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Review paper

Real-time control of respiratory motion: Beyond radiation therapy

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ABSTRACT

Motion management in radiation oncology is an important aspect of modern treatment planning and delivery. Special attention has been paid to control respiratory motion in recent years. However, other medical procedures related to both diagnosis and treatment are likely to benefit from the explicit control of breathing motion. Quantitative imaging – including increasingly important tools in radiology and nuclear medicine – is among the fields where a rapid development of motion control is most likely, due to the need for quantification accuracy. Emerging treatment modalities like focussed-ultrasound tumor ablation are also likely to benefit from a significant evolution of motion control in the near future. In the present article an overview of available respiratory motion systems along with ongoing research in this area is provided. Furthermore, an attempt is made to envision some of the most expected developments in this field in the near future.

1. Introduction

Control of respiratory motion has been a topic of special interest in radiation therapy (RT) in recent years [1–7]. Such interest was primarily driven by the translation of stereotactic approaches in intracranial applications to anatomic regions affected by respiratory motion, where control over time with a resolution of tens or hundreds of milliseconds is a key factor for treatment success – or at least thought to be such, while more clinical evidence is desired [7]. Undoubtedly, regimes of high dose administered in few fractions proved to be effective to enhance local control rates and – though less dramatically – overall survival, for example, in selected lung tumors [8–12].

Based on the reasonable assumption that smaller irradiated volumes would allow higher dose to be administered while keeping the toxicity to healthy tissues acceptable, major manufacturers of medical technology in radiation oncology have proposed devices for the explicit management of respiratory motion, ranging from long-time available gating techniques [13–17] to sophisticated motion tracking systems. Some of these are already in use [18–20] and others announced but not available yet [21–23]. The rapidly evolving field of particle therapy is also likely to contribute to the development of respiratory motion management techniques, as spatial inaccuracy translates into dosimetric uncertainty in particle therapy more than any other radiotherapy modality [17,24–27].

In the following sections, after a brief review of existing and developing systems and methods devoted to the explicit control of respiratory motion, an attempt will be made to envision how technological developments already in use or facing clinical application in the field of radiation oncology might be translated to support other types of therapeutic procedures and diagnostic examinations.

2. Background

Motion control has been the subject of intense research and development in diagnostic imaging since the appearance of 3D imaging techniques, starting from control and compensation of cardiac motion and continuing with the more challenging problem of respiratory motion and its irregularities [28–30]. When the 3D approach reached radiation therapy, the attempt to compensate for organ motion (in particular, respiratory motion) was soon a field of increased interest. The goal was to improve the spatial accuracy of the calculated and delivered dose distribution, starting a development that has been ever since mostly parallel between the fields of diagnostic imaging and radiotherapy treatment.

Control of respiratory motion in radiation therapy has seen a development and a diversification well described in AAPM Task Group Report 76 [31] and continuing at an even faster rate in recent years [32,33]. By analyzing the existing technology one can see that there are gross distinctions in the fields where the methods are applied (imaging – planning – radiation delivery) and on the strategy behind motion control (breath holding – gating – motion tracking). Some methods can be defined “stand-alone”, meaning that they are not specific to a single radiation therapy system but could be – and in selected cases are – used in other applications, including diagnostic procedures. For example, 4DCT, 4D-PET-CT and respiration-controlled MRI have demonstrated value in reducing motion artifacts, which impacts the diagnostic use of

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such imaging modalities as well as their specialized role in radiation oncology [34–39]. Other methods have the potential to bear a less obvious advantage to diverse procedures. For example, adaptive motion tracking – defined as detection of motion followed by real-time system adaptation - is likely to become a key factor in the use of focused ultrasound (FUS) systems aiming at the thermal ablation of targets that move with respiration (for example liver metastases [40]), as well as in motion-corrected MR abdominal imaging.

Roughly, control of respiratory motion can be divided in two categories: passive and active methods. Passive methods do not make use of explicit actions following the measurement of a respiratory state. A typical passive method in radiation oncology consists of estimating the most probable trajectory of a target object and planning so that the envelope of all positions is likely to be encompassed by the treatment within an acceptable probability level. The translation of passive methods to procedures different from radiation therapy is either trivial or less advantageous compared to active methods, hence only the latter will be analyzed in some detail (though many considerations applicable to active methods might in fact apply to a broader field).

A typical active control of motion is respiratory gating. Gating techniques consist in determining whether a parameter that describes the respiratory state is within a pre-defined window of acceptability, and in taking actions (typically, a binary decision between “beam on” or “beam off”) as a consequence of the measurement [31]. Gating techniques suffer from several drawbacks such as the poor correlation between a descriptive parameter (the “surrogate” signal) and the actual respiratory state [31], and the discretization of the respiratory cycle in finite bins, inevitably causing a residual geographical miss to persist – reduced only at the expense of longer treatment times and poorer duty cycles [41].

Tracking methods were introduced to obviate some of the problems mentioned above. A tracking strategy consists of actively modifying the treatment geometry in real time to conform to the actual breathing phase without losing beam-on time. The most clinically-applied tracking strategy in radiation oncology consists of redirecting the treatment beam by means of a robot [18,20] or of a gimbals-mounted linac [19,42,43]. However, other strategies now seem to be ready for routine clinical application such as couch-tracking [23,44,45] and MLC-tracking [46–49], even though evidence of regular use of such technologies is still missing. While eliminating or reducing problems related to the poor duty cycle, tracking methods suffer from difficult real-time adaptation penalized by relatively long latency times (currently in the range 50–750 ms [1,50,51]). That might cause the treatment to fall off-target frequently, if not adequately accounted for. This drawback (less critical for the simpler gating techniques) led to the development of refined motion models and prediction algorithms [52–54], capable of estimating the position of the target after the latency time and of redirecting the treatment accordingly.

Motion models are used when it is not possible or practical to directly measure the actual motion of interest with sufficient temporal resolution during the intended procedure (e.g. image acquisition or an image-guided intervention). They were first developed with the advent of 3D imaging techniques and radiation therapy applications [55]. Diagnostic imaging was actually the field where the first developments originated [56–58]. However, in the last 15 years research on motion models led to parallel advances in the diagnostic as well as the therapeutic realm. In general, motion models make use of imaging data to build a correspondence between a surrogate signal (external or internal) and the actual position of a structure, be it an organ, an anatomical reference point or a solid tumor. Another characteristic of a motion model is the use of some sort of interpolation to complete sparse imaging data and build an almost-continuous “law of motion”, capable of inferring the organ or tumor position at any instant in time.

From the anatomical standpoint, respiratory motion models have been proposed so far mainly for applications in the lungs, the heart, and the liver. Only few of them have been validated for multiple organs, being in general developed for a specific task involving one of the most common treatment applications that rely on image guidance and therefore require motion control; radiotherapy, minimally invasive cardiac interventions and ablation of liver neoplasms [55].

Models have been developed for imaging as well as treatment procedures [59–61]. In cardiac MRI, for example, the use of respiratory motion models to compensate for motion artifacts began well before radiation therapy applications took the central stage of motion management [58]. However, the scientific literature today shows a parallel development of strategies to compensate for respiratory motion in both diagnosis and therapy domains. The prospected future scenario, tentatively presented in this work, is hopefully a development of mutual benefit between disciplines. The standpoint adopted in this work, of technologies established or – in most cases – subject to ongoing research in radiation oncology and likely to benefit other fields, does not exclude the opposite path, i.e. the transfer of refined systems developed for diagnostic purposes to the realm of radiation therapy, an eventuality most likely to happen in the near future as well but not considered in this analysis.

Motion models applied to radiation therapy need to be more refined than models used for diagnostic purposes in some respects. Radiation therapy generally involves multiple treatment sessions, so that not only short-term variations but also inter-fraction changes occurring on the scale of days or weeks must be accounted for [62]. While this aspect might be of limited importance in imaging procedures, it certainly led to a deeper understanding of respiratory motion and contributed to the improved accuracy of modern motion models. Treatment procedures that rely on image guidance, e.g. thermal ablation by means of radiofrequency or ultrasound, are likely to benefit from the accurate description of complex breathing patterns.

As mentioned above, strategies to compensate for respiratory motion often make use of surrogate signals [55,63]. Surrogates are used to describe the position of soft-tissue structures that cannot be seen directly and/or to describe structures that cannot be tracked in real time due to x-ray dose constraints. The most important features of surrogates are a strong relationship with the true motion to be described and the possibility to be acquired with high temporal resolution. Examples of surrogate signals include the radiographic image of the diaphragm (one of the first surrogates to be used [64]), one-dimensional systems [65,66], 2- or 3-dimensional systems such as optical devices read by a dedicated camera [67], photogrammetry [55], ultrasound imaging [68–70], cone-beam CT projections [71,72] and MRI k-space subsampled methods, generally referred to as “MR navigators” [73,74]. The choice of a surrogate signal depends on the specific problem to be addressed and on the available technology. However, one of the most important aspects to be considered is the accuracy of the correlation between the surrogate signal and the position of the true structure to be tracked, an issue that must always be addressed by a specific quality assurance program.

Image guided procedures that suffer from a finite latency time between imaging and intervention (be it x-ray beam delivery, US focussing or other action) require a motion model able to predict the position of the tracked structure after a time interval at least equal to the latency time [54,75]. Prediction algorithms have been used over the years to estimate the position of an object (more generally: the state of a system) from sparse data [76]. Modern applications in radiation therapy such as treatment tracking by means of robot-mounted and gimbals-mounted linear accelerators rely on such algorithms to maintain a sufficient level of accuracy. It is likely that future image guided interventions other than radiation therapy will benefit from the technology currently under investigation or reaching clinical routine. This prospect will be discussed in the following sections, together with a brief analysis of already available technology, for example in focused ultrasound ablation.

Synthetically, the most advanced methods of explicit control of respiratory motion in radiation therapy are composed in four steps: 1.

detection of a surrogate signal – 2. estimation of the actual target position through a correlation model – 3. prediction of position after latency interval – 4. treatment adaptation (steps 2 and 3 might be simultaneous or exchanged in order) [75]. This scheme possibly forms the basis for the translation of the most refined breathing-motion compensation methods to quantitative imaging and treatment procedures other than radiation therapy. However, it must be noted that motion management is not an established, routine task in radiation oncology yet. For example, the couch-tracking and MLC-tracking methods mentioned before, which are in principle applicable to a relevant fraction of the worldwide installed radiotherapy systems, are still confined to research programs and have not reached the phase of broad clinical applicability yet.

3. Future prospect

Technological development in the field of radiation therapy comes at a cost. Major manufacturers of medical devices have put considerable resources into the development of respiratory motion control systems, driven by the increasing interest in high-accuracy, high-dose techniques. This is witnessed, for example, by the quantity (and quality) of lectures, seminars, courses and talks at international meetings on the topic of motion management. Hence, one of the reasons to foresee the translation of refined motion control techniques to other fields is merely economic: it is likely that manufacturers would leverage on the investment made for radiation therapy systems – which would be quite direct for RT manufacturers also involved in fields different from radiation therapy, and indirect but probably still profitable for firms selling their technology only for diagnostic use.

Other reasons that would favor the widespread application of motion control techniques are the increasing interest in image-based quantitative analysis for diagnostic purposes [77,78] and the emerging non-invasive therapy approaches alternative to radiation therapy (for example, FUS tumor ablation [79–82]).

In the following subsections some applications of respiratory motion control techniques will be analyzed. A tentative division will be made between interventional/therapeutic procedures other than radiation therapy and diagnostic imaging applications. The section will conclude with considerations on the fields where further research is most needed and on the role of the medical physicist in the envisioned scenario.

3.1. Interventional and therapeutic procedures other than radiation therapy

Image guided therapeutic procedures are developing very fast, in parallel to image-guided radiation therapy. Typical examples of image guidance are found in neurosurgery and interventional neuroradiology [83], where the problem of organ motion is negligible or at least an order of magnitude smaller than in typical extracranial sites. However, image guidance has a similar importance in the latter case as well, especially in mini-invasive approaches that require target structure position estimation in real time.

FUS for selected structures ablation heavily relies on image guidance. Targets are so far limited mostly to organs that do not move with respiration (with limitations in the brain as well, mostly because of the problem of loss of coherence of ultrasound waves through the cranium [84]). This is a severe limitation on the potential use of FUS, that might be overcome in the future by the translation of techniques originally developed for radiation therapy to this field. Possible treatments that would benefit from this extension of the applicability of FUS techniques are the ablation of liver metastases or selected pancreas tumors – i.e., treatments of abdominal regions in proximity to the diaphragm or significantly affected by its motion [85].

Studies on respiratory tracking applied to FUS were already reported in the literature ten years ago or earlier [86–88]. Roujol et al. [89] addressed the problem of MRI-guidance from the perspective of both geometric targeting and MR-based thermometry, proposing a deformable registration technique to map MR-based information on a reference anatomical space. MR-thermometry – together with other methods of quantitative imaging – is especially sensitive to respiratory-induced motion. Thermometric errors in the order of several tens of °K were reported as a consequence of a few mm mismatch [90–92]. Pernot et al., De Senneville et al., and Ries et al. report on 3D-tracking systems aimed at redirecting the US beam in real time, to compensate for breathing motion [87,88,93]. Although both methods were positively validated in phantom and ex-vivo, no clinical experience has been reported to date.

FUS techniques might benefit significantly from methods to predict the position of the target and thus compensate for system latency. The adaptation of a FUS beam to moving targets could in principle be made by means of gating or active tracking; both strategies consist of acquiring a descriptive signal, estimating the target position and making the system react to it, either switching the beam on–off or moving an array of transducers (mechanically or electromagnetically) [94]. Such sequence of actions requires time. Although information provided in the literature is still scarce, this time might be roughly in the interval 100–500 ms, depending on the complexity of the solution [95].This is a range similar to the case of latency times in radiation therapy systems [6,7], making this an ideal setting for almost-immediate translation of existing technology to a new field (especially as regards prediction algorithms). However, new difficulties shall be addressed when applying latency compensation to new techniques, like tumor ablation by means of FUS. For example, the use of MRI guidance for adjustment of the focal spot position and for MR-based real time thermometry will probably introduce latency times in the high end of the interval mentioned above.

Other therapeutic procedures that would benefit from an explicit control of respiratory motion are interstitial thermal ablation in oncology and cardiology (hyperthermia and cryoablation) [96,97,98], external-source hyperthermia [99], and targeted drug delivery [100,101] (in some cases performed by means of FUS techniques as discussed above [102]). Most considerations made for FUS techniques and related real-time thermometry remain valid for these fields as well.

Rieke et al. argue that motion is the most relevant problem for MR-based temperature monitoring, which in turn is an essential tool to make any form of focused thermal therapy clinically feasible [97]. Proposed solutions include MRI respiratory gating, navigator echo-based localization systems or a combination of both, however further research is definitely needed to make real-time MR-thermometry effective and practical in the clinical setting. Brost et al. use model-based catheter tracking for respiratory motion compensation during RF thermal ablation-based electrophysiology procedures [98]. Their approach requires imaging of a special circular mapping catheter tracked in 3D to provide real-time information of the position of the pulmonary veins.

A special case where control of respiratory motion is recognized as one of the principal criticalities is thermal ablation of pulmonary neoplasms by means of either radiofrequency, microwave or laser sources [103–105]. One of the strengths of these techniques is their mini-invasivity, making them suitable for outpatient-based procedures or for short hospitalization, and potentially offering higher quality of life to patients. From this standpoint, it is of special importance to be able to account for respiratory motion in real time, with no need for general anesthesia and immobilization. Complications and side effects such as pneumothorax, intraparenchymal hemorrhage and unintentional damage to nearby healthy tissues are also likely to be limited by control of respiratory motion during ablation. Despite the quite obvious advantages that can be envisioned, the scientific literature in this field is still quite limited.

Tumor embolization prior surgery or as a treatment option is gaining interest in recent years, especially in the liver [106]. Although the use of intravascular approaches helps directing the embolization agent to the target, respiratory motion correction is still desired

especially to assist in image-guided procedures and to prevent excessive dose due to imaging [107,108]. From the standpoint of image guidance, motion control might also be a critical factor in the translation to the clinic of modern drug delivery approaches, for example mediated by nanoparticles or liposomes [109–111].

Finally, control of respiratory motion has the potential to become standard of care in interventional procedures such as robot-assisted biopsy [112] and robot-assisted laparoscopy [113], especially in liver surgery [114]. In this field, real-time assessment and compensation of breathing movements can be achieved by means of continuous tracking of a surrogate signal correlated to internal motion via pre-calculated models or by means of real-time ultrasound imaging [115]. Translation of technology originally developed for radiation oncology to these fields is probably likely to occur as well.

These applications share the difficult - still cumbersome in most cases - implementation of real-time control of respiratory motion. If clinical evidence further supports the efficacy of mini-invasive or non-invasive procedures such as the examples above, the technological development of correlated motion control systems will probably parallel the fast development of the therapy systems themselves in the next few years.

3.2. Quantitative imaging

Real-time control of imaging in the presence of respiration is already used in many examinations including CT, MRI and PET-CT. However, the ongoing development of quantitative imaging techniques [77,116] is constantly posing new challenges linked to motion correction and will probably boost the use of explicit control of respiration to account for quantification inaccuracies.

Among imaging procedures, multi-slice CT probably possesses the highest potential – in the immediate future, at least – to provide physicians with quantitative information because of its high 3D resolution and freedom from geometric distortion [117,118]. In fact, quantification relies primarily on correct geometric information (mostly, accurate volume assessment). For this reason, patient motion is one of the most effective causes of quantification inaccuracy: any effort to limit it is likely to have a direct, significant impact on the information provided by quantitative CT. Many examples of techniques aimed at accounting for respiratory motion in CT exist. These include amplitude- or phase-based 4DCT [119], whose development has been mostly driven by the ever-increasing demand for accuracy in radiation therapy imaging techniques. In those problems description of anatomical modifications over several respiratory cycles (or at least one typical respiratory cycle) is increasingly recognized as a factor for possible treatment success. The advantages of 4DCT in diagnostic imaging are less obvious, mostly because the speed of modern scanners enables very fast acquisitions that can be easily performed in one breath-hold: explicit motion correction is therefore less used today in diagnostic CT than in radiation oncology applications. However, residual motion might be underestimated and the physiology of breath holding does not necessarily represent free-breathing states [31]. Therefore, 4DCT and/or different techniques of motion control might reveal themselves of key importance in advanced quantification CT protocols for anatomical sites affected by respiratory movements [120,121].

Nuclear medicine is the field where imaging combined to quantification is the main purpose and the primary source of information. The clinical introduction of PET-CT scanners at the beginning of the 21st century [122] and their rapid development in the following years has allowed physicians to extract ever-increasing information from PET scans in the last decade [123,124]. PET-CT imaging in radiation oncology has been used since the appearance of PET-CT [125,126], and has been subject to development of motion control techniques in parallel to radiation therapy devices [127]. Available motion control techniques today span from gating [128,129] to advanced motion compensation methods based on the analysis and processing of raw data [130–132]. There is a variety of hybrid methods that aim at taking advantage from both approaches [133,134]. While gating suffers from poor signal-to-noise ratio due to the low statistics of binned counts, clinical implementations of methods capable of recovering the full information are still sparse and, frequently, not validated yet. However, methods that allow the whole count statistics to be preserved and used for image formation would enable acquisitions brief enough to be routinely adopted in the clinical setting [135]. These might include methods based on deformable image registration, image reconstruction based on prior-knowledge, and the combination of both [136,137–140], though much work has yet to be done before these techniques become clinically available. The matching between 4DCT and 4DPET data – both for spatial localization and attenuation correction purposes - will also be subject to further study. This point is critical especially in the development of PET-MRI systems [141–144], where motion control for the associated MRI dataset is far from trivial (see also below).

Parallel to the use of PET-CT in radiation oncology, motion control has already started to provide more accurate quantitative information in diagnostic PET-CT [145]. This is of special importance in the quantification of the standardized uptake value (SUV) or other quantitative or semi-quantitative metrics. In fact, motion blurring might act both enlarging the perceived uptake volume and reducing it. Enlargement occurs for example when visual evaluation is adopted, while reduction happens if quantitative criteria such as a SUV threshold are used (other oversimplified quantification algorithms might actually result in the opposite) [146,147]. Hence, volumes estimated based un SUV might be under- or over-estimated as a function of the method used for analysis, while SUV values suffer from underestimation due to motion in general (Fig. 1).

This problem might complicate the diagnostic process and also introduce a potentially dangerous confounding element, if quantification is used for treatment decision [148]. Given the considerations above, it is conceivable that further effort will be put in refining motion control techniques in PET-CT (and PET-MRI) in the future, not only for radiation oncology applications but also for diagnostic purposes [149].

To complete the analysis in the field of nuclear medicine, it's worth noticing that similar developments regard single photon emission computed tomography (SPECT-CT) as well, particularly in perfusion imaging [150].

Motion control in MRI is commonly used in cardiac imaging to compensate for cardiac motion; compensation of breathing movements in anatomical sites that move with respiration is less frequently used in the clinical practice [151]. However, major manufacturers of MRI technology have been equipping their systems with motion control

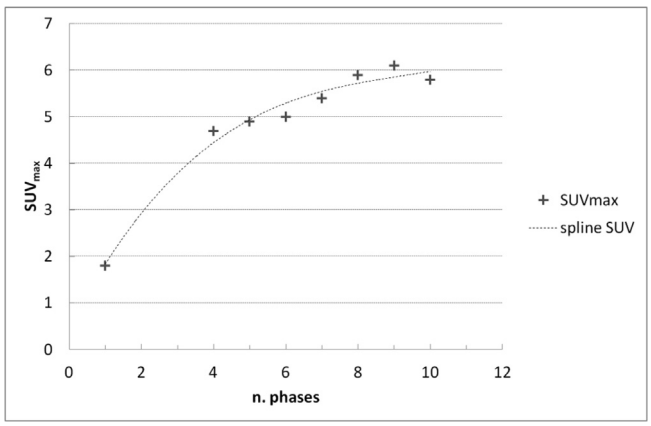

Fig. 1. SUV_{max} as a function of the number of phase bins in gated 4D-PET-CT. Lung nodule with total excursion 18 mm in sup-inf direction − 0.7 ml volume as seen in CT. 1 phase corresponds to non-gated examination. The dotted line shows a cubic spline interpolation (unpublished data).

devices or methods since the introduction of clinical scanners, from strain-gauge belts to pencil-beam excitation used as an internal surrogate signal [152,153]. Third-party manufacturers offer devices to interface to MRI systems and provide respiratory motion control. The use of multi-element coils and parallel imaging is increasingly facilitating the development of motion-correlated MRI [154,155]. Researchers have proposed methods based on image registration and image processing to extract time-series from MRI data [156,157]. Some of the above methods, however, are still cumbersome to use in clinical practice or not commercially available yet. On the other hand, the demand for motion control is implicitly increasing due to the ever-wider use of quantitative methods in MRI, including estimation of parameters related to perfusion, diffusion, oxygenation and concentration of metabolites [158–161]. Those methods were originally developed for the brain [162] and are now increasingly used in full-body applications. Similarly to CT, extraction of accurate quantitative information in MRI cannot be performed without motion control: at least, robust and reliable methods for subtraction and/or comparison of two or more spatially-correlated images are required. As quantification gains importance in routinely-performed examinations, respiratory movements must be accounted for in an ever simpler, more practical way: this will require further research and additional effort by the industry. Given the importance of multi-parametric imaging including several quantification techniques, this will probably happen in the next few years.

A special field were quantitative imaging is increasingly being performed is breast MRI [163–165]. Signal disruption caused by breathing artifacts is definitely an issue in this field, especially when tiny signals must be detected and isolated from the surrounding noise. Literature in this regard is still scarce, but studies exist that point to the direction of a respiratory-compensated image acquisition, especially in the case of multiparametric imaging [166,167].

Respiratory motion is an important source of error in cardiac MRI itself: modern cardiac MRI procedures account not only for cardiac motion through ECG-triggering or gating, but also for respiration [168,169]. Therefore, breath-hold or simple methods for respiratory motion control will probably be rapidly overcome by refined 4D-MRI techniques, especially in examinations that require long acquisition times. It can be imagined that this will be a general trend in cardiac imaging, eventually involving fluoroscopy and angiography as well [170–172].

As in CT and PET, motion control in MRI is recognized as a promising technique for accurate treatment planning and dose calculation in radiation oncology [173,174]. However, 4D-MRI is not widely used in treatment planning yet, but it is conceivable that developments in MRI motion control made for diagnostic purposes will be translated to radiation oncology as well (an opposite trend compared to CT and PET-CT). Multimodality deformable image registration – not an easy task, and still research-demanding before being widely introduced into the clinical practice – today seems the most probable candidate as a tool for the full integration of motion-controlled MRI in treatment planning [175].

Emerging x-ray technology seems to pave the way to real-time tracking techniques in CT and angiography because of the very short delay times potentially available [176–178]. These characteristics might be exploited in gated acquisitions where, thanks to the short system latency, prediction methods would become unnecessary with favourable implications on accuracy. It is not easy to predict whether faster devices or better prediction algorithms will eventually prevail in the chase for real-time tracking, in diagnostic imaging and therapeutic image guidance. However, it is probable that the combination of the two will produce systems that effectively add the temporal dimension to procedures that require high accuracy.

It is recognized that the future of diagnostic imaging will pass through a much stronger integration of modalities compared to the past, including advanced quantification methods. For the reasons mentioned above, motion control is likely to play a key role in the development of integrated techniques. Further development will probably be driven by the need for both diagnostic and therapeutic environments: the tentative separation of the two realms made above is therefore done mostly for the sake of clarity and does not reflect the complex interplay of competences, implementations and experiences that represent an important driving force behind the envisioned scenario.

4. Development strategy

Much research shall be done before control of respiratory motion will become standard of practice in most of the fields mentioned above. Limited to Radiation Oncology, the final part of AAPM TG76 report [31] recommends several topics for future research that apply to non-RT applications as well, including:

- Changes in respiratory patterns between simulation and treatment (more generally: between different phases of a medical procedure);
- relationship between respiration signals and tumor motion and changes in this relationship;
- methods, such as audiovisual feedback, that can improve respiration reproducibility;
- accurate determination of the magnitude of respiratory motion that should be explicitly managed;
- robust deformable image-registration algorithms;
- deformable phantoms to which anatomically accurate respiratory motion can be applied;
- analysis of clinical outcome data in the presence of respiratory motion.

Many of these points apply to non-RT applications as well, together with aspects described in section III. An analysis of the relevant literature and a survey of research and development trends of major manufacturers show that the strategy to implement the prospected changes into clinically usable systems might be found on the following areas:

- Hardware – Technology [179–181]
- Software – Algorithms [182–184]
- Methodology – Framework, including advanced tools for quality assurance [75,185–189]
- Multidisciplinarity – Knowledge exchange [190,191]

Today, the massive use of machine learning is involving the field of respiratory motion management as well as most medical applications. Unsupervised and supervised learning methods are used to predict respiratory motion in short time intervals – a critical factor for systems affected by latency times above 10–50 ms [192,193]. Another important field where machine learning is recently being used is image reconstruction, with possible implications in dose sparing especially when 4D imaging is concerned [194]. Finally, artificial intelligence approaches in general are used in image-guided 4D radiation therapy to fully exploit the information provided by radiographic verification and tumor tracking [195].

Both technological development and refinement of algorithms and methods will probably play an important role in the near future of motion control. However, as well as for radiation oncology applications, assessment of the impact of systems and methods aimed at controlling breathing motion shall eventually include clinical trials able to show the feasibility and efficacy of the proposed strategy.

Medical physicists should play a strategic role in the proposal, development, validation and correct clinical utilization of devices that explicitly control respiratory motion. This has not been part of the “core business” of a clinical medical physicist so far, and there might be valid alternatives to the direct involvement of medical physicists in this field. However, many driving ideas in the management of respiratory motion

in radiation oncology have come from medical physics research and practice. It is likely that the same will happen for emerging non-RT applications, provided that medical physicists will be able and willing to promote themselves in a field where their involvement is not as obvious as in more traditional settings. Many opportunities will probably open up to our profession from the prospected scenario, and medical physicists involved not just in academic research but having also clinical duties should act so that these new opportunities will become part of their cultural and professional background.

5. Conclusion

Control of respiratory motion in radiation therapy has seen an important technological and methodological development in recent years. It is foreseeable that similar advances will come in non-RT applications in the near future, including therapeutic and diagnostic procedures. One of the driving forces behind the predicted evolution will probably be the ever-increasing importance of quantitative imaging, whose accuracy is strongly affected by motion in general and by respiratory movement in particular. Originally applied to brain imaging, most examinations that rely on quantification are increasingly applied to organs that move with respiration.

Medical physicist should play a strategic role in the research, management, clinical use and quality assurance of devices and methods that allow respiratory motion control to be performed. This involvement will contribute to the vast field of non-traditional areas in which Medical Physics will probably find the ground for its future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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