

Purpose: To present a deformable image registration (DIR) model based on maximum likelihood estimation (MLE) with improved robustness to image noise and selection of registration parameters. **Method and Materials:** Optical flow based DIR, such as free-form deformable registration (FDR), usually assumes invariance of pixel intensities, which may not be true for noisy images. Moreover, the smoothing parameter must be judiciously chosen and typically remains fixed over all iterations of the registration. A robust registration model (FDR-MLE) based on minimization of smoothing term, standard for FDR, and MLE of the residual image is proposed. The advantages of the proposed model are 1) matching image pixels between the source image and the target image within an optimized variation to account for image noise; and 2) adaptive adjustment of the smoothing parameter during the registration process. Validations of FDR-MLE were carried out using a simulated digital phantom and clinical lung images. Validation criteria included correlation coefficient (CC) and average phantom error (PE). **Results:** FDR-MLE outperformed FDR and was more robust to selection of registration parameters. For the same parameters (step size = 0.3, smoothing weighting factor = 2.0), in the simulated phantom, FDR-MLE increased the CC by 11% compared to FDR. FDR-MLE had PE=0.49 pixels, compared to 1.08 pixels for FDR. Robustness was measured by computing standard deviations (STD) of CC and PE for various step sizes. Using CC, STD of FDR-MLE was 0.0066, which was only 12% of STD of CC for FDR (0.053). PE for FDR-MLE was 0.044 pixels, compared to 0.21 pixels for FDR. **Conclusion:** The proposed FDR-MLE model can significantly improve the registration accuracy, convergence, and robustness. It is well suited for DIR in a clinical environment where time constraints and limited expertise of the user limit optimization of the registration parameters.