Estimation of breathing phases during proton radiotherapy from a 4D-CT and Prompt gamma detection profiles

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Abstract

Proton radiotherapy has a potential to provide an effective cancer treatment while sparing greater volume of healthy tissue than the conventional x-ray based radiotherapy. However, in lungs this potential is hindered by motion due to breathing. An important quantity in treatment verification is the correlation between the breathing phases (BP) and the timing of pencil beam scanning (PBS). In this note, we demonstrate how the BP can be estimated using Prompt gamma (PG) detection profiles collected during a treatment. For our analysis, we utilized a 4D-CT of a patient with lung cancer, a treatment plan and a PG simulator. The treatment plan consisted of ten layers corresponding to ten proton energies. The ten BPs of the 4D-CT were interpolated using a deformable registration algorithm, so as to have fifty BPs in total. Deviations from regular breathing was introduced via time dependent frequency modulation. Fifty unique breathing patterns were generated, for which PG profiles were simulated for each pencil beam. In order to simulate the photon statistics, Poisson noise was added to each PG profile. We also computed noiseless PG profiles for each pencil beam passing through each of the fifty BPs. The BPs were estimated by comparing the two sets of PG profiles via three different methods: the BP associated with each layer was estimated 1) independently of the other layers, 2) using a linear correlation between the layers, and 3) using a quadratic correlation between the layers. The best model, the quadratic model, yielded an average error in BP estimation relative to the breathing period of 5% of the breathing period or less with a 90% confidence interval.

INTRODUCTION

Proton radiotherapy can offer better sparing of healthy tissue than a conventional x-ray based therapy. However, a major drawback of using protons over photons is the sensitivity of the former [1, 2] to, e. g. anatomical changes, imperfect conversion between the Hounsfield Units and protons' stopping power [3–5], and setup errors [6]. These sources of error translate into uncertainties in the proton range. In lungs, this problem is magnified by continuous anatomical deformations due to breathing. Therefore, having real-time information about tumor position and its surrounding anatomy is of great value in treating lung cancer with proton therapy.

Techniques involving an external surrogate [7] for instance placed on the skin of the patient, have been suggested to monitor tumor motion; however, the external surrogate may not be perfectly correlated with the actual tumor position because of anatomical changes such as the baseline shift. To overcome this problem, internal surrogates are needed. In this note, we propose to use the Prompt gamma camera (PGC) [8–12] as an internal surrogate of motion.

We investigate the correlations between the PG profiles of the breathing phases (BP) and the timing sequence of pencil beam scanning (PBS) in the presence of two sources of error: PG detection noise and irregularities in the breathing frequency. We show that, on average, such correlations can be estimated within 5% of the breathing period with 90% confidence.

METHODS

Virtual data acquisition

We began with a 4D-CT of a patient with lung cancer, a treatment plan and the the delivery timing sequence of the pencil beams (PB), which was estimated using the ScanAlgo module of the IBA Proton Therapy System [13, 14]. The ScanAlgo is a tool that simulates an ideal irradiation with nominal timing. For the present treatment plan, the timing sequence stipulated by ScanAlgo was such that PBs for a specific energy, from now on referred to as layers, occurred within a few milliseconds, followed by a pause of 2 seconds (plus/minus a few milliseconds). The 4D-CT consisted of ten 3D-CTs, each corresponding to a different BP. The BPs were separated by 0.4 seconds, adding up to a breathing period of 4 seconds. Next, we used a morphon deformable registration algorithm [15] to estimate the deformation field between two successive BPs, thus obtaining four intermediate values of the deformation field. The result was 50 CTs corresponding to 50 BPs separated by $\Delta t = 0.08$ seconds. The treatment plan consisted of 147 PBs grouped into

FIG. 1. Example of regular versus irregular breathing. A) Time versus BPs (left vertical axes) and Δt (right vertical axes). The dots represent the layers for regular breathing (red) and irregular breathing (black). The gray and the dashed lines show the time dependence of Δt for regular and irregular breathing, respectively. B) Example of tumor motion for the breathing error in A. The red line represents regular breathing and is given by the formula $s(t) = s_{exh} - s_0 \sin^4(\pi t/T - \phi)$ [19], where T is the period. The black line represents irregular breathing, given by the sum formula Eq. (1) but with t replaced by $\int_0^t f(x)dx$, which is merely the continuous version of Eq. (1). The variable s appearing on the vertical axes is the absolute value of the distance between the average and instantaneous center of mass of the tumor. s_0 is the amplitude and s_{exh} is s at exhalation. For convenience, the phase ϕ was chosen to be $\pi t_1/T$, where t_1 is the time of treatment initiation.

ten layers. Fig. 1 shows the first BP of the 4D-CT with an overlay of the planned dose distribution. The patient was treated with tomotherapy; the proton radiotherapy plan used here was created for research purposes only.

Next, we introduced breathing irregularities according to the following procedure. If the breathing was regular (no breathing errors), the timing between any two consecutive BPs would be constant, e. i. $\Delta t_0 = 0.08$ seconds. If, however, the breathing was irregular, this time difference would vary as a function of the BPs. If we let n be the integer that labels the BPs, then the relationship between real time and n can be written as:

$$\sum_{m=1}^n \Delta t(m) = t_n, \quad (1)$$

where t_n is the time corresponding to the n^{th} BP. We have chosen Δt to be:

$$\Delta t(n) = \Delta t_0 f(n), \quad (2)$$

where

$$f(n) = 1 + a_1 G(n, \mu_1, \sigma_1) + a_2 G(n, \mu_2, \sigma_2), \quad (3)$$

and $G(n, \mu, \sigma) = e^{-(n-\mu)^2/(2\sigma^2)}$. The range of a_1 and a_2 , was set to $[-0.2, 0.2]$. The parameters μ_1 and μ_2 specify the times at which the errors occur; their range was $[0, 300]$. The parameters σ_1 and σ_2 give the average duration of the breathing error in n -space and both have the range $[10, 50]$.

We generated fifty parameter sets $(a_1, a_2, \mu_1, \mu_2, \sigma_1, \sigma_2)$ sampled from a square distribution according to the aforementioned range of each parameter. Also generated for each case was the start time of the treatment between $t = 0$ seconds and $t = 4$ seconds. As shown in Figure 1, this simple model of breathing errors produces phase shifts in the breathing cycle that are consistent with observations of real patients [16–18].

The BPs corresponding to the 10 layers were then computed according to Eq. (2):

$$n_i = \min \left| \sum_{m=1}^{n_i} \Delta t(m) - t_i^{\text{treat}} \right|, \quad (4)$$

where n_i is the n^{th} BP through which the i^{th} pencil beam passes.

Finally, using an analytical simulation tool based on pre-computed Monte Carlo emission profiles [20], we simulated the PG profiles. This method has been validated by PG measurement studies [9–12]. This was repeated for every one of the 50 cases, where by “case” we mean a unique breathing irregularity and start time. In order to simulate a realistic PG signal, we added Poisson noise to all PG profiles, and repeated the procedure fifty times per case. Thus, for each unique setup and breathing error, we generated fifty “sub-cases,” adding up to 2500 cases in total. We will refer to these profiles as virtual, and label them PG^{virt} .

Simulated data acquisition

We simulated clean PG profiles (no setup errors or Poisson noise) for every pencil beam passing through all fifty BPs. To distinguish them from PG^{virt} , these profiles will be labeled as PG^{sim} . Figure 3 shows eight examples of PG^{virt} (black dots) superimposed over the fifty PG^{sim} (gray curves) for the first layer, which contained eight pencil beams.

FIG. 2. Example of PG profiles of pencil beams in the first layer. The black dots represent the PG^{virt} . The gray curves are the PG^{sim} for a same pencil beam passing through the fifty BPs.

Estimating the breathing phases

Since the pencil beams within each layer are separated by only a few milliseconds, they pass approximately through the same BP. Thus, one only needs to estimate the BPs for the 10 layers, not each individual pencil beam. To estimate these BPs, we find the breathing phase that minimizes the score function

$$d_k(c) = \sum_{b=1}^{L(k)} \sum_{m=1}^{20} |PG_{k,b,m}^{virt} - PG_{k,b,m}^{sim}(c)|, \quad (5)$$

where k and b refer to layer and pencil beam (in that layer), respectively, while m labels the detector bins. The upper bound $L(k)$ is the number of pencil beams in layer k , and c labels the BPs.

The score function in Eq. (5) compares the virtual and simulated PG profiles within each layer independently of the other layers. Thus, to minimize Eq. (5) with respect to c for each layer k ,

one only needs to list the values of $d_k(c)$ for all $0 < c < 51$ and pick the c that corresponds to the smallest d_k . Another approach is to impose a parameter-dependent correlation between the layers. For example, if the breathing frequency was increased/decreased by a constant, the breathing would still be regular and hence the BPs of all the layers would fall on a straight line. In Figure 3, we show a two-dimensional view of this approach. Part A depicts $d_1(c)$ over several breathing cycles. In part B, the functions $d_1(c)$ to $d_{10}(c)$ are represented by vertical bars, with the ten layers spanning the horizontal axes. The centers of the white circles mark the right answer. The white triangles lie over the nearest local minima and correspond to the independently-estimated BPs for each layer. The white dashed line is a result of optimizing

$$D(\alpha_1, \alpha_0) = \sum_{k=1}^{10} d_k(\alpha_1 k + \alpha_0) \quad (6)$$

with respect to α_0 and α_1 . Note that a linear correlation between the layers will lead to a good approximation only when the breathing errors are small. For larger errors, the correlation curve may be more complicated, e.g. a second order polynomial: $\alpha_2 k^2 + \alpha_1 k + \alpha_0$.

We have tested all three methods – independent, linear and quadratic – for all cases and sub-cases. For the independent estimation, we used the *Position* function in Mathematica to find the discrete value of c that minimized $d_k(c)$. For the other two methods, we used a direct random search to minimize $D(\vec{\alpha})$ with respect to $\vec{\alpha}$. The parameter set $\vec{\alpha}$ that yielded the lowest $D(\vec{\alpha})$ out of one hundred thousand samples, drawn from a square distribution, was chosen. For the linear case, the parameters α_0 and α_1 were constrained according to $\alpha_1 = m = [m_{min}, m_{max}]$, where m_{min} and m_{max} are the minimum and maximum slope, respectively, and $\alpha_0 + \alpha_1 = p$, where p is the initial phase. The slope is k -dependent: $m = 2\alpha_2 k + \alpha_1$. In order to satisfy the slope condition $m = [m_{min}, m_{max}]$, we must put constraints on α_0 , α_1 and α_2 for two cases: $\alpha_2 > 0$, a down parabola; and $\alpha_2 < 0$, an up parabola. For parabolas that are monotonically increasing ($\alpha_2 > 0$) in the domain $k = [1, 10]$, the smallest slope is always at $k = 1$, while the largest slope is always at $k = 10$. The inequalities that satisfy these conditions read

$$\begin{aligned} 2\alpha_2 + \alpha_1 &\geq m_{min} \\ 20\alpha_2 + \alpha_1 &\leq m_{max}, \end{aligned} \quad (7)$$

and their solution is $0 \geq \alpha_2 \leq (m_{max} - m_{min})/18$ and $(m_{max} - 20\alpha_2) \geq \alpha_1 \geq (m_{min} - 2\alpha_2)$. The condition for α_0 is set by restricting the initial phase: $0 \leq \alpha_2 + \alpha_1 + \alpha_0 \leq p$. For the case $\alpha_2 < 0$ refer to Table 1, which shown all the parameter conditions for the linear and the quadratic model for $m_{min} = 20$, $m_{max} = 30$ and $p = [1, 50]$.

FIG. 3. A) Example of phase, c , versus $d_k(c)$ for layer 1. B) A density plot for $d_1(c)$ through $d_{10}(c)$ as a function of layers and phases. The center of the white circle indicates the correct phase for each layer, k . The white triangles, referring to the independent method; their centers coincide with the local minima, i.e. the estimated phase for each k . The white line is the best linear fit stipulated by the minimum of Eq. (6).

TABLE I. Parameter ranges for the linear and the quadratic model for $m = [20, 30]$ and $p = [0, 50]$.

Parameter	Linear	Quadratic ($\alpha_2 < 0$)	Quadratic ($\alpha_2 > 0$)
α_2	0	$[-5/9, 0)$	$(0, 5/9]$
α_1	$[20, 30]$	$[20-20\alpha_2, 30-2\alpha_2]$	$[20-2\alpha_2, 30-20\alpha_2]$
α_0	$[\alpha_1+1, 50+\alpha_1]$	$[1-\alpha_2-\alpha_1, 50-\alpha_2-\alpha_1]$	$[1-\alpha_2-\alpha_1, 50-\alpha_2-\alpha_1]$

RESULTS

The success of the BP estimation was quantified by comparing the minimal distance between the estimated BP and the virtual BP. For example, if the virtual BP was 46 and the estimated BP was 1, then the absolute value of the error was $51 - 46 = 5$ (or 0.4 seconds), since 1 is the same BP as 51. Fig. 5 shows the results yielded by the three models in terms of an average estimation

FIG. 4. Distribution of $\langle \Delta BP \rangle$ for the independent A, the linear B, and the quadratic method C. The vertical dashed lines in the histograms on the left indicate the 90th percentile mark. The plots on the right show the average and the standard deviation of the estimation error in seconds for each layer.

error, ΔBP , defined by

$$\langle \Delta BP \rangle = \frac{1}{M} \sum_{k=1}^M |\Delta BP_k|, \quad (8)$$

(left), and by the average and standard deviation of the estimation error for each layer (right). On average, the quadratic model gives the most accurate BP estimation; however, it has more outliers than the independent model. On a layer to layer basis, the averages of the independent and the quadratic models are very similar; however, the former has smaller standard deviation in layers 3 and 4. The linear model is the least accurate of all, both on average and on layer to layer basis.

Discussion

We have demonstrated that, in the presence of detection noise and irregularities in the breathing frequency, PGC can be used to estimate BPs with model-dependent degrees of accuracy. Of the

three models considered – independent, linear and quadratic – the quadratic model was the most accurate, with an uncertainty of $< 5\%$ of the breathing period with 90% confidence, but somewhat less reliable than the independent model, due to more prevalent outliers. Although less accurate on average than the quadratic model, the advantage of the independent model is that it is not affected by sudden changes in breathing; whereas the quality of the linear and the quadratic models relies on relatively smooth breathing irregularities.

One possible application of the methods presented herein could be to detect interfractional anatomical changes. Observing a failure of the correlation between the BPs estimated by an external surrogate and those estimated via the present method (internal surrogate) would indicate a deformation in the anatomy. Although the PGC is not sensitive enough to reveal the nature of the deformation, a large enough mismatch between the two techniques would be a basis for stopping the treatment. Another variation of this approach would be to employ the proposed internal surrogate for treatments involving mechanical breathing [21]. In such a setting, the breathing irregularities would be dramatically reduced, which would increase the accuracy of the proposed internal surrogate, thus making it more sensitive to finer anatomical changes.

In order to evaluate the proposed techniques, more work will be needed to test the PGC as a BP estimator, e. g. against irregularities in the breathing amplitude and patients setup errors.

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