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Responses to comments by the Associated Editor and Referees for the paper entitled *Multiscale Registration of Planning CT and Daily Cone Beam CT Images for Adaptive Radiation Therapy*, **Manuscript #08-192**.

Dear Editor,

Thank you very much for your quick review of the paper entitled "Multiscale Registration of Planning CT and Daily Cone Beam CT Images for Adaptive Radiation Therapy," co-authored with Doron Levy (Department of Mathematics and Center for Scientific Computation and Mathematical Modeling, University of Maryland) and Lei Xing (Department of Radiation Oncology, Stanford University). We very much appreciate your efforts, as well as the helpful and insightful comments made by the Associate Editor and Referees. We are pleased that you find the technique novel and worthy of publication. We have made the corrections, revisions, and updates, as suggested by the Associate Editor and Referees, and appreciate their thoughtful comments on improving our manuscript for publication in *Medical Physics*. A point-by-point response to the comments of the Associate Editor and Referees is included below. We hope that this clears the way for a quick publication of the manuscript.

Sincerely,

Dana Paquin

Associate Editor's Comments

1. We have labeled the axes in the mutual information similarity measures figure (the horizontal axis is *Slice Number* and the vertical axis is *Mutual Information Measure*).

2. We added a *Computation* section which addresses the computational costs of the multiscale registration algorithm. In particular, we have discussed the time required for each of the three steps of the multiscale algorithm presented in Figures 1, 2, and 3. We have also added a discussion of the effects of the computation time on clinical implementation of the algorithm.

3. We have added a *Synthetic Results* subsection in the Results section which includes a thorough quantitative evaluation of the multiscale algorithm. Using pairs of images in which the exact transformation between the images is known,

we obtained a precise quantitative evaluation of the algorithm. We considered both rigid (translation and rotation) and non-rigid (vector field deformation) transformations. We performed approximately 100 additional registration examples (50 rigid and 50 non-rigid) using CT and simulated noisy deformed CBCT images of the rectum, and quantitatively compared the transformations computed by the multiscale registration algorithm with the known exact transformations. For the rigid registration examples, we used a known transformation of 13 mm translation in X, 17 mm translation in Y, and 10 degree rotation about the center of the image. To quantitatively evaluate the results of the multiscale algorithm for rigid registration, we compared the output parameters of the registration algorithm (X translation, Y translation, and rotation angle) with the known parameters of 13, 17, and 10, respectively. For the non-rigid registration examples, we used a known B-spline deformation vector field in which the CT image is deformed by assigning random deformation vectors at each B-spline node of the image. To quantitatively evaluate the results of the multiscale algorithm for non-rigid registration, we computed the sum of mean square differences between the magnitude of the vector deformation at each pixel computed by the multiscale algorithm and the magnitude of the known vector deformation at each pixel. In each case, we simulated the noise and artifacts that are present in CBCT images but not in CT images, by artificially adding noise to the deformed CT images. The quantitative results demonstrated with these examples confirm that the multiscale registration algorithm accurately registers soft tissue and bony structures.

Referee #1's Remarks: Referee #1 did not recommend any revisions or additions.

Referee #2's Remarks

1. In the manuscript *Hybrid multiscale landmark and deformable image registration, Mathematical Biosciences and Engineering, vol. 4, pp. 711–737, 2007*, we extended the multiscale image representation using hierarchical (BV, L^2) decompositions of Tadmor, Nezzar, and Vese to three-dimensional images, and presented the details of the computational implementation of the (BV, L^2) image decomposition for three-dimensional images. Thus, the multiscale image registration algorithm that we have presented in the current manuscript can potentially be extended to three-dimensional CT and CBCT series of two-dimensional images to account for large motion that cannot be recovered in 2D-2D image registration. However, in the current manuscript, our goal is to present the details of the multiscale image registration algorithm and to quantitatively and qualitatively evaluate its use for registration of CT and CBCT images (and, more generally, for clinical applications in which one of the images to be registered contains noise or other artifacts not present in the other

image). Thus, we leave the extension of the algorithm to three dimensions for a future study.

2. We have added numerous examples with CT and CBCT rectum images to demonstrate that the multiscale image registration algorithm accurately registers low contrast CT and CBCT images and to demonstrate that soft tissue regions are accurately matched with one another. We also added numerous registration examples (see previous discussion on the *Synthetic Results* section that we added to the manuscript) in which the exact transformation between the images was known a priori, and quantitatively demonstrated that the multiscale registration algorithm accurately recovers the known deformation. As a future study, we plan to work on registration and segmentation problems for inconsistent daily air cavity in head-neck images and inconsistent daily rectum filling.

3. We added the two suggested citations of literature on CT-CBCT registration to the Introduction section of the manuscript.

Referee #2's Detailed Comments

1. We updated the discussion of B-splines registration in section 2.1 to address the questions and comments of the referee.

2. We updated the discussion of landmark-based registration in section 2.2 to address the questions and comments of the referee.

3. We updated the discussion in section 2.3.2 following Figures 1, 2, and 3, to address the questions and comments of the referee. The landmark-based registration is used only for the coarsest scales of the images. Each successive registration is performed using B-splines deformable registration, at each stage using the transformation computed by the previous scale registration algorithm as the starting point for the current registration. The iterative deformable registration component of the algorithm fine-tunes the registration result obtained with the coarse-scale landmark-based registration.

4. We modified section 3 based on the suggestions and comments of Referee 2 regarding the presentation of examples. We removed several of the examples that illustrated similar types of results, and added a rectum example to illustrate soft tissue matching.

5. We clarified the meaning of *ordinary deformable registration* in the text of the paper. The meaning is B-splines deformable registration (without the multiscale decomposition).

6. We added a *Computation* section which addresses the computational costs of the multiscale registration algorithm. In particular, we have discussed the time required for each of the three steps of the multiscale algorithm presented in Figures 1, 2, and 3. We have also added a discussion of the effects of the computation time on clinical implementation of the algorithm.

7. We have labeled the axes in the mutual information similarity measures figure (the horizontal axis is *Slice Number* and the vertical axis is *Mutual Information Measure*).