Sweden. “The spectral data produced by the system are accessible to the advanced user, in addition to the spectral applications that are made available by Philips.”

Spectral mammography can be implemented using a sample’s attenuation to equivalent thicknesses of two reference materials – in this study, aluminium (Al) and poly-methyl methacrylate (PMMA). Fredenberg and co-investigators used the MicroDose SI to study five benign and 56 malignant solid breast lesions. During imaging, they positioned a step wedge made of Al and PMMA alongside the sample to provide a reference grid of thickness/material combinations. The sample’s X-ray attenuation can then be determined by mapping the high- and low-energy counts obtained from a region-of-interest (ROI) against those obtained from ROIs on the step wedge.

The researchers acquired spectral images of ROIs in the samples and mapped the signals to equivalent thicknesses of the reference materials. They then plotted the Al-PMMA vector (equivalent PMMA thickness versus equivalent Al thickness) for all solid samples, as well as for previously published cyst fluid and water measurements.

Spot the difference

No significant difference in attenuation was seen between benign and malignant solid breast lesions. However, the attenuation of solid breast lesions (benign and malignant) did differ significantly from that of cyst fluid, in terms of PMMA- and Al-equivalent thicknesses. Solid breast-lesion attenuation also differed significantly from cyst attenuation in terms of the angle of the Al-PMMA vector, which is dependent upon the (effective) atomic number of the sample material, suggesting that the effective atomic number of cyst fluid is slightly higher than that of solid lesions.

The researchers also used the measured PMMA- and Al-equivalent thicknesses to calculate linear attenuation coefficients of the solid breast lesions, for a range of X-ray energies relevant to mammography. Comparing these with previously calculated linear attenuation coefficients for cyst fluid, they found that the difference in density of the cyst was small compared with expected density differences between solid breast and cystic lesions.

“Spectral imaging enriches tissue screening data, with less than 2% difference on average in the 10–40 keV energy interval. However, we note that it is still possible to distinguish between cyst fluid and solid lesions because the shapes of the linear attenuation curves are different (as clearly seen when data normalized to the linear attenuation coefficient of water are plotted).”

Intra- and inter-image variabilities did not differ significantly from the expected quantum noise, indicating that the sample homogeneity in each ROI and system stability were good. Compared with measurements on cyst fluid and water, the spread between different solid samples was relatively large, attributed mostly to natural variation of tumour tissue.

The researchers concluded that the significant separation between average cyst fluid and tumour attenuation suggests that it may be possible to distinguish cystic from solid breast lesions using screening with spectral mammography. These results laid the groundwork for a pilot clinical study, the results of which were published earlier this year (Investigative Radiology 51 340).

“The results of the study were quite promising and led to the foundation of a large multi-site trial, which will most likely be up and running before the end of 2016,” Fredenberg told medicalphysicsweb.
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Creating tissues from textiles

Tissue engineering provides a way to repair or replace damaged tissues, by seeding stem cells on a scaffold. As the cells proliferate and create new tissue, the scaffolding material is gradually replaced, leaving behind the desired tissue.

Nonwoven materials – created by bonding fibres together – show great promise as scaffolds. For tissue engineering applications, they are mostly manufactured by electrospinning, which uses electrostatic forces to draw thin fibres from polymer solutions or melts. The fibres have diameters of several hundred nanometres, similar to natural fibres in the extra-cellular matrix, and provide an ideal environment for cellular growth. Unfortunately, large-scale fabrication of electrospun fibrous scaffolds is time consuming and can result in mechanical properties inferior to the native tissue.

The focus on electrospun nonwoven scaffolds stems from a desire to create the most biomimetic scaffold possible. “However, if we can achieve similar results, in terms of desired cell behaviour, with other manufacturing techniques, many of the hurdles to achieving commercialization might be avoided,” said Elizabeth Loboa, dean of the University of Missouri’s College of Engineering.

With this aim, Loboa and colleagues from UNC-Chapel Hill and NCSU studied three high-throughput nonwoven fabrication techniques: meltblowing, spunbond and carding. These methods offer repeatable and economic production, making them more suitable for translating tissue engineering to the clinic (Biomat. Mater. 1101912).

Meltblowing and spunbond nonwovens are made by forcing molten polymer through fine orifices to create continuous fibre filaments. The filaments are then drawn as a molten state for meltblowing and the solid state for spunbond – and collected on a moving belt to form a nonwoven web. In the carding process, short fibres are separated and entangled by specialized combed rollers to form an unbonded web.

The researchers used the four manufacturing methods to fabricate scaffolds from poly(lactic acid) (PLA) – an attractive material as it is already cleared by the US FDA for certain applications. The scaffolds exhibited varying structures, with average fibre diameters of 1.1, 4.8, 12.8 and 26.9 μm, pore sizes of 2.6, 27.2, 24.0 and 655 μm, and thicknesses of 160.8, 343.2, 562.3 and 965.7 μm, for electrospun, meltblown, spunbond and carded fabrics, respectively.

Each scaffold was seeded with human adipose derived stem cells (hASCs) and cultured in complete growth medium (CGM) for seven days. Some scaffolds were then placed for 14 days in osteogenic (ODM) or adipogenic differentiation medium (ADM).

The cells successfully adhered to all scaffolds, with seeding efficiencies of 84%, 82%, 78% and 64% for electrospun, meltblown, spunbond and carded fabrics, respectively. Live/dead cell staining revealed that all scaffolds supported an increase in viable cells over the first seven days. Cells on electrospun, meltblown and spunbond scaffolds exhibited typical hASC morphology and attached across multiple fibres, while hASCs on carded samples were more elongated and initially attached to single fibres.

At the end of the 21-day experiment, electrospun, meltblown and spunbond scaffolds were uniformly covered in viable cells for all culture media, whereas carded samples showed concentrated cells in regions of fibre overlap, with ingrowth into adjacent pore volumes. All scaffolds exhibited increased hASC proliferation over time, with no significant differences between scaffold types at day 21. At earlier timepoints, however, meltblown and spunbond scaffolds had more viable cells than electrospun and carded scaffolds, attributed to cellular infiltration into the thickness of these scaffolds.

Cell differentiation
On day 21, the researchers investigated the presence of adipogenic and osteogenic cell phenotypes by assessing lipid and calcium accretion, respectively. Oil Red O staining revealed lipid vacuoles in hASCs on all scaffolds cultured in ADM, while Alizarin Red S staining indicated calcium accretion for all scaffolds cultured in ODM.

Quantitative measurements confirmed that all ADM-treated scaffolds exhibited a significant increase in lipids compared to controls, with no statistical differences between fabric types. All scaffolds exhibited a significant increase in calcium content when treated with ODM. Here, no differences were observed between electrospun, meltblown and carded scaffolds, but a small but significant decrease was observed on spunbond scaffolds.

The researchers concluded that nonwoven manufacturing methods can create scaffolds with similar viability, proliferation, adipogenesis and osteogenesis properties to gold-standard electrospun scaffolds.

“We hope that we have demonstrated that there are many nonwoven options for tissue engineering applications and that we are not limited to electrospinning,” said Loboa. “Successful in vivo animal model studies using our materials are the next step to bringing these products to clinical practice.”

Microbubbles drive in the drugs

Scientists at Nanyang Technological University (NTU) in Singapore have invented a way to deliver cancer drugs deep into tumour cells using ultrasound. The technique works by creating micron-sized gas bubbles coated with cancer drug particles and iron oxide nanoparticles, and then using magnets to direct the bubbles to surround a specific tumour.

Next, ultrasound is employed to vibrate the microbubbles, providing the energy to direct the drug particles into a targeted area. This approach may help solve the problems of current chemotherapy drugs, which are largely non-targeted and can damage both healthy and cancerous cells (NPJ Asia Materials e260).

“The first unique characteristic of our microbubbles is that they are magnetic. After injecting them into the bloodstream, we are able to gather them around the tumour using magnets and ensure that they don’t kill the healthy cells,” explained NTU’s Chenjie Xu. “More importantly, our invention is the first of its kind that allows drug particles to be directed deep into a tumour in a few milliseconds. They can penetrate a depth of 30 cell layers or more. This helps to ensure that the drugs can reach the cancer cells on the surface and also inside the core of the tumour.”

The researchers successfully used the microbubbles to deliver drug-containing particles to tumours in mice. They next plan to test their drug delivery system on lung and liver cancer in animal models and, eventually, in clinical studies. They estimate it will take another eight to 10 years to reach human clinical trials.
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Sprayed stem cells tackle gum repair

Left untreated, gum disease can develop into periodontitis, a condition that progressively destroys bone and soft tissue structures surrounding teeth and results in tooth loss. Patients with significant tissue loss may need surgery, including bone and soft tissue grafts.

In situ tissue engineering, where stem and differentiated cells are applied to the damaged area, has the potential to improve treatment as it does not require donated grafts.

Researchers in the US are developing a spray that could eventually deliver such cells into the oral cavity. The technique is less invasive and potentially much quicker than conventional surgery. In their latest work, Wojtek Tutak and Gili Kaufman from the American Dental Association’s Dr Anthony Volpe Research Center and co-authors sprayed viable, multipotent cells using their device (Biomed. Phys. Eng. Express 2035007).

**Novel aerosol brush**
The gas brush or g-brush has a coaxial geometry where culture medium containing the cells is delivered through a 0.41 mm diameter needle by a syringe pump. Carbon dioxide is pumped through an outer annulus that, upon exiting a nozzle, mixes with the liquid. The resulting shear stresses break the liquid into droplets. Spraying the cells in a liquid, the approach differs from existing clinical techniques; treatments for burns and scar tissue use a water-based gel. However, though gels protect the cells upon impact on the wound and provide nutrition, they also have disadvantages.

"Gels physically compress cells, restrict gas diffusion and provide a bio-chemical environment that is different from the environment in the patient’s wound," said Tutak. "Ultimately, all these factors may slow down tissue regeneration." Instead, the researchers’ long-term goal is to simultaneously spray several cell types that are needed to repair periodontal tissues with biomimetic scaffolds and proteins that mimic the oral cavity’s biochemistry.

The researchers sprayed multipotent human bone marrow stromal cells (hBMSC) and mouse gingival fibroblasts (ESK-1) in separate, 0.25 ml “shots” onto plates in as little as 9 s. The cells were cultured for up to 21 days. Quantifying viability with parameters including DNA concentration revealed no significant difference between g-brushing and pipetting, a technique commonly used to place cells on scaffolds and devices before implantation. Higher levels of viable cells were observed when high concentrations were sprayed. The researchers hypothesize that at high concentrations, proportionally less cells are damaged by high shear stresses that occur at the gas-droplet interface.

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"We are very excited about the potential of this technique in clinical use," said Kaufman, but added more basic research was needed before animal studies could begin.

In parallel work, the researchers have observed promising results spraying a biomimetic scaffold that they developed. They are also optimizing their technique to deliver human cells including fibroblasts and epithelial, pulp and periodontal ligament cells. "We want to know whether these cells are viable upon deposition, and if they can be sprayed in sequence, patterned and layered," Tutak told medicalphysicsweb.
Implant restores motion after paralysis

Researchers from Ohio State University and Battelle have restored finger, hand and wrist movements in a paralysed patient for the first time, by using signals recorded from the patient’s motor cortex (Nature 533 247).

Paralysis, which involves disruption of signal pathways between the brain and the muscles, affects millions of people worldwide. Systems that translate neural activity into control signals for assistive devices such as robotic arms have been developed for human patients, and also applied to activate paralysed muscles in non-human primates. Until now, however, no such approach had been shown to work in real-time to restore movement in humans.

In this study, Ali Rezai, a neurosurgeon at Ohio State’s Wexner Medical Center, implanted a microelectrode array in the motor cortex of a 24-year-old patient with a spinal cord injury due to injury of his upper spinal cord and is the first person to use this technology. The electronic device reconnects the brain directly to muscles, bypassing the injured spinal cord, allowing voluntary and functional control of a paralysed limb controlled by the patient’s thoughts. The neural bypass technology combines machine-learning algorithms that decode the user’s brain activity and a high-definition muscle stimulation sleeve that translates neural impulses from the brain and transmits new signals to the paralysed limb to control the activation of forearm muscles.

“We’re showing for the first time that a quadriplegic patient is able to improve his level of motor function and hand movements,” said Rezai. The chip was implanted into Burkhart’s brain in April 2014, after which the researchers worked to determine the correct sequence of electrodes to stimulate in order to allow Burkhart to move his fingers and hand functionally. As part of the study, Burkhart worked for months using the electrode sleeve to stimulate his forearm to rebuild his atrophied muscles so they would be more responsive to electrical stimulation.

Burkhart first demonstrated the neural bypass technology in June 2014, when he was able to open and close his hand simply by thinking about it. Now, he can perform isolated finger movements, as well as six different wrist and hand motions, allowing him to grasp, manipulate and release objects, and significantly improving his quality-of-life. “During the last decade, we’ve learned how to decipher brain signals in patients who are completely paralysed and now, for the first time, those thoughts are being turned into movement,” said study co-author Chad Bouton. “Our findings show that signals recorded from within the brain can be re-routed around an injury to the spinal cord, allowing restoration of functional movement and even movement of individual fingers.”

Although further improvements in the microelectrode technology, the electrical stimulator system and the algorithms are needed to allow these results to be more widely applicable, the authors propose that this work will advance neuroprosthetic technology for people living with the effects of paralysis. “We’re hoping that this technology will evolve into a wireless system connecting brain signals and thoughts to the outside world to improve the function and quality of life for those with disabilities,” said Rezai. “One of our major goals is to make this readily available to be used by patients at home.”

Burkhart is the first of a potential five participants in a clinical study. A second patient is scheduled to start the study in the summer. “Participating in this research has changed me in the sense that I have a lot more hope for the future now,” Burkhart said. “Always did have a certain level of hope, but now I know, first-hand, that there are going to be improvements in science and technology that will make my life better.”

DSSP cleans up biomagnetic data

A new algorithm that removes signal-obscuring interference from biomagnetic imaging data without relying on secondary noise recordings has been developed by researchers from Japan and the US. The technique—known as DSSP (Dynamical Signal Subtraction Process) – has the potential to simplify clinical imaging processes (J. Neural Eng. 13 036007).

Functional electrophysiological imaging comes in many flavours – including electroencephalography, magnetoencephalography (MEG) and magneto-tomography — but all are prone to significant difficulties in the face of interference, which often occurs at magnitudes that are considerable in comparison to the signal-of-interest. While many approaches compensate for these disruptions, they typically rely on secondary measurements designed to record the properties of the interference, such as so-called “empty room” data, resulting in more complicated and often more time-consuming imaging procedures.

Kensuke Sekihara, from Tokyo Medical and Dental University, and colleagues, propose a new solution – the dual signal subspace projection (DSSP) – which estimates the interference subspace as an intersection between two time-domain subspaces – is based on an existing, but different algorithm called temporal signal space separation (ISSS).

On a simplistic level, Sekihara explains, the algorithm works in two stages. First, it creates a pseudo sensor signal in which components coming from the source space (the heart, for example, in the case of cardiac imaging) are suppressed. In this way, the pseudo sensor signal contains only the interference and sensor noise, and not the signal-of-interest. “The second step looks for components that are highly correlated between the original sensor data and the pseudo sensor data,” Sekihara explains. “Such components are identified as the interference”. Once the interference signals have been identified, they can be statistically subtracted from the original image data.

To demonstrate DSSP’s effectiveness, the researchers used the algorithm to successfully remove interference from both simulated and real-life biomagnetic measurements. First, the researchers pitted DSSP against the stimulus-induced artefacts generated in spinal cord evoked field (SCEF) measurements of a healthy patient.

To demonstrate the versatility of DSSP, they also applied their algorithm to a comparable problem found with MEG recordings. When imaging patients with vagal nerve stimulators (VNS) – which use electrical pulses to prevent epileptic seizures – interference from the stimulator implant and its wires can often completely obscure the signal of interest.

Overall, Sekihara says, “the algorithm is effective for removing overlapping interference in a wide variety of biomagnetic measurements”.

Javier Escudero—an engineer from the University of Edinburgh, who was not involved in this study – calls the approach taken with DSSP “interesting”, and notes the potential for the new algorithm to streamline clinical practice. “The most common biomagnetic measurement is MEG,” he notes, adding: “The results of the new algorithm are promising … but further work is needed to demonstrate how well it can eliminate physiologically artefacts in MEG. Until then, tSSS may still have the upper hand.”

With their initial study complete, the researchers are now looking to apply the DSSP algorithm to the removal of the eye-blink and cardiac artefacts also encountered in MEG imaging.

Imaging neural activity in live mice

University of Oregon scientists have looked into the brains of living mice to see in real time the processing of sensory information and generation of behavioural responses. To achieve this, they developed a line of transgenic mice whose brains express a green fluorescent protein that lights up when neurons are activated. They then used a customized wide-field microscope with dual lenses to capture images of the brain.

The technique allows visualization of neural activity across the cortex, the outer surface of the brain. The system also incorporates two-photon imaging, which allows visualization of individual active neurons. By combining wide-field and two-photon imaging, the researchers can study activity from the brain-wide global scale down to the local scale of groups of individual neurons.

The transgenic mice can be followed throughout their lives, enabling study of changes in brain function over extended periods of time. It also opens the possibility to explore brain issues associated with early development, adolescent behaviour, schizophrenia and age-related deterioration of the brain. The researchers compare the technique with functional MRI (fMRI), used for human brain studies. “This is like fMRI but with far greater temporal and spatial resolution,” said author Christopher Niell. “We deliver sensory inputs that trigger decision-making by the mouse. As the inputs are registered and behaviour begins, we can watch the flow of activity across the brain. You see it all in real time, and very quickly, nearly at the speed of thought.”
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