1. Aims

This research is motivated by the need to improve the treatment of lung cancer, the leading cause of cancer death worldwide (18%) with 1.2 million new cases per year.[1] Despite many efforts to improve treatment outcomes the 5-year survival rate is only 16%.[2] Internationally, 36-71% of lung cancer patients (~44% in Australia) receive radiotherapy.[3] More targeted radiotherapy will improve outcomes: a 1-Gy increase in tumour dose is associated with a 4% improvement in survival[4] and a 1-Gy decrease in overall mean lung dose is associated with a 2% reduction in pneumonitis.[5] Achieving simultaneous tumour dose increase and lung dose decrease requires improved image-guided radiotherapy methods. One of the confounding issues for lung cancer is respiratory motion as the tumours typically move 0.5-1 cm and up to 5 cm with breathing.[6]

There has been a continued (over 50%) increase in the adoption of image-guided radiotherapy over the past 10 years.[7, 8] One of the evolving image-guidance methods to account for lung cancer motion during each treatment session, with applications in liver, pancreas and other thoracic/abdominal malignancies, is 1st generation four-dimensional cone beam computed tomography (4D CBCT). The projection images and respiratory signal are synchronously acquired, and post-processed into respiratory correlated phase bins, such as end-inhale, mid-inhale etc. This method was first published on in 2005[9] and commercially available in 2010. However, in the current implementation there is no communication between the respiratory signal and image acquisition. This results in bunched angular projections, with the reconstructed CBCT images suffering from poor image quality and streak artefacts (*Figure 1* left, *Figure 2* middle). The poor image quality limits the use of current images for online guidance and anatomic and functional adaptation.

To overcome the problem of 1st generation 4D CBCT, we have conceived the idea of a 2nd generation 'respiratory modulated' (RM) 4D CBCT system, analogous to our previously US-NIH funded, patented and published work in 4D CT imaging. The innovation of RM 4D CBCT is the respiratory signal actively controls image acquisition resulting in a substantial improvement in image quality. Preliminary data on image quality improvement is shown in *Figure 1*, quantitatively this results in a 3-fold increase in image quality. Our research goal is to develop and investigate RM 4D CBCT.

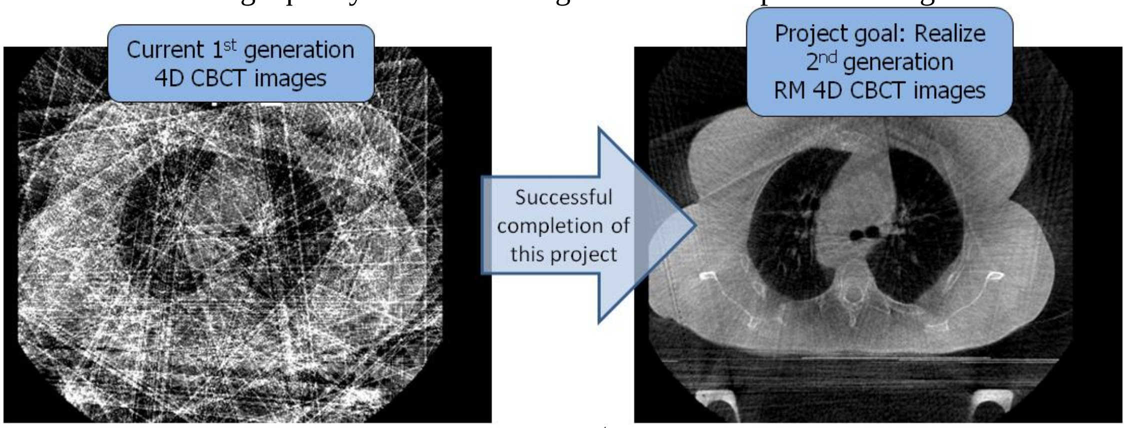

Figure 1. *Our research goal is to transform current 1st generation artefact-filled 4D CBCT images (left) into substantially improved clinically useful images (preliminary data right) by developing and investigating RM 4D CBCT. Note the same amount of data (240 projections) was used to create both images. The images have the same windowing settings.*

To achieve our goal, we will perform the following studies:

Aim 1. Perform ground-truth simulation study: Optimize image acquisition parameters and quantify the improvement in image quality with RM 4D CBCT.

Aim 2. Apply the RM 4D CBCT technique to existing patient image data in a simulation study.

Aim 3. Develop and investigate a clinically usable RM 4D CBCT prototype.

Successful completion of this research will improve the science and clinical practice of lung cancer radiotherapy. RM 4D CBCT will enable (1) identifying and targeting primary lung tumours and positive nodes, (2) identifying and avoiding critical structures, (3) reducing false positives and false negatives during image interpretation, (4) improving rigid and deformable registration algorithm performance to facilitate online corrections and adaptive radiotherapy strategies, (5) reducing margins and (6) facilitating online functional avoidance through CT-ventilation imaging procedures. This project will ensure Australia is at the forefront of technological developments and clinical improvements as the 4D CBCT technique is adopted into clinical cancer centres worldwide.

2. Background

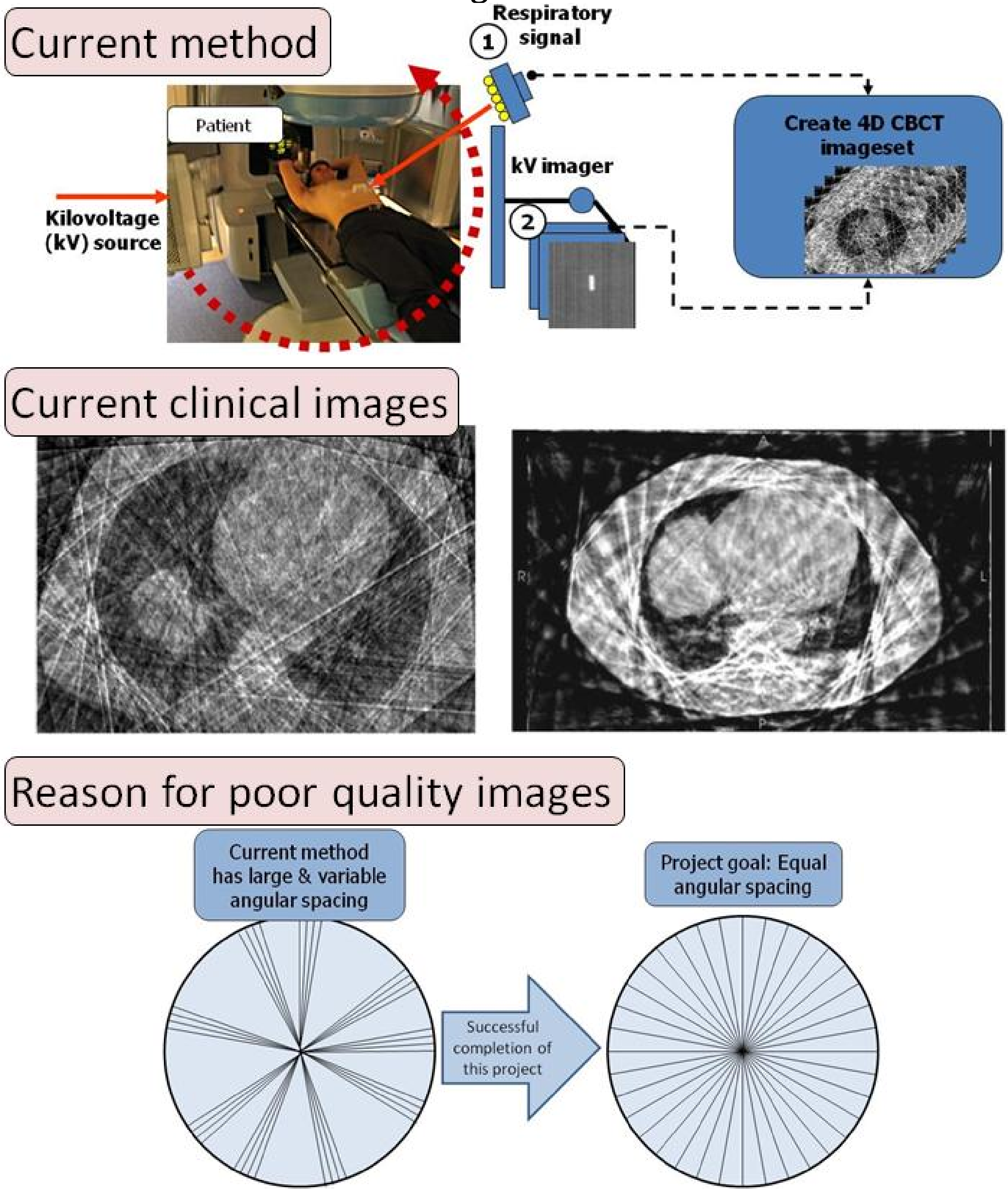

***Figure 2. Top**: in the current 4D CBCT method there is no feedback of the respiratory signal to the imaging system. **Middle**: this limitation causes streak artefacts in clinical images. **Bottom**: the reason for poor quality clinical images[10, 11] is large angular spacing between projections with fixed rotation speed (left). The solution is to obtain equispaced projections by the proposed RM 4D CBCT (right).*

2.1. Rationale for 4D CBCT thoracic and abdominal imaging

CBCT integrated with a linear accelerator is a powerful tool for image-guided radiotherapy. It allows volumetric imaging of the patient prior to treatment to facilitate aligning the radiation beam with the tumour. CBCT was utilised <10% in 2004 growing to >65% in 2009.[8] However, as respiratory motion induces artefacts in CBCT, 1st generation 4D CBCT was developed.[9] 4D CBCT is used to determine the mean position, trajectory and shape of a moving tumour just prior to treatment. This reduces respiration induced geometrical uncertainties, potentially enabling safe delivery of 4D radiotherapy, such as gated radiotherapy, with small margins.

2.2. Problems with current technology

1st generation 4D CBCT suffers from artefacts due to irregularly spaced projections (*Figure 1* left and *Figure 2* middle). The problem is that in a fixed gantry rotation speed, binning of the CBCT projections into breathing phases leads to clustering at those rotation angles where projections for a given breathing phase were acquired and leaves large angular gaps where the patient's breathing is in other phases of the respiratory cycle, as shown in *Figure 2* (bottom). This bunched sampling pattern increases the artefact level in the reconstructed images. Angular projection gaps of ~24 degrees are common. Variations of 3-6 degrees will produce acceptable image quality, so a factor of four improvement is needed. When the same number of cone-beam projections are utilized, streaking artefacts in the case of bunched sampling are much more severe than when using uniform angular sampling.[10] Consequently, significant streaking artefacts are observed in 4D CBCT images.[11-14] An example of these streaking artefacts is shown in *Figure 1* (left) and *Figure 2* (middle). In developing the RM 4D CBCT method, our goal is to regularize the angular separation to reduce or eliminate artefacts.

2.3. Growth of 4D CT and 4D CBCT thoracic imaging

Despite the problems with 1st generation methods, there has been a significant growth in 4D CT imaging since it was first published[15, 16] and clinically released in 2003. In 2009, usage was over 40% with a continuous upward trend. 4D CBCT was first published in 2005[9] and clinically released in 2010. By inference, 4D CBCT imaging will grow at a similar rate to 4D CT, as the same benefits are offered for 4D CBCT at the time of treatment as 4D CT for treatment planning. By developing and investigating 2nd generation RM 4D CBCT, we will be at the forefront of technological developments and clinical image improvements as the 4D CBCT technique is adopted in clinical cancer centres worldwide. A summary of the Chief Investigator A's (CIA's) contribution to the development of 1st and 2nd generation 4D CT and 4D CBCT is given in the Track Record.

2.4. Alternative approaches to improving 4D CBCT image quality

To address the limitations of 1st generation 4D CBCT, other research groups have devised improvements. The details and relationship of other international efforts to our current research proposal are summarized in *Table 1*.

Table 1. *The three key existing/ongoing methods to improve the image quality of 4D CBCT.*

Method and Reference	**Comments**	**Relationship to current RM 4D CBCT proposal**
Multiple gantry rotation/slow gantry rotation[12, 13]	Similar goal- to reduce angular projection spacing- though limited to fixed gantry speed without consideration of patient's breathing regularity or feedback to data acquisition.	Subset of RM 4D CBCT with solutions converging when patient's breathing is perfectly regular. Obviated by RM 4D CBCT.
Prior image constrained	Promising method to reduce artefacts. As prior data is used, can suffer from	PICCS method will be improved with RM 4D CBCT with the

compressed sensing (PICCS)[17]	'model error'. Also limited by truncation artefacts if detector smaller than patient.	projections used as input being equispaced rather than bunched.
Projection interpolation[11, 14]	Only tested on 4D CT data. Requires joint estimation of deformation and projection- deformation unknown at time of 4D CBCT. Problem extrapolating to extreme (end-inhale/end exhale) phases.	If method proves successful, may work in parallel with RM 4D CBCT to reduce the total number of projections needed and therefore reduce patient dose.

Upon successful completion of the research, our future work will involve integrating, as appropriate, the RM 4D CBCT method with one or more of these methods as they (or new methods) evolve. It is also probable that during the course of the research improvements in CBCT reconstruction, such as iterative algorithms[18] and improved physics such as scatter[19] and beam hardening[20] corrections will further improve image quality. The RM 4D CBCT is complimentary to these efforts as, for a given number of projections, maximally equispaced angular sampling maximizes the information variance between projections, as opposed to projections at a small angular spacing where there is more common information contained between projections, meaning that the necessary information for artefact free reconstruction is missing.

3. Research plans

3.1. Respiratory modulated 4D cone beam CT (RM 4D CBCT) method

Our proposed RM 4D CBCT method is shown schematically in *Figure 3*. The respiratory signal (1) and the projection images (2) are input into the two main computational tasks to determine if the respiratory signal is regular (3) and to compute the new gantry trajectory (4). The new gantry position signal and beam on/pause signal is then fed back in real-time to the image acquisition system.

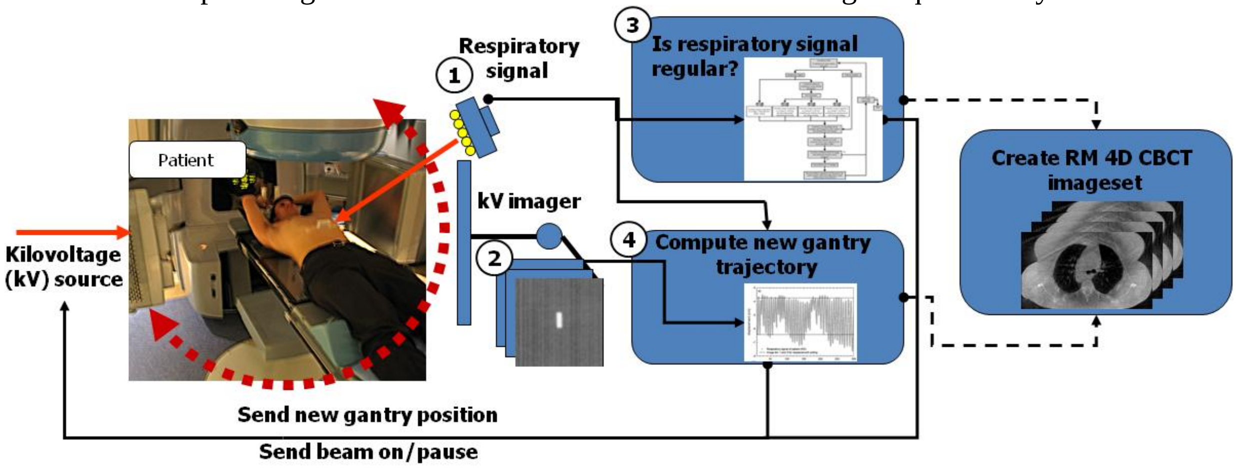

Figure 3. *A schematic of the proposed RM 4D CBCT method in which the respiratory signal is actively used to modulate gantry rotation and image acquisition.*

To investigate and experimentally realise respiratory-modulated 4D CBCT, we will perform the following studies:

3.2. Aim 1. Perform ground-truth simulation study: Optimise image acquisition parameters and quantify the improvement in image quality with RM 4D CBCT

3.2.1. Aim 1.1. Develop an RM 4D CBCT software simulation system, and integrate with existing phantom projection images and a large existing tumour and respiratory motion database

Theoretical framework

Our two main computational tasks are to determine if the respiratory signal is regular (box 3 in *Figure 3*) and to compute the new gantry trajectory (box 4 in *Figure 3*). The method we will use to determine if the respiratory signal is regular is an extension of that developed by the CIA for improving 4D CT images.[21-24] Tolerance values for variability in the breathing displacement period are input, then adapted as necessary to ensure sufficient images are acquired for reconstruction. A 50% reduction in the magnitude and frequency of artefacts is expected over current 4D CT.[24]

To compute the new gantry trajectory (box 4 in *Figure 3*) we can state this problem formally as an optimisation problem. At any time T during the acquisition process, our goal is to find the gantry trajectory that minimizes the expected angular separation for each of the respiratory phase bins. If the acquisition starts at time $t=0$, then given the measured respiratory signal, $\tilde{R}(\phi,t)$, projections acquired, $\tilde{P}(\phi,\theta,t)$ and current gantry angle $\hat{G}(\theta)$, then for future times $\forall t' \in [T,T']$ estimate $\hat{G}(\theta,T+t',H(T+t')):\Delta\theta$ in $P=\{\tilde{P}(\phi,\theta,t),\hat{P}(\phi,\theta,t)\}$ is minimized $\forall \phi \in N$ subject to the mechanical gantry rotational velocity $\dot{G} \in [-\upsilon_{\max},\upsilon_{\max}]$ and acceleration constraints $\ddot{G} \in [-a_{\max},a_{\max}]$. Our first step will be to estimate the respiratory signal $\hat{R}(\phi,t)\forall t' \in [T,T']$. We will perform this using a kernel density estimation (KDE) method[25, 26] that is currently integrated into our real-time DMLC adaptive radiotherapy system. From the respiratory signal, we will calculate the estimated gantry angle trajectory to minimize the angular separation of the projection set for each phase using an appropriate optimization method. The CIA has previously used a number of optimization algorithms to solve radiotherapy problems, including maximum likelihood and least squares.[27, 28] As a fallback, we will use the Sparse Nonlinear Optimisation (SNOPT) system that we use in collaboration with the Stanford Systems Optimisation Laboratory for a separately funded 4D planning project. Note that for Aims 1 and 2 there is no need for the solution to be computed quickly as these are simulation studies. Given the magnitude of the problem, it is likely to be solved in near real-time if coded in a modern language such as C# and implemented onto modern hardware. The optimization methods,[27, 28] the prediction algorithm[25, 26] and a leaf sequencing algorithm[29] (a direct optimization problem) have all been implemented into a real-time DMLC adaptation system using C#. This demonstrates that we have expertise in implementing fast computation of complex problems.

The estimate of the respiratory signal, and therefore the optimal gantry trajectory $\hat{G}$, at increasing time t' becomes increasingly inaccurate. However, this calculation needs to be repeated as every new respiratory signal or projection is input, so the estimate of the optimal gantry angle trajectory is constantly updated when new information is available.

The image reconstruction occurs as a separate process to the image acquisition. For this task we will use Exxim's Cobra implementation of the Feldkamp-Davis-Kress (FDK) algorithm for 3D cone-beam CT (CBCT) reconstruction.[30] Cobra was used to create the images in *Figure 1*.

We anticipate the software development phase, a robust system set up to perform the large scale simulations described in Aims 1 and 2 and the real-time experimental prototype in Aim 3, will take most of the first year of the research.

Patient imaging databases

Table 2. *The image types and sources used in this project.*

Aim/Study	Image type	Source
1.2 Optimisation study of RM CBCT parameters	Lung phantom CBCT data	Scanned on linear accelerator
2.1 Ground truth study using motion-free patient data	Breath hold CBCT data	7 patient 27 CBCT imagesets from US NCI-supported study
2.2 Ground truth study with motion-inclusive patient computed projections	Projections generated from 4D CT images with respiratory signals	14 patient 14 4D CT imagesets from US NCI-supported study

2.3 Lower-bound performance study with motion inclusive patient measured projections	4D CBCT projections with respiratory signals	14 patient >200 4D CBCT imagesets from US NCI-supported study

Motion databases

For aims 1-3, we need realistic patient motion databases. The CIA has previously acquired three suitable databases:

- Synchronous tumour and respiratory motion data from 143 treatment fractions of 42 abdominal and thoracic lung cancer patients.[31]
- Respiratory motion data from repeat sessions with and without audiovisual biofeedback for 24 lung cancer patients.[32] The audiovisual system has been shown to reduce baseline shifts[33] which may improve the efficacy of both 4D CBCT and RM 4D CBCT (to be investigated as part of this research).
- Respiratory motion data from repeat sessions with and without audiovisual biofeedback for 10 volunteers using an improved audiovisual biofeedback system.[34]

3.2.2. Aim 1.2 Perform a parametric image quality study with acquisition time, projection number and gantry rotation speed as variables for 1st and 2nd generation 4D CBCT, comparing with ground truth fully reconstructed CBCT images. The derived optimal imaging values and their sensitivities will be used for Aims 2 and 3.

After the software development phase of RM 4D CBCT is completed, we will optimise the image acquisition parameters using existing phantom image data for which the geometry and composition is known. We will use two types of phantoms: an image quality phantom, CatPhan, and an anthropomorphic phantom, Rando. As shown in *Figure 4*, the respiratory traces described in §3.2.1 will be used as input to both the RM 4D CBCT method and the conventional method. Whilst looping over all of the respiratory motion inputs, we will perform parametric studies of the respiratory tolerances, number of projections and gantry speed. This study will require high computational power to complete the reconstructions in a timely manner and a large storage system to maintain the acquired images. We will compare RM 4D CBCT and conventional 4D CBCT based on several metrics: signal/noise ratio, contrast/noise ratio, spatial resolution and streak-reduction ratio (SRR). The SRR was proposed by Leng[10], based on computing the total variation of the image as an overall figure of merit.

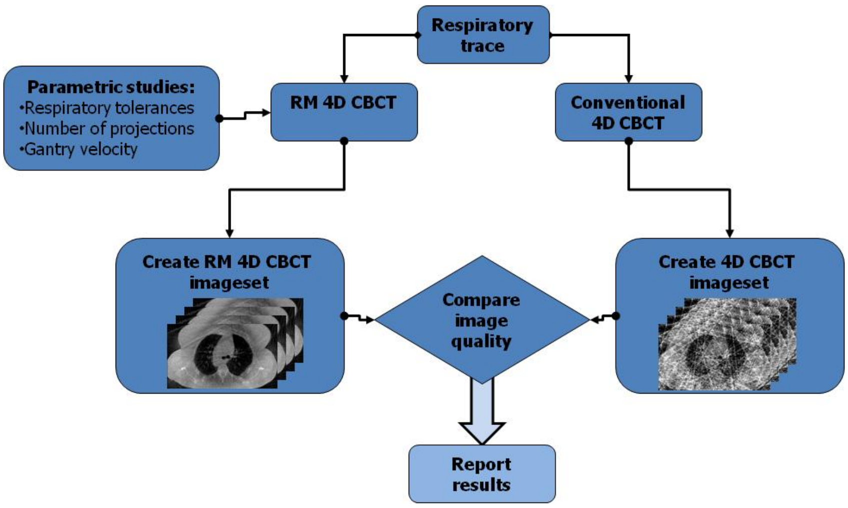

Figure 4. *Flowchart for the method to optimize image acquisition parameters and quantify the improvement in image quality with RM 4D CBCT used in Aims 1 (phantom data), 2 (clinical data) and 3 (prototype experimental data).*

To maintain a fair comparison between RM 4D CBCT and conventional 4D CBCT, we will use the same number of projections corresponding to the same imaging dose to the patient. However, the data will also be available to quantify the patient dose reduction with RM 4D CBCT to achieve the same image quality as conventional methods. Some additional clinically relevant questions we plan to answer are:

- At what angular interval does the spoke artefact become clinically unacceptable?
- How many phase bins are required to reduce intra-phase bin blur (mid in/exhale being the worst) to a clinically acceptable level?
- What is the optimal gantry speed to balance 4D CBCT image quality with patient time on treatment couch?

3.3. Aim 2. Apply the RM 4D CBCT technique to existing patient image data in a simulation study

Until RM 4D CBCT is clinically realised, a patient evaluation is not possible. However, whilst working towards this goal (Aim 3), we can use existing patient breath-hold CBCT, 4D CT and 4D CBCT data to quantify the improvement in clinical image quality with RM 4D CBCT.

3.3.1. Aim 2.1 Perform a ground truth study using motion-free patient data. Compare 1st and 2nd generation 4D CBCT on motion-free (breath hold acquired) patient CBCT data

As motion introduces artefacts in addition to the angular variation of 1st generation 4D CBCT, a study with motion-free (breath-hold) patient data allows the study of the impact of regularizing the angular projections as the single variable parameter. To achieve this aim, we will use the breath hold data described in *Table 2* used and the method of *Figure 4* followed. Common image analysis and comparison is described in §3.2.2.

3.3.2. Aim 2.2 Perform a ground truth study with motion-inclusive patient computed projections. Compare 1st and 2nd generation 4D CBCT from projections generated with existing 4D CT patient data

The impact of motion will be introduced and the RM 4D CBCT method simulated by creating projections from existing 4D CT scans (described in *Table 2*). We will create CBCT projections by constructing the source and detector geometries using an already created voxel traversing program (a fast voxel traversal algorithm for ray tracing) available in the Matlab file exchange. Creating fine angularly-spaced projections will allow both RM and conventional 4D CBCT methods to be simulated for a large number of breathing traces. The 4D CT scans are contoured, which will allow the comparison of target delineation between RM 4D CBCT and conventional 4D CBCT images with the 4D CT ground truth values. Common image analysis and comparison is described in §3.2.2.

3.3.3. Aim 2.3 Complete a lower-bound performance study with motion inclusive patient measured projections. Compare 1st and 2nd generation 4D CBCT from existing 4D CBCT patient projections

Pre-existing 4D CBCT data has fixed gantry angle and respiratory phase/displacement values. Nevertheless, the data acquisition is 8-10 minutes[35] and there is oversampled information as a result. In this study, we will select the closest-available-projections to the desired gantry angle at each phase for RM 4D CBCT using the patient 4D CBCT imageset described in *Table 2*. This study is termed ‘lower bound’ as it represents achievable with today’s technology but not optimised RM 4D CBCT results.

3.3.4. Common analysis for Aims 2.1-2.3

We will perform common analysis for aims 2.1-2.3 and follow the *Figure 4* workflow. We will acquire both RM 4D CBCT and conventional 4D CBCT images for a large number of respiratory trace inputs to allow the results to be generalised to the population. The respiratory tolerances and number of projections will be varied. RM 4D CBCT and conventional 4D CBCT will be compared based on several metrics: signal/noise ratio, contrast/noise ratio, spatial resolution and streak-reduction ratio

(SRR).[10] Dose reduction for the same image quality between RM 4D CBCT will be quantified and the clinically relevant questions answered (§3.2.2).

3.4. Aim 3. Develop and investigate a clinically usable RM 4D CBCT prototype

3.4.1. Aim 3.1 Develop an experimental prototype by integrating the real-time respiratory signal with real-time gantry angle control

By taking the gantry angle reading as input and developing a device to control gantry rotation, we will integrate the RM 4D CBCT software system developed in Aims 1 and 2 to create the first experimental RM 4D CBCT prototype (*Figure 3*). To actualise the motion for the experimental implementation of RM 4D CBCT, we will purchase and use a 4-axis programmable motion phantom available from Washington University.[36] This phantom allows programmable and synchronous 1D respiratory signal and 3D tumour motion to be actuated. The CIA has extensive experience with the phantom during his time at Stanford University. The phantom has been an essential tool in the experimental studies of new real-time tumour localization methods and real-time radiotherapy response methods.[37-40]

Prior to experimental studies, we will determine the system latency using analogous methods to that for real-time DMLC tumour tracking.[39] We will implement the same prediction algorithm used to estimate the future respiratory signal described in §3.2.1[25, 26] to account for the latency.

3.4.2. Aim 3.2 Experimentally quantify the improvement in image quality with 2nd generation 4D CBCT in a clinically realistic scenario by imaging a 4D programmable phantom fed with tumour and respiratory motion data

We will perform an in-depth experimental study using a wide range of respiratory motion data programmed into a motion phantom to compare RM 4D CBCT with conventional 4D CBCT. The respiratory motion data we will use to drive the phantom is described in §3.2.1.

The experimental investigation will parallel the simulation approach taken in Aim 1 (*Figure 4*). We will image an image quality phantom, CatPhan, and an anthropomorphic phantom. We will acquire both RM 4D CBCT and conventional 4D CBCT images for a large number of respiratory trace inputs to allow the results to be generalised to the population. The respiratory tolerances and number of projections will be varied. Note that in the experimental system, the maximum gantry speed is fixed (1 rotation/minute due to IEC) and cannot be changed. This limitation does not apply to freestanding cone beam CT systems or O-ring gantries. This rotational speed limitation is being reviewed by the IEC as new linear accelerator designs are developed with software and hardware collision avoidance systems. Independently of the current limitation, the apparent maximum gantry speed can be simply investigated by scaling the time axis of the respiratory signal used as input to the experimental system, thereby allowing investigation of this important variable.

We will compare RM 4D CBCT and conventional 4D CBCT based on several metrics: signal/noise ratio, contrast/noise ratio, spatial resolution and streak-reduction ratio (SRR).[10] We will quantify dose reduction for the same image quality between RM 4D CBCT and conventional 4D CBCT and answer the clinically relevant questions (§3.2.2).

Table 3. *Estimated timeline to complete project.*

Aim	Year 1	Year 2	Year 3	Year 4	Year 5
1.1 Develop software infrastructure	■				
1.2 Optimise 4D RM CBCT parameters in phantom study		■			
2.1 Ground truth study using motion-free patient data			■	■	
2.2 Ground truth study with motion-inclusive projections			■	■	
2.3 Lower-bound study with patient measured projections				■	■
3.1 Develop experimental prototype		■	■		
3.2 Conduct experimental investigation of 4D RM CBCT				■	■

Project risks

Aims 1 and 2 are simulation studies involving algorithm development, testing and investigation of image quality using three cohorts of existing patient data and existing respiratory motion databases. Therefore, the risk of not being able to complete the tasks is low. Aim 3 involves creating an experimental prototype system by closing the feedback loop of *Figure 3* for an existing linear accelerator. We will try three levels of approaches:

1. Collaborating with a manufacturer. The ideal situation is to work directly with a linear accelerator manufacturer to develop the prototype, during which direct access to the linac gantry control would be enabled in research mode. The CIA has had several successful industrial collaborations with eight different companies that have resulted in scientific articles, IP and commercial licenses. To allow time for legal agreements to be completed prior to the research commencing, early in the project we will approach the two main linear accelerator vendors in Australia, Elekta and Varian, to collaborate.
2. Should the above not be possible or take too long to negotiate, we will reprogram the existing pendant gantry rotation system. The pendant system allows gantry rotation. Using existing engineering diagrams, the gantry rotation circuit can be reprogrammed to receive an external signal input provided from the RM 4D CBCT computer. Spare compatible pendants are available at Canberra Hospital.
3. Our fallback approach is to use a robotically control pendant. This method has been demonstrated in principle by manual gantry adjustment during rotational imaging.

We will obtain the current gantry angle information either directly through direct research access that the CIA has for projects on real-time treatment beam adaptation or by including a USB inclinometer, of which many inexpensive solutions are available.

4. Outcomes and significance

4D CBCT is an emerging commercially available method that will likely become mainstream. Our research aims to develop and investigate our 2nd generation RM 4D CBCT method utilize the respiratory signal to modulate the acquisition to ensure image quality and data sufficiency.
RM 4D CBCT will enable:

1. Identifying and targeting primary lung tumours and positive nodes during treatment
2. Identifying and avoiding critical structures during treatment
3. Reducing false positives and false negatives during image interpretation
4. Improving rigid and deformable registration algorithm performance to facilitate online corrections and adaptive radiotherapy strategies
5. Reducing margins, particularly for stereotactic body radiotherapy trials such at the TROG 09.02 CHISEL trial (http://www.anzctr.org.au/trial_view.aspx?ID=320898),
6. Facilitating online functional avoidance through CT-ventilation imaging procedures.

Our research is aligned with the National Research Priorities *Promoting and Maintaining Good Health, Breaththrough Science* and *Promoting an Innovative Culture and Economy*. The long term goal of our research is to clinically implement the method across major equipment vendors. Successful completion of our research will improve the science and clinical practice of radiation oncology for thoracic and abdominal cancers. In addition, there will be societal and economic benefits from a healthier population (cancer is Australia's leading broad cause of disease burden (19% of the total)[41]) and economic benefits from potential commercialization of the Respiratory-Modulated 4D CBCT concept.

Associate Investigator Contributions

Dr. David Ball is a Professorial Fellow of the University of Melbourne, based at the Peter MacCallum Cancer Centre, with a focus on thoracic radiation oncology. He is the Chairperson for the Trans-Tasman Radiation Oncology Group's CHISEL trial, in which stereotactic body radiation therapy is being compared to conventional treatment in a phase III prospective randomized multicenter clinical trial. Dr. Ball's role on this project is to augment the quantitative image quality comparisons of respiratory modulated 4D CBCT to conventional 4D CBCT with a qualitative critical assessment based on his vast experience in thoracic image-guided radiation oncology.

Mr. Ben Cooper is a Ph.D. student at the University of Sydney. He is also an ACPSEM-accredited Medical Physicist at The Canberra Hospital. The hospital has allocated protected time to pursue his Ph.D. for this project and supports collaborative work with world-class leaders in Medical Physics that will ultimately improve cancer patient care in Australia and beyond. Mr. Cooper, who has adapted the reconstruction algorithm leading to the preliminary data for this proposal, will continue to contribute to the theoretical developments, simulation studies and implementation of experimental phantom studies investigating respiratory modulated 4D CBCT.

Dr. Geoffrey Hugo is an Assistant Professor in the Department of Radiation Oncology at Virginia Commonwealth University. He is the Principal Investigator of the US NIH/NCI grant R01CA116249 "Image-guided Integrated Active Breath Hold Radiotherapy" and has acquired 27 breath-hold CBCT datasets from 7 patients. Part of this data was used for the preliminary research in the application. Dr. Hugo will share his entire database for Aim 2 of the current proposal. In addition, Dr. Hugo has agreed to review and provide feedback on the reconstructed images for RM 4D CBCT and relate these to his clinical experience.

Dr. David Levy is an Associate Professor in the School of Electrical Engineering at the University of Sydney. He has expertise and research interests relevant to this grant in areas of computer engineering, real-time systems and embedded systems. His role on this work will be to assist with the optimal and efficient solution of the theoretical framework proposed in Aim 1.1 and to advise on the design and implementation of the integrated prototype experimental system in Aim 3.

Professor Jeffrey Williamson is the Principal Investigator of an ~$10M US NIH/NCI Program Grant which is developing and investigating new methods to improve the accuracy of image-guided radiation therapy, including lung cancer radiotherapy. Professor Williamson is, along with Dr. Keall, a co-inventor of the respiratory-modulated 4D CBCT imaging method. Dr. Williamson also has expertise and industrial funding for artefact reduction methods in 3D CBCT, which will be synergistic to the image quality improvements proposed here. Professor Williamson will contribute to this project by critically reviewing the formalism, methods, results and image quality achieved with the RM 4D CBCT.

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Professor Paul Keall (CIA)
In 2010 Professor Keall moved from Stanford University, where he was Director of the Radiation Physics Division of the Radiation Oncology Department, to the University of Sydney to take up an NHMRC Australia Fellowship specialising in innovations in radiation physics to improve human health.

Dr. Keall's main scientific interests are in developing image-guided radiation therapy techniques and equipment that take into account anatomic and physiologic changes in healthy and pathologic tissue throughout a radiation treatment course. His work has led to innovative new methods for medical imaging and image-guided radiation therapy, and several of his research creations have been translated into clinical practice. These research activities have resulted in over 140 scientific articles (h-index 35) and several awards and honours. In addition to the Australia Fellowship, his research is currently supported by two US National Cancer Institute grants.

Dr. Keall is an editorial board member for several journals in the radiation oncology field and participates in a number of professional activities and committees of the American Association of Physicists in Medicine (AAPM) and the American Society for Radiation Oncology (ASTRO). In 2009 he was the Scientific Program Director for Radiation Therapy at the AAPM meeting, the world's largest annual medical physics conference. From 2010-2012 he is the Co-chair of the Physics Scientific Program for the ASTRO annual meeting, the world's largest annual radiation oncology conference.

Key contributions to research
Relationship of the proposed 2nd generation RM 4D CBCT with developments in 4D CT imaging and Prof. Keall's involvement/funding of 4D imaging research.

Technology generation	4D CT for treatment planning	4D CBCT for online guidance
1st. No communication between respiratory signal and image acquisition	**Key results:** First developed and published in 2003.[15] Estimated to be used in 50% of cancer centres in 2011.[7] First commercial system available from GE in 2003. **CIA involvement:** Corresponding author of joint 1st paper and 1st with clinical images.[15] Author of first paper on helical multislice 4D CT acquisition. Papers[15, 42] awarded *Phys Med Biol* citation awards in 2007 & 2008 with 208 & 164 citations respectively (to 2/11). **Grant support:** US NIH/NCI R01 93626, Keall CIA	**Key results:** First published by Netherlands Cancer Institute in 2005. First commercial system available from Elekta in 2010. **CIA involvement:** Chief investigator of an adaptive thoracic radiotherapy project based at Virginia Commonwealth University including a clinical imaging study of which daily 4D CBCT is part of the treatment protocol for lung cancer patients.[35, 43] **Grant support:** US NIH/NCI P01 116602, Keall CIA thoracic project
2nd. Respiratory signal actively controls image acquisition	**Key results:** To address artefacts in 90% (45/50),[44] a complete simulation system was developed: 50% reduction in magnitude and frequency of artefacts achieved.[21-24] **CIA involvement:** Mentor and senior author of only work published in this area. US patent awarded 2011. **Grant support:** US NIH/NCI P01 116602, Keall CIA thoracic project	**Key results:** First investigations shown as preliminary data in *Figure 1*. A 3-fold increase in image quality computed (based on least square difference from fully reconstructed image). **CIA involvement:** Project lead. **Grant support:** Proposed in this application

1. *4D thoracic CT imaging*: In 2003 Dr. Keall's group first investigated this method now used by over 44% of radiation therapy centres. 4D CT improves tumour delineation and motion management during cancer treatment of thoracic and abdominal malignancies. Two publications were awarded the 2007 and 2008 Citation Prizes from *Physics in Medicine and Biology*
2. *A method to track three-dimensional target motion with a dynamic multi-leaf collimator*: This work to align the radiation beam with the moving tumour throughout a course of radiation therapy has been developed jointly with Varian Medical Systems. This method is likely to become the standard method of accounting for motion given the widespread availability of the MLC on modern linear accelerators. Five different institutions are performing pre-clinical studies. A US patent has been granted for this technology, with a world-wide patent application submitted for an improved method. One publication was awarded the 2006 Citation Prize from *Physics in Medicine and Biology* (currently 203 citations to 2/11).
3. *Pulmonary function tests using 4D CT*: 4D CT is a technology developed in radiation oncology, and therefore an interesting question is the utility of this method within and beyond the discipline. Using deformable registration with 4D CT can yield an estimate of lung ventilation that is higher resolution, faster and cheaper than current methods of measuring ventilation, such as SPECT. We have a US patent on this method, and are collaborating with Philips Digital Imaging on the clinical validation of this method.
4. *A method for respiratory audio-visual biofeedback for imaging and radiotherapy treatment*: In collaboration with the Music and Design Schools at Stanford we have developed a method to learn a patient's breathing and then use a representative sample of the patient's breathing as a guide with which to match their real time breathing through visual and audio biofeedback. This device is in clinical use at Stanford and Virginia Commonwealth University.
5. *Methods to determine real-time tumour position*: Current modern linear accelerators have three information streams available with which to measure and build estimates of real-time 3D tumour position: optical, kilovoltage and megavoltage imagers. Dr. Keall's group has developed a number of methods to use different combinations of these data streams. Two of the inventions have been licensed to Varian Medical Systems and several US patent applications have been submitted.
6. *A coaxial plasma proton accelerator for radiotherapy*: Proton radiotherapy offers clear advantages with the ability to reduce the radiation dose to normal tissue by a factor of 2-3 compared with x-ray treatments. The limiting factor in the widespread application of proton radiotherapy is the cost: $150M for a proton centre. In this work, funded by the US National Cancer Institute, in collaboration with Mechanical Engineering at Stanford we are developing a compact coaxial plasma accelerator for radiotherapy that could potentially replace x-ray linear accelerators.
7. *MRI-linear accelerator development.* Dr. Keall is the Director of the Australian MRI-Linac program, leading a $7.5M Health and Hospitals Funded project. He is scientifically involved with (1) the inline MRI-linac design (a US patent application has been filed), (2) the effect of the magnetic field on beam generation and methods to overcome these effects, (3) fast MR image acquisition and segmentation for radiotherapy guidance.