Clinical necessity of multi-image based ($4D_{MIB}$) optimization for targets affected by respiratory motion and treated with scanned particle therapy – a comprehensive review

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Abstract

4D multi-image-based ($4D_{MIB}$) optimization is a form of robust optimization where different uncertainty scenarios, due to anatomy variations, are considered via multiple image sets (e.g., 4DCT). In this review, we focused on providing an overview of different $4D_{MIB}$ optimization implementations, introduced various frameworks to evaluate the robustness of scanned particle therapy affected by breathing motion and summarized the existing evidence on necessity of using $4D_{MIB}$ optimization clinically. Expected potential benefits of $4D_{MIB}$ optimization include more robust and/or interplay-effect-resistant doses for the target volume and organs-at-risk for indications affected by anatomical variations (e.g., breathing, peristalsis, etc.). Although considerable literature is available on the research and technical aspects of $4D_{MIB}$, clinical studies are rare and often contain methodological limitations, such as, limited patient number, motion amplitude, motion and delivery time structure considerations, number of repeat CTs, etc, therefore, the data are not conclusive. In addition, multiple studies have found that robust 3D optimized plans result in the dose distributions within the set clinical tolerances and, therefore, suitable for a treatment of moving targets with scanned particle therapy. We, therefore, consider the clinical necessity of $4D_{MIB}$ optimization, when treating moving targets with scanned particle therapy, is still to be demonstrated.

1. Introduction

For the past several decades, the treatment of moving targets with particle therapy has been pointed out as a challenge due to range dependence [1], [2], [3]. With the introduction of scanned particle therapy (also referring to as pencil beam scanning or spot scanning), the interplay effect becomes a significant concern [4], [5], [6], [7]. Many motion mitigation approaches have been proposed [8], [9], [10], [11], [12] with several being clinically implemented [13], [14], [15], [16].

The aim of radiation therapy treatment, either for static or moving targets, is to provide appropriate target coverage according to dose prescription while minimizing the dose to organs at risk (OARs). The planned dose distribution, especially in the case of moving targets, should be robust with respect to set-up, range, and intra- and inter-fraction anatomical changes. The robustness of a treatment plan should be assessed with respect to the target coverage and normal tissue sparing [17], [18], [19], [20].

Traditionally, uncertainties in radiotherapy have been handled by adding margins. The clinical target volume (CTV) is expanded to a larger planning target volume (PTV), which is irradiated with the prescribed dose. When motion occurs, CTV variations in position, shape and size throughout all motion phases can be considered using different concepts, such as an internal target volume (ITV) [21] or mid-position (midP) / mid-ventilation techniques (midV) [22], [9]. However, the geometrical margin

approach, which is based on the assumption that dose is invariant for set-up uncertainties, has several limitations, especially in scanned particle therapy. Therefore, robust optimization methods have been developed to incorporate uncertainties directly into the treatment planning. Robust optimization refers to the optimization of the dose distribution under the consideration of various uncertainty scenarios. The review by Unkelbach et al. provides a comprehensive overview of robust treatment planning approaches [20].

With more modern centres treating moving targets with scanned particle therapy [14], comprehensive methodologies have been developed to realistically assess the impact of organ motion in clinical practice. In the literature, multiple approaches are referred to as 4D optimization. We will shortly address some of them in the discussion section of this review. Here, we will focus on multi-image-based (MIB) optimization, which is a form of robust optimization where different uncertainty scenarios, due to multiple anatomical variations, are considered via multiple image sets. Moreover, we will focus on the use of MIB optimization in terms of intra-fraction changes due to respiratory motion. In that context, MIB optimization is often referred to as 4-Dimensional (4D) optimization, which considers multiple images, representing different phases of a 4DCT, during the optimization process. To clarify the focus on MIB optimization throughout this review, we will use the abbreviation $4D_{MIB}$ optimization. When considering additional uncertainties, for example in the set-up or range, we will refer to robust $4D_{MIB}$ optimization. It is worth mentioning that $4D_{MIB}$ and robust $4D_{MIB}$ are the only approaches currently available in commercial particle beam treatment planning systems allowing for a consideration of the deforming anatomy during optimization.

To summarize, in this paper we focus on reviewing work that assesses $4D_{MIB}$ optimization for proton therapy in a clinical context. To do so, we (1) give an overview of different $4D_{MIB}$ optimization implementations, (2) introduce different frameworks to evaluate the $4D_{MIB}$ optimization and (3) summarize the existing evidence for the benefit and necessity of using $4D_{MIB}$ optimization clinically.

2. $4D_{MIB}$ optimization implementations

$4D_{MIB}$ optimization implementations can differ in terms of the number of considered images (motion sampling), the optimization approach and the consideration of the delivery time structure.

Number of images / motion sampling

A 4DCT represents the motion present during image acquisition. Depending on the patient, this motion might be representative of the motion during treatment delivery. Sparse motion consideration in $4D_{MIB}$ optimization via 4DCT can range from the inclusion of 4DCT phases representing extreme motion states to an iterative incorporation of all 4D phases, representing periodic regular motion. To

extend the motion information and consider continuous, irregular, and variable motion, different model approaches have been suggested [23], [24], [25]. Figure 1 illustrates different levels of motion consideration.

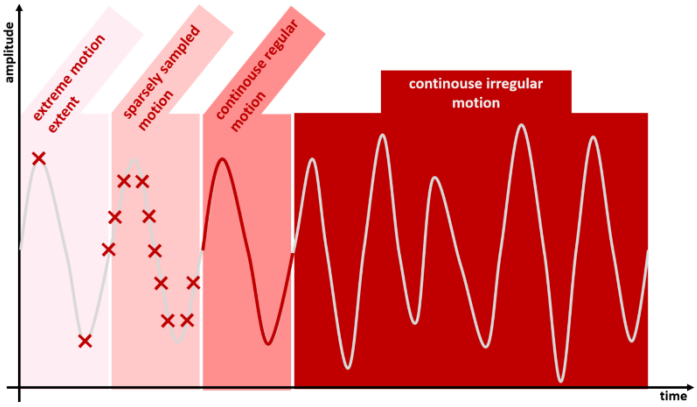

Figure 1: Different levels of motion consideration.

Besides motion consideration solely via CT imaging, motion information can also be taken into account via other imaging modalities. Bernatowicz et al. suggested using four-dimensional computed tomography-magnetic resonance imaging (4DCT-MRI) that combines patient 4DCT with motion information extracted from multi-respiratory cycle 4DMRI [26]. This combination allows the creation of multi-respiratory cycle 4DCTs. Similarly, 4DCT and 4DCBCT information could be combined. Generally, also synthetic 4DCTs based on 4DCBCT could be used to enable daily internal motion consideration [27].

The more images are considered, the more computationally expensive the optimization process becomes, which limits its use in the clinical setting as a standard tool [28]. Currently, the only imaging modality widely supported for particle dose calculation is CT. Both, amplitude- or phase-based methods can be used for 4DCT reconstructions. These methods may lead to different motion artifacts if the acquisition protocol is not optimized for the patient's breathing pattern (down- or over-sampling of the raw data) or if the breathing pattern is not constant during the acquisition [29], [30].

Optimization approach

Mathematically, different uncertainty scenarios can be incorporated into treatment planning in two ways:

(i) The stochastic programming approach optimizes the expected (average) plan quality.

(ii) The minimax approach optimizes plan quality for the worst error considered.

Details for both approaches can be found in [20].

In addition to the uncertainty scenarios due to motion, other uncertainties, such as set-up and range uncertainties, can be considered during $4D_{MIB}$ optimization [11], [31], [32]. These combined optimization approaches are hereafter referred to as robust $4D_{MIB}$ optimization. The consideration of the full motion extent in combination with other uncertainty sources can result in compromises in plan quality due to the consideration of unnecessarily improbable scenarios and can lead to long plan optimization times. Investigators, therefore, have suggested a method to preselect a limited set of relevant treatment uncertainty scenarios to reduce plan computation times and memory consumption, without compromising plan quality or robustness [28], [33].

In the emerging practice of $4D_{MIB}$ optimization, robustness objectives are set against uncertainty scenarios based on good practice rules (straight combination of systematic setup uncertainties of ± x mm and range uncertainties of ± y %). However, the counterpart used in photon therapy, the PTV, is typically based on a quantitative robustness objective, for instance using a margin that ensures target coverage for at least 90% of the patients. Perko et al. and Sterpin et al. have implemented robustness evaluation strategies that also attempt to quantify confidence levels [34], [35]. Research efforts for providing similar features also at the optimization level have focused on developing a probabilistic optimization strategy based on the same statistical objectives as margin recipes [36], [37], [38]. The integration of comparable approaches in commercial treatment planning systems could help to achieve an improved standardization and quantitative comparison of treatment planning strategies.

To accelerate the optimization, Pepin et al. and Shan et al. suggested a GPU-based 4D-dose calculation [39], [25]. In the presence of heterogeneities such as in the thorax, Monte Carlo dose calculation has been shown to be superior to analytical pencil beam algorithms [40], [41]. Additionally, acceleration can be achieved by using GPU-based Monte Carlo engines, which are available in several treatment planning systems today [42].

Delivery time structure

By considering motion via multiple images, $4D_{MIB}$ does not explicitly address the interplay effect. To do so, $4D_{MIB}$ optimized plans need to be combined with rescanning and/or gating. Alternatively, the $4D_{MIB}$ optimization approach may be extended to include the delivery time structure based on simulations. Considering the delivery time structure during the optimization is often referred to as dynamic 4D optimization or staying with our notation as dynamic $4D_{MIB}$ optimization. The delivery time structure of a plan depends on daily parameters and will not be identical between two deliveries of the same plan. Accordingly, simulated time structures cannot predict the delivery time structure of a given plan without any uncertainty. The impact of these variations in the delivery time structure on the results of dynamic $4D_{MIB}$ optimized plans needs further investigation. Possibilities to incorporate

delivery time structure during optimization have been explored [43] but are not available commercially yet.

Frameworks to assess the clinical benefit of $4D_{MIB}$ optimization

When assessing the quality of $4D_{MIB}$ optimized plans, it is important to use a framework that considers all relevant uncertainty sources, specifically motion. Only a limited number of approaches available today can evaluate the impact of the interplay effect. For that, the timing of the motion as well as the time structure of the treatment delivery must be considered. This can, for example, be achieved by calculating dose contributions on images of corresponding motion states, and subsequently accumulating the dose on a reference image, as is illustrated in Figure 2. The beam delivery time structure can be derived from log files or can be simulated as discussed above. In the following sections, we discuss robust 4D dose evaluation and 4D dose reconstruction and accumulation implementations that can assess the impact of the interplay effect.

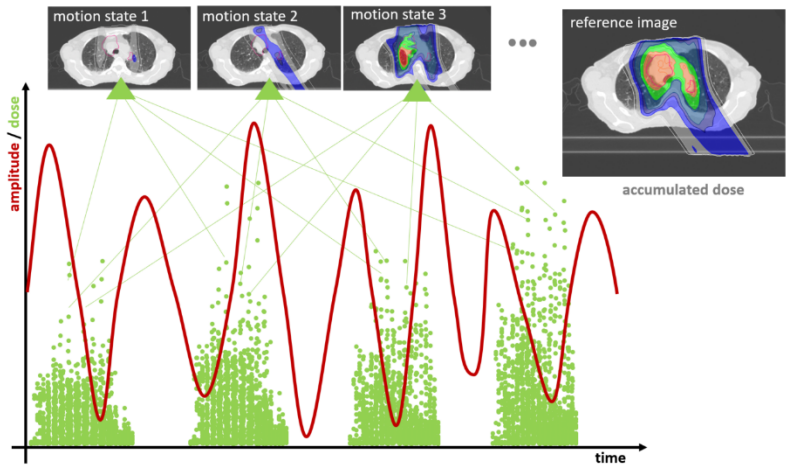

Figure 2: Consideration of the beam delivery time structure.

Robust 4D dose evaluation

Robust 4D dose evaluation allows for a prospective assessment of the treatment quality by re-calculating the treatment plan, assuming different motion and uncertainty scenarios and then analysing the different resulting scenario dose distributions. An early implementation and demonstration of feasibility in the research software TRiP98 was performed by Bert et al. [44]. Furthermore, many groups have implemented and validated a 4D dose calculation routine to prospectively assess the interplay effect by considering simulated delivery time structures [11], [45], [46], [47]. Ribeiro et al. recently developed a more comprehensive 4D robustness evaluation method to realistically and efficiently assess several possible events impacting scanned proton therapy treatments [48]. In this implementation, a combination of interplay patterns, set-up uncertainties,

machine uncertainties, anatomical changes, variations in breathing motion and range uncertainties are considered. Souris et al. [49] developed a comprehensive Monte Carlo based 4D robustness evaluation system, with realistic sampling of systematic and random set-up uncertainties, range uncertainties, and breathing motion, including the interplay effect. Similar work has recently been reported by Shan et al. with irregular breathing motion considered using an analytical dose engine in a GPU-accelerated in-house treatment planning system [25], which makes the real-time robust 4D dose evaluation possible in the routine clinics. The polynomial chaos expansion method developed by Perko et al. [34] enables a detailed analysis of the robustness of a given plan for various values of the uncertainties and could be generalized to 4D dose evaluation. Both of the methods developed by Souris et al. and Perko et al. enable a precise quantification of the confidence levels associated with treatment objectives and constraints [35].

Comprehensive 4D dose evaluation techniques are being implemented in commercial systems via application programming interfaces (API) scripting capabilities. However, more sophisticated 4D evaluation techniques will require highly advanced scripting skills, which are not necessarily broadly available in radiotherapy departments. Therefore, without commercially released 4D evaluation pipelines, implementations and adoption of such tools are highly institution specific.

4D dose reconstruction and accumulation

4D dose reconstruction and accumulation allows for a retrospective dose evaluation considering a specific motion and/or dose delivery scenario. The concept uses a motion signal acquired during dose delivery to assign each delivered pencil beam to a specific motion phase. The delivered dose can then be computed by accumulating the contribution of all beams on a reference phase of a 4DCT [50] using deformable image registration. In clinical practice, the synchronization of the beam delivery records to the motion signal is often challenging, due to closed and not fully integrated systems. Typically, only a single 4DCT is used in clinical practice, whereas for a realistic 4D dose reconstruction, daily updated images would preferably be used. The same type of motion surrogate should be used during 4DCT imaging and dose delivery, and the motion phase assignment of pencil beams should follow the same methodology as the assignment of CT raw data, for example amplitude or relative phase-based algorithms.

Richter et al. studied single fractions and the accumulated dose of a carbon ion therapy treatment course for liver lesions [51]. The reconstructions were based on a single 4DCT for each patient and showed variations in the interplay pattern for shifts of 250 ms between beam records and motion signal. Meijers et al. implemented 4D dose reconstruction and accumulation in a clinical system, in which based on treatment delivery log files and breathing pattern records, dose contributions to

different motion states represented by different 4DCT phases can be calculated and accumulated to obtain an estimate of the delivered dose to a moving anatomy [52]. Early clinical results for scanned proton beam treatments of lung and lymphoma patients showed no clinically relevant loss of target dose homogeneity in the fraction-wise reconstructed 4D dose distributions. Interplay effects smeared out throughout the course of fractionated scanned proton treatment [53], [54] .

In the future, online range estimates from prompt gamma emission or via proton radiography could be included into the reconstruction algorithm. Online image data could be incorporated into 4D motion models to simulate real-time CTs of the moment [55].

As for 4D evaluation, implementations of 4D dose reconstruction and accumulation in commercial treatment planning systems heavily rely on scripting capabilities and require a high level of scripting expertise. Furthermore, the implementation would depend on availability of treatment delivery log files with accurate timing information and ability of the users to parse the log files in order to obtain the relevant information. Formatting of the treatment delivery log files is highly vendor specific.

3. Clinical assessments

ITV-based robust (3D) optimization

Before looking at $4D_{MIB}$ optimization, we give a short overview of studies investigating the adequateness of ITV-based robust (3D) optimized plans for the treatment of moving targets with scanned particle beams. Studies looking at $4D_{MIB}$ optimization often take ITV-based robust (3D) optimized plans as reference. In Table 1, a summary of key parameters of all reviewed ITV-based robust (3D) optimization and $4D_{MIB}$ optimization studies can be found. In Table 2, key conclusions of the discussed papers are summarized.

Liu et al. showed that even though ITV-based worst-case-scenario optimization only considers the geometrical extent of respiratory motion, motion-resistant treatment plans could be produced [56]. However, the study was limited to targets that moved less than 10 mm and the employed evaluation method neglected the influence of the interplay effect. For the same patient data set, Liu et al. found that robust (3D) optimization with a small spot-machine significantly improves heart and esophagus sparing, with comparable plan robustness and interplay effects compared with robust (3D) optimization with a large-spot machine [46]. The use of small-spot IMPT to treat mobile tumors was further supported by comparison studies between IMPT and volumetric-modulated arc therapy (VMAT) in both lung cancer [57] and distal esophageal carcinoma [58]. Both studies showed that small-spot IMPT decreases doses to nearby normal tissues compared to VMAT as well as achieves clinically acceptable plan robustness. Taasti et al. investigated ITV-based min-max optimized plans for lung

tumours with motion amplitudes up to 26 mm [59]. For evaluation, three different robust evaluation approaches were employed, although the investigators did not account for the interplay effect. The proposed ITV-based planning method investigated here was found to provide plans with adequate tumour coverage. Fracchiolla reported on the robustness of ITV plans for two thymoma patients with limited motion. The clinical approved plans passed robustness evaluation considering the interplay effect [60]. Inoue et al. evaluated ITV based 3D robustly optimized IMPT plans considering the interplay effect. When rescanning was employed additionally, these plans did compensate for the impact of set-up and range uncertainties, breathing motion, and interplay effects on target coverage, dose homogeneity, and organ-at-risk dose parameters [61]. They provide robustness against intra-fractional motion with amplitudes < 10 mm. Meijers et al. employed 4D dose reconstructions to investigate the robustness of 3D optimized ITV plans delivered with five times rescanning against interplay effects. For eight lung and two lymphoma patients with a mean motion of up to 2.2 mm and point maximum motion of up to 20 mm, out of 221 reconstructed fractions the dose to the target volume (D98) remained within 5% from the prescription dose, with only 6 fractions being an exception [53]. In these 6 fractions, anatomical changes unrelated to respiratory motion caused dose degradation. In no case did accumulated treatment course dose distributions show major variations from the prescription dose. Evaluations were performed considering weekly repeated CTs.

$4D_{MIB}$ optimization

Compared to an ITV-based robust (3D) optimization approach, robust $4D_{MIB}$ optimization has the advantage of including field-specific, motion-induced range changes while operating on the same target for all fields [62]. Therefore, multiple-field optimization with implicitly defined range margins is possible [63], which otherwise requires complex modifications of the ITV representation [64] and/or density replacements. In the following sections, we will review publications that address the performance of $4D_{MIB}$ optimization in a clinical context.

An exploratory methodology study by Liu et al. showed that compared to robust (3D) optimization, robust $4D_{MIB}$ optimization produced more robust and interplay-effect-resistant plans for targets, with comparable dose distributions for normal tissues [11]. Patient characteristics like target location, size and motion varied largely in the investigated cohort. For most of the patients, the dosimetric differences between robust (3D) and robust $4D_{MIB}$ optimized plans were small with no clear correlation between dose deterioration and any of the patient characteristics. Cummings et al. compared robust (3D) optimized and robust $4D_{MIB}$ optimized plans in seven lung cancer patients [65]. For the robust $4D_{MIB}$ optimization three motion phases (extreme phases and a mid-phase) as well as the average CT were considered. Plan evaluation was performed via dose recalculation on four motion phases of the

planning 4DCT and the corresponding average CT. The robust $4D_{MIB}$ optimization was found to maintain better target dose coverage. For extreme motion phases and for comparisons on a repeated verification 4DCT performed for 2 patients target dose coverage of 3D optimized plans was lower than target dose coverage of robust $4D_{MIB}$ optimized plans. In that study, no motion characteristics for the investigated patient population were reported, and interplay effects were neglected in the evaluation approach. Ge et al. compared PTV-based, robust (3D) optimized and robust $4D_{MIB}$ optimized plans in 10 lung patients with motion up to 12.2 mm and found that robust $4D_{MIB}$ optimized plans had superior clinical target volume coverage and dose robustness compared to PTV-based and robust (3D) optimized plans [66]. This study evaluated the impact of set-up and range uncertainties as well as of motion but also did not assess the impact of the interplay effect. Pfeiler et al. compared non-robust field-specific PTV optimized singe field uniform dose (SFUD) plans with $4D_{MIB}$ IMPT plans in hepatocellular carcinoma and performed 4D dose calculations as a measure for interplay effect [67]. 4D dose calculations were performed using an empirical beam time model and assuming constant breathing cycle during the plan delivery. Interplay simulations were performed on the planning 4DCT data set. Pfeiler et al. observed that $4D_{MIB}$ plans compared to non-robust field-specific PTV optimized SFUD plans did not significantly improve target dose homogeneity, but they did spare OARs slightly better for hepatocellular carcinoma cases. Ribeiro et al. compared robust (3D) optimization and robust $4D_{MIB}$ optimization for 20 thoracic tumours with mean motion amplitudes < 10 mm [68]. The employed 4D evaluation method considered the combined effect of set-up and range uncertainties, machine delivery uncertainties, changes in patient anatomy, breathing motion and the interplay effect. In that study it was found that the robust (3D) optimized IMPT plans were robust and clinically suitable for most of the investigated patients. Using a sophisticated 4D evaluation approach, no clinical gain was observed for robust $4D_{MIB}$ optimized plans compared to 3D robustly (3D) optimized plans [68]. In a study presented by Feng et al. 13 distal esophageal carcinoma cases were included [32]. Both, 3D and $4D_{MIB}$ optimized plans were generated to compare the plan quality in terms of target coverage, OARs sparing and robustness against uncertainty scenarios, and interplay effect. The $4D_{MIB}$ optimized plans were superior to robustly 3D optimized plans. As stated by authors, the study had certain limitations, e.g. including only two extreme phases (maximum inhale/exhale) in the $4D_{MIB}$ optimization approach, nevertheless, presenting the suitability of this concept for IMPT treatments with small spots of distal esophageal carcinoma.

For lung cancer patients with multiple lesions, Anderle et al. compared PTV-based, non-robust $4D_{MIB}$ optimized carbon IMPT plans with SBRT plans and showed comparable target coverage and reduced OAR dose for the $4D_{MIB}$ IMPT plans [63]. That study did not perform any robustness evaluation of the plans. For the same patient population, Wolf et al. showed that CTV-based, robust $4D_{MIB}$ optimization

delivers superior plans in comparison to PTV-based, none-robust $4D_{MIB}$ optimization [31]. In that study, the robustness of the carbon IMPT plans was evaluated via dose recalculations accounting for modelled breathing motion and delivery time structures to consider the interplay effects. Siregar et al. compared non-rescanned with rescanned robust $4D_{MIB}$ optimized plans in nine hepatocellular carcinoma patients with motion amplitude between 4 - 15 mm [69]. The evaluation was performed by computing 4D dose distributions based on an empirical beam time model and assuming a constant breathing period. The results showed that rescanned delivery of robust $4D_{MIB}$ optimized plans reduced the impact of the interplay effect to a clinically acceptable level. Mastella et al investigated two different strategies for the treatment of lung cancer patients with pencil beam scanning proton therapy. The authors analysed 4DMIB with the inclusion of all breathing phases in the optimization problem, combined with free-breathing dose delivery, against 4DMIB including 3 breathing phases (the extreme- and mid-phases of the gating window), in combination with gated dose delivery. The 4DMIB-restricted approach provided a better sparing of lung tissue dose, while maintaining the same robustness against inter-fraction variation, and a reduction of the interplay effect in different dynamic conditions [70]. Rana et al. presented a 4DMIB optimization of ten lung cancer cases with the use of volumetric rescanning to evaluate the impact of interplay effect on plan quality [71]. Plans for nine patients were clinically acceptable, with one presenting a minor deviation. In general, the number of repaintings was shown to be patient dependent.

As a proof of principle, Engwall et al. showed that dynamic $4D_{MIB}$ optimization reduces the risk of plan vulnerability to the interplay effect [43]. That study was based on plan comparisons in three lung cancer patients with mean motion up to 12.2 mm. $4D_{MIB}$ and different dynamic $4D_{MIB}$ optimized plans with and without rescanning were compared. Plan evaluation was based on single fraction dose recalculation considering the interplay effect but neglecting other sources of uncertainties.

	Publication	Indication	target motion extend [mm]	# of patients	3D optimization	$4D_{MIB}$ optimization (considering multiple CT images)	3D evaluation	4D evaluation (considering the interplay effect)
ITV-based robust (3D) optimization	**Liu 2015** [56]	Lung	<10	9	(i) IMPT, PTV (ITV+5mm), av. CT (ii) IMPT, ITV, worst-case optimization (set-up 5mm, range ±3.5%), av. CT		(i) Recalculation on extreme 4DCT phases, (ii) Recalculation on all 4DCT phases, (iii) Recalculation on extreme 4DCT phases considering different combinations of set-up and range uncertainties * no repeated images	
	Taasti 2021 [59]	Lung	4-26	16	IMPT, ITV (no density override), minmax optimization (set-up 5mm, range ± 3%), av. CT		Three evaluation strategies using dose recalculations at 4DCT phase, dose warping, dose accumulation and VWmin/max doses * no repeated images	
	Fracchiolla 2019 [60]	Thymoma	<8	2	SFO, PTV obtained from ITV + 5 mm, av. CT used for planning		Worst case evaluation: the plan is calculated on each phase of the 4DCT, the worst calculation is evaluated.	Iinterplay effect evaluation was performed by using log-files data and patient breathing pattern
	Inoue 2016 [61]	Lung	1.8 – 6.5 (mean)	10	IMPT, ITV, minmax optimization (set-up 5mm, range ±3 %), av. CT, rescanning			dose recalculations considering (i) set-up and range uncertainties, (ii) breathing motion, (iii) interplay effects (periodically repeated 4DCTs images with an assumed breathing cycle of 4.5s in combination with modelled delivery time structure) and combinations of (i) and (ii) * no repeated images
	Meijers 2020 [53]	Lung	0.6 – 2.2 (mean)	8	IMPT, ITV (density override for lung patients), minmax optimization robust optimized (set-up 6mm for lung patients / 5mm for lymphoma patients, range ± 3%), av. CT, rescanning			4DCT based dose reconstruction considering synchronized online motion records and delivery log files as well as weekly repeated 4DCT data sets
		Lymphoma	0.9 – 2.1 (mean)	2				
Comparison ITV-based robust (3D) optimization and	**Liu 2016** [11]	Lung	2-15	11	IMPT, ITV, worst-case optimization (set-up 5mm, range ± 3.5%), av. CT	IMPT, CTV, worst-case optimization (set-up, range), all 4D phases* *number of reconstructed phases not given		dose recalculation considering modelled time-dependent spot delivery on periodically repeated 4DCT images to incorporate interplay effect with randomized starting phases of each field per fraction *no repeated images

	Cummings 2018 [65]	*Lung*	*NA*	*7*	*IMPT, ITV (density override), worst-case optimization (set-up 5mm, range 4%), av. CT*	*IMPT, CTV, worst-case optimization (set-up 5mm, range 4%), three 4DCT phases (extreme motion states and mid-phase) plus average CT*	*Recalculations on four 4DCT phases and the av. CT; for 2 patients recalculation on four phases of a repeated 4DCT and the corresponding av. CT*	
	Ge 2019 [66]	*Lung*	*2.5 – 12.4*	*10*	*(i) IMPT, PTV (ITV (density override) + 5mm), av. CT* *(ii) IMPT, ITV (density override), worst-case optimization (set-up 5mm, range ±3,5%), av. CT*	*IMPT, CTV, worst-case optimization (set-up 5mm, range ±3,5%), ten 4DCT phases*	*Recalculations on ten 4D CT phases considering set-up and range uncertainties* **no repeated images*	
	Pfeiler 2018 [67]	*Hepatocellular carcinoma*	*4-15*	*9*	*Non-robust SFUD, field-specific PTV (2 mm uniform expansion of iCTV, and 2 mm + 3,5% in the beam direction).*	*IMPT, CTV, minimax optimization (2 mm setup, 5% range), ten 4DCT phases*		*Spot sorting based on an empirical beam time model onto phases of a 4DCT. Constant respiratory cycle length. Iteration of starting phase. Phase doses mapped to a reference phase via deformable image registration.* ** no repeated images*
	Ribeiro 2021 [68]	*Lung*	*1.8 - 5.7 (mean)*	*10*	*IMPT, ITV (density override), minmax optimization (set-up 6mm for lung patients / 8mm for oesophagus patients, range ± 3%), av. CT, rescanning*	*IMPT, CTV, minmax optimization (set-up 6mm for lung patients / 8mm for oesophagus patients, range ± 3%), ten 4DCT phases*		*dose recalculations considering the combined effects of set-up and range uncertainties, machine delivery uncertainties, changes in patient anatomy, breathing motion and the interplay effect (periodically used, weekly repeated 4DCT images with an assumed breathing cycle of 5s in combination with delivery time structures based on log-files from dry-run-deliveries)*
		Oesophagus	*3.1 -9.1 (mean)*	*10*				
	Feng 2021 [32]	*Esophageal carcinoma*	*5 – 10 mm*	*13*	*IMPT, ITV worst-case optimization, (set-up 5 mm, range ± 3%), av. CT (density override), iso-layer repainting*	*IMPT, CTV (high4d)/CTV(low4d), (set-up 5 mm, range ± 3%), iso-layer repainting, two extreme respiratory phases used in optimization, no density override; 4D optimization according to Liu 2016*	*Recalculation on the average 4DCT with density override*	*Dose recalculation on extreme phases; the dose on each phase/uncertainty scenario (13, i.e. nominal + 12 perturbed) summed to get 4D accumulated doses; equal weight among 10 phases assumed* ** No repeated images*
$4D_{MIB}$ optimization	***Anderle 2018*** [63]	*Lung (multiple lesions)*	*0.5 – 17*	*8*		*(i) IMPT (carbons), PTV (CTV + 3mm), ten 4DCT phases, rescanning* *(ii) SBRT plans*	** Only dose comparison, no robustness evaluation*	
	Wolf 2020 [31]	*Lung (multiple lesions)*	*0.5 – 17*	*8*		*(i) IMPT (carbons), PTV (CTV + 3mm), ten 4DCT phases, rescanning* *(ii) IMPT (carbons), CTV, worst-case optimization (set-up 3mm, range ± 3.5%), ten 4DCT phases, rescanning*		*dose recalculations considering set-up and range uncertainties in combination with simulated delivery time structures and modelled periodic sinusoidal breathing motion to investigate the impact of the interplay effect* ** no repeated images*

	Siregar 2020 [69]	*Hepatocellular carcinoma*	*4-15*	*9*		*(i) IMPT, CTV, minmax optimization (set-up 2mm, range ±5%), ten 4DCT phases, (ii) (i) with different number of rescannings*	*Dose recalculations considering combinations of set-up uncertainties, range uncertainties and two 4DCT phases (0% and 50%)*	*Spot sorting based on an empirical beam time model onto phases of a 4DCT. Constant respiratory cycle length. Iteration of starting phase. Phase doses mapped to a reference phase via deformable image registration. * no repeated images*
	Mastella 2020 [70]	*Lung*	*(5.0 ± 2.8) (mean ± 1σ) (0.8 – 13.1) range*	*20*		*IMPT (protons), CTV, set-up 3mm, range ± 3%, 5-rescanning i) 10 phases (All breathing cycle) & free-breathing delivery ii) 3 phases included in the gating window (max exhale, 20% exhale, 20% inhale) & gated delivery*		*- Target coverage (D98%, HI), homolateral lung dose (mean, V10%-V20%) - Dose recalculation on two subsequent re-evaluative 4DCTs - end-to-end test on an heterogeneous moving phantom*
	Rana 2021 [71]	*Lung*	*3.8 – 13.2 mm (3D vector LR/AP/SI)*	*10*		*(i) SFUD, CTV, ten 4DCT phases, (set-up 5 mm, range ± 3.5%), (ii) volumetric repainting, no. of repaintings patient dependent*		*Worst-case scenario analysis of each breathing phase with treatment delivery starting in each of ten phases; interplay effect impact evaluation*
dynamic $4D_{MIB}$ optimization	***Engwall 2018*** [43]	*Lung*	*3.7–12.2 (mean)*	*3*		*(i) IMPT, CTV, ten 4DCT phases (ii) (i) with rescanning (iii) (i) considering constant breathing cycle time and a simulated delivery time structure (iv) (iii) with rescanning (v) considering two types of varying breathing cycle times and a simulated delivery time structure (vi) (V) with rescanning * for all plans it is assumed that the delivery is the same in all fractions with a fixed starting phase*		*dose recalculations considering periodically repeated and varying scaled 4DCT images in combination with an assumed delivery time structure * averaging effects due to fractionation were neglected * robustness towards set-up and range uncertainties was not tested * no repeated images*

Table 1: Key parameters of the discussed articles: indication, target motion extent, number of investigated patients, 3D optimization characteristics, $4D_{MIB}$ optimization characteristics, 3D evaluation characteristics, 4D (considering the interplay effect) evaluation characteristics.

	Publication	***conclusion 3D optimization***	***conclusion $4D_{MIB}$ optimization (considering multiple CT images)***
ITV-based robust (3D) optimization	***Liu 2015*** [56]	*Worst-case scenario optimization is superior to PTV-based conventional optimization in terms of plan robustness and optimality. ITV based worst-case-scenario optimization produces motion-resistant treatment plans.*	
	Taasti 2021 [59]	*The ITV-based planning method was found to provide plans with adequate tumour coverage and no OAR overdosage even for large tumor movement.*	

	Fracchiolla 2019 [60]	*The ITV-based planning method was found to provide plans with adequate tumour coverage and no OAR overdosage for small amplitude tumor movement.*	
	Inoue 2016 [61]	*For robustly optimized IMPT for stage III NSCLC, setup and range uncertainties, breathing motion, and interplay effects have limited impact on target coverage, dose homogeneity, and organ-at-risk dose parameters.*	
	Meijers 2020 [53]	*Robust (3D) optimized ITV plans delivered with five times rescanning showed to be robust against motion and interplay effects.* *Accumulated treatment course dose distributions showed no major variations from the prescription dose.*	
Comparison ITV-based robust (3D) optimization and robust $4D_{MIB}$ optimization	***Liu 2016*** [11]		*$4D_{MIB}$ optimization produced significantly more robust and interplay-effect resistant plans for targets with comparable dose distributions for normal tissues than robust (3D) optimization.*
	Cummings 2018 [65]		*$4D_{MIB}$ optimization produced robust plans compared to robust (3D) optimization.* *$4D_{MIB}$ improved target coverage compared to robust (3D) optimization.* *No significant difference in OAR sparing.*
	Ge 2019 [66]		*$4D_{MIB}$ optimization improves the optimality of plans compared to robust (3D) optimization in terms of robustness of target coverage and target dose homogeneity.*
	Pfeiler 2018 [67]		*$4D_{MIB}$ plans compared to non-robust PTV based plans did not significantly improve target dose homogeneity, but did spare OARs slightly better.*
	Ribeiro 2021 [68]	*Robust (3D) optimized IMPT plans were robust and clinically suitable.*	*No clinical gain was observed for robust $4D_{MIB}$ optimised plans compared to robust (3D) optimized plans.*
	Feng 2021 [32]		*4DMIB optimized plans created better target coverage, as well as better sparing of organs at risk and robustness to uncertainties and interplay effect when compared to 3d optimized plans.*
$4D_{MIB}$ optimization	***Anderle 2018*** [63]		*PTV-based, none-robust $4D_{MIB}$ optimized carbon IMPT plans showed similar target coverage and reduced OAR dose when compared to SBRT plans.*
	Wolf 2020 [31]		*CTV-based, robust $4D_{MIB}$ optimization delivers superior plans in comparison to PTV-based, none-robust $4D_{MIB}$ optimization.*
	Siregar 2020 [69]		*Rescanned delivery of robust $4D_{MIB}$ optimized plans reduced the impact of the interplay effect.*
	Mastella 2020 [70]		*$4D_{MIB}$-restricted combined with gating improved normal tissue sparing and was more robust to single fraction deliveries and large motion amplitude.*
	Rana 2021 [71]		*$4D_{MIB}$ optimized plans of ten lung cancer cases with the use of volumetric rescanning to evaluate the impact of interplay effect on plan quality*
dynamic $4D_{MIB}$ optimization	***Engwall 2018*** [43]		*Dynamic $4D_{MIB}$ optimization reduces the risk of vulnerability to the interplay effect compared to $4D_{MIB}$ optimization*

Table 2: Key conclusions concerning robust (3D) optimization characteristics and $4D_{MIB}$ optimization.

4. Discussion

An increasing number of particle therapy centres treat malignant tumors affected by respiratory motion and peristalsis, including thoracic and upper gastrointestinal malignancies. In this review, we summarized findings concerning the clinical application of $4D_{MIB}$ optimization in relation to the clinical application of ITV-based robust (3D) optimization for scanned particle treatments.

Compared with robust (3D) optimization, robust $4D_{MIB}$ optimization allows for consideration of the deforming anatomy due to organ motion during plan optimization. This includes changes in the entrance channels of each field, which are not captured by density replacement strategies. In principle, the inclusion of a priori available motion information should lead to more exact placement of the high dose volume as well as better OAR sparing. The extent of this possible advantage appears to be highly patient specific and dependent on tumour location and motion amplitudes and variability.

Clinical studies investigating $4D_{MIB}$ optimization strategies are still rare and it is important to be aware of their limitations. Conclusions are often based on small patient populations (on average less than 10 patients per indication) that feature particularly limited motion amplitudes and neglect variations in the breathing cycle as well as inter-fractional anatomical changes. Most studies to date are performed for lung cancer patients and some featured plan characteristics that do not comply with clinical standards.

Treatment plans resulting from $4D_{MIB}$ optimization are not inherently superior, as shown by Ribeiro et al. and Pfeiler et al. [67], [68]. $4D_{MIB}$ optimization is often restricted to a few 4DCT phases or a single 4DCT scan as motion surrogate due to computational limits. Several studies have highlighted the impact of variability in the motion patterns on various timescales, during and between treatment fractions [72], [49], [73], [27], [25]. Variations not contained in the 4DCT that exceed either the added margins or the chosen robust $4D_{MIP}$ optimization scenarios may still lead to dose degradation.

One should be aware of the danger of overfitting or rather neglecting motion variations that occur during delivery, which increases with the complexity of the 4D optimization strategy. This danger increases with the complexity of the 4D optimisation strategy. The impact of this requires to be assessed in carefully designed studies that are able to capture the complexity of the clinical situation.

Only a few of the studies investigating $4D_{MIB}$ optimization employ 4D evaluation concepts that consider the full range of uncertainties, including the impact of the interplay effect and anatomical changes as observed on repeated CTs. If delivery time structures are considered, they are often based on simulations rather than on actual delivery logs. Furthermore, the variability of both, the patient anatomy and the respiratory motion have rarely been addressed in 4D evaluations. Meijers et al.

found that failures of robust evaluation in robust (3D) optimized plans were due to anatomical changes, unrelated to respiratory motion.

Some $4D_{MIB}$ optimization implementations as well as 4D evaluation relied on deformable image registration (DIR). Deformation vector fields are subject to discrepancies when different algorithms are applied, leading to dosimetric uncertainties of accumulated dose distributions [74], [75], [76]. The influence of DIR uncertainties on $4D_{MIB}$ optimization and the impact on 4D dose accumulation has not yet been addressed and needs further investigation. However, a major challenge in investigating DIR is the lack of ground truth.

Besides addressing intra-fractional anatomical changes due to respiratory motion, $4D_{MIB}$ optimization has also been proposed to address intra-fractional changes like movements of gas and/or solid contents in bowel, oesophagus, stomach or inter-fractional changes like different bladder and/or rectal fillings [77], [78], [79], [80], [81]. $4D_{MIB}$ optimization and 4D robustness evaluation could improve the robustness against, and assessment of, the impact of such motion for individual patients.

In the literature, the term 4D optimization has been used for a wide variety of different approaches. It is important to distinguish the $4D_{MIB}$ optimization approach from strategies that try to compensate for motion instead of mitigating its effect. Various strategies have been proposed to achieve a conformal delivered dose distribution to moving targets, including delivering a fixed sequence of spots intended to a specific motion phase [82], [26], [83], or delivering in each fraction a library of treatment plans synchronized to the observed motion phase [84], [62]. The former approach results in a single treatment plan that is in principle compatible with conventional delivery systems, but variations in the breathing pattern result in poor synchronization between spot delivery and breathing motion and tend to translate directly into either very inefficient deliveries or dose uncertainties. In contrast, motion-synchronized plan libraries require a dedicated delivery system [85], [86], but they are flexible in the delivery timing and, therefore, robust against variations in breathing period or starting phases. Unfortunately, synchronized delivery is technically challenging in a clinical setting and not available to most of the operational proton centres. In both cases, uncertainties in breathing amplitude or baseline drifts need to be compensated for by margins or robust optimization, similar to an ITV or $4D_{MIB}$ optimization [87]. These strategies likely benefit only patients with large motion amplitudes, but there are currently a lack of studies to demonstrate a possible clinical advantage of such strategies. The implementation of treatment library delivery into the research version of the clinically certified CNAO dose delivery system might help to further investigate this approach under clinical conditions [85]. A detailed discussion and review of these approaches is out of the scope of this review.

From a clinical perspective, the objective of radiotherapy treatments in general and particle therapy in particular is to find a treatment approach that is as efficient as possible and as safe as possible. While the establishment of robust optimized plans is time, labour, and computationally intensive, once approved, robustly optimized plans ideally should decrease the need for subsequent adaptive replans and thus not require further resources throughout the fractionated treatment course. Safety of robustly optimized plans is warranted by their robustness against uncertainties. However, robustly optimized plans, especially when considering a large set of uncertainty scenarios, might not efficiently modulate dose in terms of target dose conformity and normal tissue dose sparing. In practice, the extent of dose distribution quality degradation due to anatomical changes can be significant on a patient-by-patient basis and a priori compensation against such changes may be either unachievable or at the significant cost of plan quality. The most efficient dose modulation may be achieved via real-time adaptive treatment approaches, which, however, are time, labour, and computationally expensive throughout the whole fractionated treatment course. A considerable effort is still needed to realise a clinically efficient and safe treatments of moving targets with scanned particle therapy on a large scale. This includes a high degree of automation, fast and accurate dose calculation engines and large data handling capabilities. What the optimal clinical trade-off between robust optimization and adaptation for moving targets treated with scanned particle therapy will be, and what the role of $4D_{MIB}$ optimization thereby will be, remains to be determined.

5. Outlook / Conclusions

For now, only a relatively small number of papers, generally fraught with methodological limitations (limited patient number, limited motion, limited motion and delivery time structure considerations, limited evaluation approach etc.), have investigated $4D_{MIB}$ optimization for scanned particle treatments of targets affected by respiratory motions. The availability of a consensus on 4D dose evaluation would allow investigators to set up studies in a more consistent and systematic manner, minimizing methodological limitations and inconsistencies. Potential benefits of $4D_{MIB}$ optimization such as higher robustness and higher interplay-effect-resistance of the target dose with comparable normal tissue sparing were reported and compared to robust (3D) optimized plans. However, many studies also found that robust (3D) optimized plans were suitable for treating motion affected targets with scanned particle therapy and resulted in dose distributions within institution-specific clinical tolerances. We therefore conclude that a further investigation of the clinical necessity of $4D_{MIB}$ optimization when treating moving targets with scanned particle therapy is warranted.

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