Nonlinear regression-based method for pseudoenhancement correction in CT colonography

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In CT colonography (CTC), orally administered positive-contrast tagging agents are often used for differentiating residual bowel contents from native colonic structures. However, tagged materials can sometimes hyperattenuate observed CT numbers of their adjacent untagged materials. Such pseudoenhancement complicates the differentiation of colonic soft-tissue structures from tagged materials, because pseudoenhanced colonic structures may have CT numbers that are similar to those of tagged materials. The authors developed a nonlinear regression-based (NLRB) method for performing a local image-based pseudoenhancement correction of CTC data. To calibrate the correction parameters, the CT data of an anthropomorphic reference phantom were correlated with those of partially tagged phantoms. The CTC data were registered spatially by use of an adaptive multiresolution method, and untagged and tagged partial-volume soft-tissue surfaces were correlated by use of a virtual tagging scheme. The NLRB method was then optimized to minimize the difference in the CT numbers of soft-tissue regions between the untagged and tagged phantom CTC data by use of the Nelder-Mead downhill simplex method. To validate the method, the CT numbers of untagged regions were compared with those of registered pseudoenhanced phantom regions before and after the correction. The CT numbers were significantly different before performing the correction ($p < 0.01$), whereas, after the correction, the difference between the CT numbers was not significant. The effect of the correction was also tested on the size measurement of polyps that were covered by tagging in phantoms and in clinical cases. In phantom cases, before the correction, the diameters of 12 simulated polyps submerged in tagged fluids that were measured in a soft-tissue CT display were significantly different from those measured in an untagged phantom ($p < 0.01$), whereas after the correction the difference was not significant. In clinical cases, before the correction, the diameters of 29 colonoscopy-confirmed 3–14 mm polyps affected by tagging that were measured in a soft-tissue CT display were significantly different from those measured in a lung CT display ($p < 0.0001$) or in colonoscopy ($p < 0.05$), whereas after the correction the difference was not significant. Finally, the effect of the correction was tested on automated detection of 25 polyps ≥ 6 mm affected by tagging in 56 clinical CTC cases. The application of the correction increased the detection accuracy from 60% with 5.0 FP detections per patient without correction to 96% with 2.9 FP detections with correction. This improvement in detection accuracy was statistically significant ($p < 0.05$). The results indicate that the proposed NLRB method can yield an accurate pseudoenhancement correction with potentially significant benefits in clinical CTC examinations. © 2009 American Association of Physicists in Medicine.

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I. INTRODUCTION

Although colorectal cancer is the second leading cause of cancer deaths in the United States,¹ it would be largely preventable by early detection and removal of its benign precursor lesions.² Computed tomographic colonography (CTC) may facilitate a practical large-scale colorectal screening scheme where conventional optical colonoscopy would need to be performed only on patients with clinically significant CTC findings.³

To yield a satisfactory detection accuracy in CTC, orally administered positive-contrast tagging agents can be used for opacifying feces and fluid in the CTC data.⁴ However, tag-

ging agents can also introduce pseudoenhancement of the observed CT numbers of nearby untagged materials.^{5,6} This presents the fundamental problem that CT numbers cannot be used for differentiating reliably between tagged and untagged materials across CTC cases, thereby limiting the scope and accuracy of automated image processing and visualization methods in clinical CTC cases.⁵

Previously, an image-based adaptive density-correction (ADC) method was developed to minimize the pseudoenhancement effect in CTC data.⁶ The principle of the application of the method is explained in Sec. II B 2. Because the method provides an image-based correction, it can be applied to CTC data retrospectively. The application of the method to

FIG. 1. Two examples of the nonlinear characteristic of pseudoenhancement effect. In the images on the left, small circle indicates the location of a sampled CT number in a simulated polyp and a haustral fold, respectively, in an empty phantom. The bar plots in the images on the right indicate the CT number at that location in the empty phantom (white bar) and in tagged phantoms filled with 300, 600, and 900 HU tagging fluids. A nonlinear exponential model (solid curve) fits these measurements more precisely than a linear model (dotted line).

clinical CTC cases was shown to yield significant improvement in the accuracy and consistency of automated polyp detection.

The ADC method has two components: (1) Initial parameter optimization and (2) subsequent application of the optimized method. One of the limitations of the previous study was that the optimization component had been designed to reduce pseudoenhanced CT numbers of untagged materials to values smaller than 100 HU (Hounsfield units) rather than to minimize the actually observed pseudoenhancement error at individual voxels. That is, even though the method reduced pseudoenhanced CT numbers to values lower than 100 HU, the CT number of an individual voxel might have been overcorrected or undercorrected in comparison with its true unenhanced CT number. Another limitation was that the pseudoenhancement effect was approximated by a linear model, whereas the actual pseudoenhancement effect may be nonlinear (Fig. 1).

Although pseudoenhancement correction was shown to improve the accuracy and consistency of automated polyp detection, the above limitations reduced the accuracy of the ADC method in minimizing the precise pseudoenhancement error at individual voxels. A more precise correction is desirable because clinical cases and the anthropomorphic colon phantom are composed of multiple types of materials, the radiodensity of which varies between different regions and voxels. Moreover, although the correction algorithm is fast, the initial calibration of the method for CTC involved a time-consuming brute-force optimization step. Although the calibration needs to be performed only once, it is nevertheless desirable to explore faster options for performing the initial optimization.

In this study, we extended the previous work by developing a nonlinear regression-based (NLRB) pseudoenhancement correction model. The pseudoenhancement effect is approximated by a more general nonlinear rather than linear parametric model. The model is calibrated by minimization of the observed difference between the CT numbers of unenhanced and pseudoenhanced CTC data. Because the CT data of different phantoms are not precisely aligned, it was also necessary to develop a registration scheme that correlates the different CT data by use of spatial registration and virtual tagging methods. The calibration is implemented by use of a dedicated optimization algorithm that is computationally much faster than the previous brute-force algorithm. For avoiding artifacts, it was also necessary to develop a suitable objective function with appropriate regularization terms. The development of the methods is described in Sec. II B.

We evaluated the NLRB method by use of phantom data and clinical CTC data. Figure 2 presents an overview of the study design. The materials are described in Sec. II A. The phantom data were used for validating the correction by comparison of the CT numbers of an untagged phantom with those of tagged phantoms and by performing polyp size measurement in the phantoms. Clinical data were used to demonstrate the resulting improvement in the polyp size measurement and in automated detection of polyps covered by tagged materials. Precise estimation of polyp size is important in CTC because the maximum polyp diameter correlates with cancer risk and it is therefore used for determining whether polypectomy is required,⁷ whereas automated detection is important for improving the accuracy and consistency of radiologists' interpretation performance in CTC.⁸ The results are described in Sec. III. The discussion and conclusions are presented in Secs. IV and V, respectively.

II. METHODS

II.A. Materials

For the development and validation of the correction method, an anthropomorphic colon phantom (Phantom Laboratory, Salem, NY) was designed to imitate features of human CTC scans.⁹ In the phantom, observed CT numbers of simulated soft-tissue (ST) materials vary between -50 and 100 HU (mean: 30 HU), and those of simulated fatty tissue vary between -350 and 0 HU (mean: -100 HU). The phantom was filled partially with nonionic 300 mg organically bound I/ml iodinated contrast (Oxilan, Guerbet, Inc., Bloomington, IN) diluted to $1:5$, $1:10$, and $1:20$ of contrast into normal saline to yield tagged fluids with observed radiodensities of approximately 300 , 600 , and 900 HU.⁹ The phantom was scanned by use of an eight-channel CT scanner [Lightspeed Plus, General Electric (GE) Medical Systems, Milwaukee, WI] with 1.25 – 2.5 mm collimations, 1.25 – 3.0 mm reconstruction intervals, and 30 – 70 mA currents with 140 kVp voltage. The scan parameters reflect those used in our institution for clinical CTC.

For clinical evaluation, we collected retrospective clinical CTC cases where the patients had been subjected to a 24 h bowel preparation with a clear-liquid diet and bowel cleans-

FIG. 2. Overview of the study.

ing by 90 ml of sodium phosphate and 10 mg of bisacodyl.⁴ Positive-contrast tagging was performed with 500 ml of barium (2.1% by weight) and 120 ml of diatrizoate. The CT acquisition was performed with a four-channel or eight-channel CT scanner (GE LightSpeed or LightSpeed Ultra, GE Medical Systems, Milwaukee, WI) with 1.25–2.5 mm collimations, a table speed of 15 mm/s, a reconstruction interval of 1 mm, and a current of 100 mA with 120 kVp. The locations of colonoscopy-confirmed polyps were correlated with CTC data in reference to colonoscopy reports and prospective CTC reading reports.

II.B. The nonlinear regression-based correction model

II.B.1. Overview

The pseudoenhancement correction scheme has two components: An optimization step and a correction step. The optimization step calibrates the parameter functions of the correction step to minimize observed pseudoenhancement at known tagging levels. The correction step performs pseudoenhancement corrections based upon the optimized parameter functions.

The correction step is summarized in Sec. II B 2. Unlike in the previous study that used linear parameter functions,⁶ the current study uses exponential parameter functions (see Sec. II B 5).

In this study, the optimization step was designed to minimize the observed pseudoenhancement error at individual voxels. To perform such a correction, it is necessary to register the phantom CT data (Sec. II B 3), to correlate the partial-volume surface regions of the registered data (Sec. II B 4), and to prepare a suitable objective function (Sec. II B 6). The objective function is substantially different from that of the previous study where the CT numbers of pseudoenhanced untagged voxels were simply reduced to values lower than 100 HU.

II.B.2. Image-based pseudoenhancement correction

In this section, we briefly summarize the principle of the ADC method which is used as the basis of the NLRB correction scheme. The method performs a retrospective image-based pseudoenhancement correction on reconstructed CT data. The details of the method were described by Näppi and Yoshida.⁶

The observed CT number of a voxel p is considered to have two components:

$$v_p = \hat{v}_p + v_p^{\text{PEH}}, \quad (1)$$

where $\hat{v}_p$ denotes the actual radiodensity and v_p^{PEH} represents the effect of pseudoenhancement at p . For estimating v_p^{PEH} , the pseudoenhancement energy that is emitted by nearby voxels q is modeled as

$$r^0(p) = \sum_q \frac{C}{\sqrt{2\pi}\sigma_1(v_q)} \exp\left(-\frac{1}{2}\left(\frac{D(p,q)}{\sigma_1(v_q)}\right)^2\right), \quad (2)$$

where $\sigma_1(\cdot)$ is a parameter function, $D(p,q)$ represents the spatial distance between the voxels p and q , and C is a scaling constant. The initially distributed energy is redistributed iteratively according to

$$r^i(p) = \sum_q \frac{r^{i-1}(q)}{\sqrt{2\pi}\sigma_2(r^{i-1}(q))} \exp\left(-\frac{1}{2}\left(\frac{D(p,q)}{\sigma_2(r^{i-1}(q))}\right)^2\right), \quad (3)$$

where $\sigma_2(\cdot)$ is a second parameter function. The iteration over Eq. (3) ends when the distributed energy becomes negligible. From Eq. (1), the corrected CT number of p is

$$\hat{v}_p = v_p - v_p^{\text{PEH}} \approx v_p - \sum_i^N r^i(p), \quad (4)$$

where N is the number of iterations.

FIG. 3. Two examples of spatial registration. The crosshairs in the images indicate the same spatial (x, y, z) location within the phantoms. (a) The ROI of untagged reference phantom. (b) The ROIs of two different tagged phantoms before the registration. (c) The ROIs of the two tagged phantoms after the registration.

II.B.3. Registration of phantom CT data

To yield accurate corrections over different colon regions and cases, we optimized the parameter functions $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$ of Eqs. (2) and (3) to minimize the difference between the CT numbers of the soft-tissue regions of an untagged reference phantom and those of tagged phantoms. It is desirable to use several tagged phantoms to provide representative examples of different cases of pseudoenhancement, ranging from low-density tagging (negligible pseudoenhancement) to high-density tagging (significant pseudoenhancement).

Because the phantom is composed of homogeneous materials and it is filled with homogeneously tagged fluids, the densitometry of different spatial regions including the same materials varies little within each CT scan volume. Therefore, we did not use the entire region of the phantom but performed the optimization on a smaller 1000 cm³ region of interest (ROI) that included representative examples of the regions of air, colonic wall, tagged fluid, and polyps. The ROIs were extracted manually from the same relative location of the CTC data of each phantom.

The image data of the different CT scan volumes do not match precisely because, in order to cleanse and refill the phantom with different tagging solutions, it is necessary to reseat the phantom multiple times in the CT scanner. Therefore, the ROIs that are extracted from tagged phantoms need to be registered spatially with the ROI of the untagged reference phantom. We performed the registration by use of an automated adaptive multiresolution method.¹⁰ The method involves a multiresolution refinement strategy that has been observed to yield more robust results than does a comparable single-scale method.

Figure 3 shows two examples of the spatial registration. The crosshairs that are displayed in the images indicate the same absolute (x, y, z) location within the phantoms. In (a), the ROI of the untagged reference phantom is shown, and in (b), two unregistered phantoms are shown. The (x, y, z) loca-

FIG. 4. An example of the ringlike artifact around polyps (the partial-volume region between white and black arrows) that occurs when the optimization algorithm attempts to match uncorrelated partial-volume interfaces of untagged and tagged phantoms.

tions of the crosshairs do not match between (a) and (b). However, in (c), the ROIs are shown after registration, where the locations of the crosshairs are seen to match those of the reference phantom precisely.

II.B.4. Virtual tagging for the correlation of tagged partial-volume interfaces

Even if the phantom data were registered spatially at sub-voxel accuracy, this would not be adequate for the parameter optimization. This is because the partial-volume material interfaces between ST and air in the untagged reference phantom do not match with those between ST and tagging in the tagged phantoms. In fact, these interfaces have opposite characteristics: The CT numbers of the reference phantom decrease in the direction from ST toward the lower-density lumen air, whereas the CT numbers of the tagged phantoms increase from the ST toward the higher-density tagging.

Figure 4 shows an example of the type of artifact that would occur if the partial-volume effect above was ignored in the optimization of the NLRB model. In an attempt to match the partial-volume polyp surface regions, the NLRB method performs an excessive correction of the CT numbers within the partial-volume region, thereby yielding a ringlike low-density artifact around the polyp.

To correct for this artifact, we simulated the material interface of tagged phantoms by applying virtual tagging to the untagged reference phantom. The virtual tagging was implemented by mapping of the CT numbers according to

$$\hat{v}_I = t_T - \left(\frac{t_T - t_{ST}}{t_A - t_{ST}} \right) * v_I, \quad (5)$$

where t_T represents the CT number of the tagged region, t_{ST} and t_A represent the CT numbers of ST (25 HU) and air (−1000 HU), and v_I denotes the observed CT number at the voxel.

Figure 5 demonstrates the application of the virtual tagging method. In (a), the untagged reference phantom is shown in transverse plane. In (b), a physically tagged phantom is shown. In (c), virtual tagging has been applied to the untagged reference phantom. Note that the virtually tagged phantom does not have any pseudoenhancement: This is de-

FIG. 5. Application of virtual tagging. (a) A transverse plane of the original untagged reference phantom. (b) A physically tagged phantom. (c) Virtual tagging has been applied to the untagged phantom. (d) The virtually tagged reference phantom has been correlated with the tagged phantom. The white line along the wall of the colon phantom indicates the partial-volume region that has been reconstructed by the application of virtual tagging. The regions that are not included in the optimization are indicated as air (<-900 HU; black).

sirable for the subsequent optimization. In (d), the partial-volume surfaces of the virtually tagged reference phantom have been correlated with those of the tagged phantom. Here, voxels that represent air in the reference phantom or those that are located beyond the region of colonic wall have been excluded. Only the shown nonair voxels are used for the optimization.

II.B.5. Nonlinear parameter functions

The application of the pseudoenhancement correction scheme requires the optimization of the parameter functions $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$ of Eqs. (2) and (3). The former function is used for estimating the initial pseudoenhancement energy of a voxel based upon its observed CT number, whereas the latter function is used for distributing the pseudoenhancement energy. Unlike in the previous work that used linear approximation,⁶ here we used a more general nonlinear model,

$$\sigma_1(v_q) = a \exp\left(\frac{v_q - b}{c}\right) + d, \quad \sigma_2(r) = e \exp\left(\frac{r}{f}\right) + g. \quad (6)$$

Therefore, for calibrating the correction model, it is necessary to optimize the parameter vector $V = (a, b, c, d, e, f, g)$. The optimization is performed by use of the multidimensional Nelder-Mead downhill simplex method¹¹ as explained in Sec. II B 6.

II.B.6. Objective function

The objective function of the optimization step is based upon the mean-square error of the CT numbers between the correlated untagged reference and tagged phantoms. Initially, we experimented with an unconstrained objective function that minimizes the error between the CT numbers of ST voxels:

$$E_{ST}(v_i) = \frac{1}{N_{ST}} \sum_i^{N_{ST}} (v_i^{\text{tag}} - v_i^{\text{un}})^2, \quad (7)$$

where N_{ST} is the number of ST voxels in the reference phantom, and v_i^{tag} and v_i^{un} represent the CT numbers of ST voxels in the tagged phantoms and untagged reference phantom, respectively. It should be noted that the objective function is

FIG. 6. Two examples of failed correction with the unconstrained objective function of Eq. (7). In (a), soft-tissue region has been corrected excessively. In (b), tagged region has been corrected excessively.

calculated simultaneously over all phantom regions, to determine parameter functions that minimize pseudoenhancement simultaneously over a wide range of tagging conditions rather than over a specific sample.

However, if the optimization was performed according to Eq. (7), the corrected data would contain artifacts such as those shown in Fig. 6 which demonstrates outcomes of optimization from two different phantom experiments. In (a), there is too much correction on the ST region. In (b), there is too much correction on the tagged region. These artifacts occur because high-density tagging dominates by introducing more pseudoenhancement error in the CT numbers of ST voxels than does low-density tagging. Therefore, when minimizing the observed error over different phantoms based on Eq. (7), the optimization can converge to global solutions that reduce the largest error in high-density tagged phantoms at the cost of increasing the error in low-density tagged phantoms. To avoid such correction artifacts, we introduced two regularization terms, $E_{ST}(\bar{v}_{ST})$ and $E_{\text{tag}}(\bar{v}_{\text{tag}})$, which are defined by

$$E_{ST}(\bar{v}_{ST}) = \begin{cases} \exp((c_1 - \bar{v}_{ST})/c_2) & \text{if } \bar{v}_{ST} < -100 \text{ HU} \\ 0 & \text{otherwise,} \end{cases} \quad (8)$$

$$E_{\text{tag}}(\bar{v}_{\text{tag}}) = c_3 \exp(-c_4 * \bar{v}_{\text{tag}}), \quad (9)$$

where c_1 , c_2 , c_3 , and c_4 represent scaling constants, and $\bar{v}_{\text{tag}}$ and $\bar{v}_{ST}$ denote the average CT number of the tagged and ST regions, respectively, in the tagged phantoms.

Figure 7 shows the plots of the two regularization terms $E_{ST}(\bar{v}_{ST})$ and $E_{\text{tag}}(\bar{v}_{\text{tag}})$ as a function of the CT number. The values of the scaling constants were set manually to $c_1 = 924$, $c_2 = 50$, $c_3 = 200$, and $c_4 = 0.02$ to yield appropriate penalty values: The regularization term $E_{ST}(\bar{v}_{ST})$ that is shown in (a) constrains the corrected CT numbers of ST voxels to values > -200 HU that are typical of soft-tissue regions, whereas the penalty term $E_{\text{tag}}(\bar{v}_{\text{tag}})$ that is shown in (b) constrains the corrected CT numbers of tagged voxels to values > 200 HU which yield a clear separation between tagged and untagged materials. Our experiments indicate that the precise values of the scaling constants c_1 to c_4 are not critical as long as the regularization terms exceed the mean-square error that falls into the penalized range.

Thus, from Eqs. (7)–(9), the final objective function is

FIG. 7. Plots of the regularization terms $E_{ST}(\bar{v}_{ST})$ of Eq. (8) and $E_{tag}(\bar{v}_{tag})$ of Eq. (9) as a function of CT numbers $\bar{v}_{ST}$ and $\bar{v}_{tag}$, respectively. The term $E_{ST}(\bar{v}_{ST})$ that is shown in (a) constrains the correction to maintain ST values above -200 HU in the phantoms. The term $E_{tag}(\bar{v}_{tag})$ that is shown in (b) constrains the correction to maintain tagged values above 200 HU.

$$E_{total} = \alpha * E_{ST}(v_i) + E_{ST}(\bar{v}_{ST}) + E_{tag}(\bar{v}_{tag}), \quad (10)$$

where α is an empirically determined scaling constant. The optimization continues until the observed reduction in E_{total} becomes smaller than 0.0001 .

II.C. Evaluation methods

For the optimization of the NLRB method, the anthropomorphic phantom was scanned without and with the three tagging solutions (Sec. II A) by use of an eight-channel CT scanner with 1.25 mm collimation, 1.25 mm reconstruction interval, and 50 mA current with 140 kVp. Next, the NLRB was optimized to minimize pseudoenhancement in the tagged phantoms as described above. The computation time was estimated by use of a standard desktop computer (2.4 GHz Opteron, AMD, Sunnyvale, CA).

We conducted four experiments to evaluate the effect of the pseudoenhancement correction on the anthropomorphic phantom and on clinical CTC cases. The measurements were made by a trained research associate (Tsagaan) supervised by CTC experts [coauthors Näppi and Yoshida and an expert radiologist (Michael Zalis, Massachusetts General Hospital)]. Specifically, the research associate was provided the spatial location of the center of each polyp with instructions on how to make the measurements; the measurements were made with one of the experts watching, and the measurements were reviewed for consistency by the panel of the experts on a consensus basis.

II.C.1. Experiment 1

First, we investigated the effect of the pseudoenhancement correction on nine anthropomorphic phantoms that were filled partially with the three different tagging solutions. The CT data were acquired with the combinations of 1.25 and 2.5 mm collimations, 1.25 and 2.5 mm reconstruction intervals, and 30 , 50 , and 70 mA currents with 140 kVp. Standard and soft CT reconstruction kernels were used. To evaluate the effect of the correction, we measured the average CT number and its standard deviation in transverse CT images before and after the correction within a 25 mm^2 re-

gion at the center of 12 simulated polyps and colonic wall regions that were covered by the tagged fluid in the phantoms. The measurements obtained before and after the correction were compared among each other and among those made from the untagged reference phantom. Statistical significance was tested by use of the unpaired and paired Student's t -tests, and standard deviations were compared by use of the chi-square test.

II.C.2. Experiment 2

Second, we tested the effect of the correction on polyp measurement in the phantoms with a soft-tissue CT display (STCTD) (linear display range: 0 ± 200 HU) setting. The largest diameter of each of the 12 polyps was measured in transverse images by use of a CTC reading workstation (Viatronix Explorer, Viatronix Inc., Stony Brook, NY) before and after the correction. The measurements were compared by use of the paired Wilcoxon signed-rank test.

II.C.3. Experiment 3

Third, we tested the effect of the correction on polyp measurement in the STCTD setting on clinical CTC cases (Sec. II A). We identified 29 colonoscopy-confirmed polyps that were at least partially covered by tagged materials in 17 clinical CTC study cases among the reviewed 52 so-called training cases provided by Walter Reed Army Medical Center's Virtual Colonoscopy Center. The largest diameter of each polyp was measured on transverse images by use of a CTC reading workstation (Viatronix Explorer, Viatronix Inc., Stony Brook, NY) with a wide lung CT display (LCTD) (linear display range: 0 ± 1000 HU) and with STCTD settings before and after the correction. The LCTD setting was used to estimate true polyp size as observed in CTC: a wide LCTD range was used to avoid the pseudoenhancement from affecting the measurements. The CTC measurements were blinded to the polyp size measured in optical colonoscopy. The colonoscopy measurements of the polyps were collected from colonoscopy reading reports: There were 9 polyps ≥ 10 mm, 12 polyps $6\text{--}9$ mm, and 8 polyps $3\text{--}5$ mm in diameter. In CTC, 21 of the polyps were covered completely by the tagged fluid, 2 polyps were covered by a thick coating layer of the tagged matter, and 6 polyps were partially covered by the tagged fluid. We also measured the average CT number at the centers of the polyps before and after the correction. The measurements were compared by use of the paired Wilcoxon signed-rank test, and standard deviations were compared by use of the chi-square test.

II.C.4. Experiment 4

Fourth, we evaluated the effect of the correction on automated polyp detection by use of clinical cases, in which at least 50% of the polyp surface was covered by tagged material. The automated polyp detection scheme has been described previously.⁵ The scheme was trained with clinical CTC cases that were completely independent from those of this study as has been described previously.¹² The training cases were not prepared with a tagging agent and therefore

FIG. 8. Plots of the optimized parameter functions. (a) $\sigma_1(\cdot)$. (b) $\sigma_2(\cdot)$.

they did not have pseudoenhancement. Because most polyps are covered by tagged materials in only one scan position (supine or prone) of a patient, we reviewed the CT scans of the 450 clinical cases provided by the Walter Reed Army Medical Center to identify cases where all of the clinically significant polyps (adenomas/cancers ≥ 6 mm) were covered by tagging. A total of 23 patients with 25 polyps ≥ 6 mm were identified in this manner. In colonoscopy, where the polyps were measured by a calibrated linear probe,⁴ 10 polyps were ≥ 10 mm and 15 polyps were 6–9 mm in diameter. For statistical analysis, we added 33 randomly selected CT scans where colonoscopy had not reported polyps. Thus, a total of 56 CT scans of 56 different patients were analyzed by automated detection. A polyp was considered detected correctly if the distance between its center and that of computer-segmented region of the detection was within the size of the polyp.

The improvement in detection accuracy was tested before and after the pseudoenhancement correction by use of jack-knife free-response operating characteristic (JAFROC) analysis.¹³ In addition, we compared the polyp detection performance with that obtained by use of the linear pseudoenhancement correction model developed previously.⁶

III. RESULTS

III.A. Parameter optimization

The downhill simplex method (Sec. II B 5) was initialized to reflect parameter values that had been established in our previous study.⁶ The search domain was constrained to 0.1–2.0 times the initial values. The value of the scaling constant of Eq. (2) was set to $C=100$. The value of the scaling constant of Eq. (10) was set to $\alpha=100$. The optimization converged in approximately 10 min. This was much faster than with the previous brute-force optimization approach that would have taken several days to optimize with the exponential model.

Figure 8 shows plots of the optimized parameter functions $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$. In (a), the plot of $\sigma_1(\cdot)$ indicates that voxels with a high observed CT number have higher pseudoenhancement energy than do voxels with a low CT number. In (b), the plot of $\sigma_2(\cdot)$ indicates that distributed high energies have a lesser effect than do low residual energies during the

FIG. 9. Examples of the average correction of CT numbers within the colonic wall, in a 14 mm polyp, and in a 25 mm polyp. Horizontal axis indicates the parameters of the experiments, whereas the vertical axis represents the average correction in Hounsfield units.

iteration. Therefore, the correction will be relatively lower on tagged regions than on pseudoenhanced ST or air-filled regions. Thus, tagged regions tend to retain their observed high CT numbers while the overall energy of the system decreases to converge into a stable numerical solution.

In general, the computation time of the optimized NLRB correction method depends on the amount and radiodensity of tagged regions in the input CTC data. If the CTC data do not contain tagged regions, the computation time is less than 1 second. In cases that include large amounts of high-density tagging, the correction can take up to 2 min on average.

III.B. Effect on CT numbers in phantoms

Before pseudoenhancement correction, the average CT numbers in the sampled pseudoenhanced regions of polyps and the colonic wall between the untagged reference phantom (mean: 25 HU) and tagged phantoms (mean: 59 HU) varied significantly ($p < 0.01$). The correction step yielded a significant reduction in the average CT number of the pseudoenhanced regions (mean correction: 64 HU; $p < 0.01$). After the correction, the difference between the CT numbers of the untagged reference phantom and corrected tagged phantoms (mean: 21 HU) was no longer significant ($p > 0.05$). The CT numbers did not vary significantly in regions that were not affected by pseudoenhancement before or after the correction ($p > 0.05$). Also, the standard deviations of CT numbers (range: 45–84 HU) did not vary significantly before or after the correction.

Figure 9 shows examples of the average correction of CT numbers and how the correction varies in different situations. The light gray bars represent average correction in CT number (in HU) within a region of the colonic wall, whereas the gray and dark gray bars represent correction within a 14 mm polyp and a 25 mm polyp. The horizontal axis indicates the radiodensity of the tagged fluid along with the CT scan parameters of each experiment. The leftmost column indicates the results of the untagged phantom scan; this clearly shows that the NLRB does not affect the untagged case. The three large bins on the right show that, as the radiodensity of the tagged fluid becomes higher, the magnitude of the correction

FIG. 10. Transverse images of simulated (a) 18 mm and (b) 10 mm polyps and (c) a 3 mm thin fold submerged in 900 HU tagging solution before and after pseudoenhancement correction. Top row: Before correction in LCTD window. Middle row: Before correction in STCTD window. Bottom row: After correction in STCTD window.

becomes larger. The figure also shows that differences in CT scan parameters have little effect on the correction of CT numbers. It should also be noted that regions within polyps tend to be corrected more than regions within the colonic wall. This is because polyps protrude from the colonic wall into the colonic lumen and therefore they tend to be surrounded and affected most by pseudoenhancing tagged material, whereas a region inside the colonic wall is mostly surrounded by soft tissue that does not cause pseudoenhancement.

Figure 10 visualizes the application of the optimized NLRB method in a phantom with a high-density, 900 HU tagging solution. In the STCTD window before correction, the lesions are distorted because of the pseudoenhancement. In the STCTD window after correction, the NLRB method has clearly reduced the observed pseudoenhancement.

III.C. Effect on polyp measurement in phantoms

Table I shows the results of the polyp measurement in phantoms. The measurements were made once over 12 polyps. Before the correction, the average polyp size that was measured in tagged phantoms was smaller than that measured in the untagged reference phantom, whereas after the

TABLE I. Results of polyp size measurement in phantom cases. Abbreviation: HU=Hounsfield units. The p value indicates statistical significance as compared with the untagged case where the measured polyp size was 17.9 ± 5.2 mm.

Tagging level (HU)	Before correction	p value	After correction	p value
300	14.2 ± 4.0	0.004	17.9 ± 5.1	0.83
600	13.9 ± 4.1	0.001	18.2 ± 5.2	0.15
900	12.5 ± 3.8	0.001	17.9 ± 5.1	1.00

correction there was no statistically significant difference. The average size at the 600 HU tagging level after the correction is marginally higher than that of the other measurements, but this intraobserver difference is much smaller than the in-plane resolution of CTC images and it is statistically insignificant.

III.D. Effect on polyp measurement in clinical cases

Table II shows the results of polyp measurement in clinical cases. The upper row ("All polyps") shows the result for all polyps. Before the correction, the average polyp size that was measured in the STCTD window was significantly different from that measured in the LCTD window ($p < 0.0001$) or in colonoscopy ($p < 0.05$). However, after the correction, the differences were no longer statistically significant ($p > 0.05$). Furthermore, the correction increased the measured polyp size in the STCTD window by 23% on average ($p < 0.0001$), and the average CT number within polyp regions was reduced from 85 HU down to 14 HU ($p < 0.0001$). The average CT number level of 14 HU in the corrected CT images is comparable to that of polyps not affected by pseudoenhancement effects in clinical cases. The standard deviations of CT numbers did not vary statistically significantly before or after the correction.

The bottom row of Table II ("Highest pseudoenhancement") shows the measurement result for the special case of eight most highly pseudoenhanced polyps that were all covered by high-density tagging (800 HU or higher in CTC). For these polyps, the correction increased the measured polyp size by 54% on average ($p < 0.05$). Before the application of the correction, the measured average sizes in STCTD were significantly smaller than those of LCTD or OC measurements ($p < 0.05$), whereas after the correction there was no significant difference ($p = 1$). For these polyps, the NLRB reduced the average CT number significantly from 189 HU down to 37 HU ($p < 0.01$).

Figure 11 shows two visualizations of the application of NLRB to clinical CTC cases where the polyp was covered (a) by moderately radiodense or (b) by highly radiodense tagged fluid. The images are shown in the STCTD window. In both examples, the left images show the polyp before and the right images after the correction: The application of NLRB clearly reduces the pseudoenhancement within the polyps.

III.E. Effect on automated detection in clinical cases

Before the pseudoenhancement correction, the per-polyp detection performance of automated polyp detection was 60% at 5.0 FP detections per patient for lesions ≥ 6 mm. After the correction, the detection accuracy increased to 96% with 2.9 FP detections per patient on average. Figure 12 shows the free-response receiver operating characteristic curves of the performance of automated detection.

The JAFROC test indicated that the improvement in detection accuracy due to pseudoenhancement correction was statistically significant ($p < 0.05$). More specifically, the improvement was significant in the detection of polyps 6–9 mm

TABLE II. Results of polyp measurement in clinical cases. Abbreviations: STCTD=soft-tissue CT display, LCTD=lung CT display, OC=optical colonoscopy, HU=Hounsfield units, before=before the correction, after=after the correction.

	Average polyp diameter					CT numbers (HU)	
	STCTD before (mm)	STCTD after (mm)	Change (%)	LCTD (mm)	OC (mm)	Before	After
All polyps ($n=29$)	5.6 ± 4.6	6.9 ± 4.2	+23	7.3 ± 4.3	7.1 ± 5.8	85 ± 48	14 ± 45
Highest pseudoenhancement ($n=8$)	4.1 ± 3.6	6.3 ± 2.9	+54	6.4 ± 3.0	6.4 ± 2.1	189 ± 59	37 ± 29

in diameter ($p < 0.05$), whereas it was not significant for larger polyps ($p = 0.08$). The detection sensitivity was 100% (10/10) for large polyps ≥ 10 mm and 100% for polyps ≥ 8 mm, with 2.9 FP detections per patient and 93% (14/15) for 6–9 mm polyps with 1.8 FP detections per patient.

IV. DISCUSSION

Previous efforts to address pseudoenhancement effects in CT data have included quantitative assessment¹⁴ or the development of advanced CT reconstruction algorithms.¹⁵ In CTC, pseudoenhancement complicates the application of automated image processing and visualization methods because the interpretation of CT numbers may vary among different regions and cases.⁵ Early studies avoided addressing the pseudoenhancement problem by thresholding tagged materials with a CT number threshold that was higher than the average pseudoenhancement error. The problem of this approach is that other than clearly tagged residual materials are then misinterpreted as soft tissue. Because providing optimal physical tagging that would label all residual materials without introducing pseudoenhancement remains a challenging problem in CTC, several dedicated postprocessing methods have been developed recently for correcting pseudoenhanced CTC data. The ADC method that preceded the current study implemented an iterative image-based correction scheme that facilitated simultaneous application of the same automated polyp detection scheme with high detection accuracy in both clearly tagged pseudoenhanced fluid-tagging CTC cases as well as in less clearly tagged minimally prepared fecal-tagging CTC cases. More recently, a scale-based method was developed to reduce pseudoenhancement in clearly tagged pseudoenhanced fluid-tagging CTC cases.¹⁶ The method re-

duced CT numbers in pseudoenhanced regions based upon an estimate of the size and radiodensity of tagged regions, and the application of the method was shown to yield statistically significant improvement in automated detection of polyps 6–9 mm submerged in the tagged fluid. In another recent study, a vector-quantization scheme was introduced to identify pseudoenhanced regions for improving the quality of electronic cleansing.¹⁷ By dividing tagged regions into multiple subclasses for the initialization of an expectation-maximization method, the proposed electronic cleansing scheme yielded statistically significant visual improvement over a previous method. The results of these and the current study indicate that pseudoenhancement correction can be used to improve the performance of computer-assisted detection significantly for polyps 6–9 mm and to improve the overall performance of electronic cleansing when positive-contrast tagging is used to opacify residual materials.

In the present study, the pseudoenhancement correction was designed to minimize the observed error between unenhanced and pseudoenhanced voxels. We observed three problems in correlating the CT data of tagged and untagged phan-

FIG. 11. Two examples of the application of pseudoenhancement correction to clinical cases with (a) moderately (700–800 HU) and (b) highly radiodense (800–1300 HU) tagged fluid. In both examples, the left figures show a polyp (10 and 6 mm, respectively; arrows) before correction and the right figures after the correction.

FIG. 12. Free-response receiver operating characteristic curves of the accuracy of automated detection for clinically significant polyps covered partially or completely by tagged material before (dotted line) and after (solid line) the pseudoenhancement correction. The improvement in detection accuracy by the application of pseudoenhancement correction is statistically significant ($p < 0.05$).

toms. First, the CT scan volumes do not match precisely but need to be registered spatially. Second, even if the CT data are registered spatially, the partial-volume surfaces of ST material interfaces have opposite characteristics in tagged and untagged phantoms that would cause a ringlike correction artifact in optimized correction. Third, even if the CT data and partial-volume interfaces were correlated, straightforward optimization by minimizing the difference between CT numbers could cause image artifacts due to excessive correction in some phantoms. However, our results indicate that the above three problems can be overcome if spatial registration of the CTC data is done by virtual tagging of the untagged reference phantom and by introduction of exponential regularization terms in the objective function.

The CT scan parameters of the phantom and those of clinical evaluation cases did not match precisely because the phantom data were collected previously and reflect the CT scan parameters used in our institution. Therefore, our results are conservative: A more precise match between the scan parameters of the phantoms and clinical cases would improve the accuracy of the correction.

Another approach to optimize the method would be to use small regions extracted from inside the polyps. However, such an approach may be disadvantageous because the resulting correction would be inaccurate due to the fact that regions other than polyps are not considered. It would also require manual labor and yield irreproducible results. Furthermore, because the observed pseudoenhancement effect declines as a function of distance,⁶ limiting the correction to regions inside polyps would be likely to undercorrect for pseudoenhancement within the polyp surface region where the pseudoenhancement has the most effect.

The quantitative results indicate that the pseudoenhancement correction can provide significant improvement in the accuracy of polyp measurement in a STCTD window. A more conventional approach to avoid the effect of pseudoenhancement in polyp measurement or colon visualization would be to expand the display range of the CT display window. However, because the optimal display setting for interpreting CTC data can vary among different cases and regions, the need to adjust the display window among different colon regions or across cases would complicate the workflow and increase the likelihood of diagnostic errors. Furthermore, the use of a wide display range would not solve the measurement problem in applications such as automated polyp measurement.¹⁸

In this study, the optical colonoscopy and CTC size measurements matched rather closely. This is not surprising considering that clinical studies have reported a wide range of conclusions on the accuracy of CTC measurement. It is possible that currently available visualization and image processing tools do not adequately compensate for preparation-dependent issues such as the pseudoenhancement effect, and thus, their performance may depend upon the specific characteristics of the bowel preparation and/or CTC software.¹⁹

In a previous study, we observed that a pseudoenhancement correction can improve the overall accuracy and consistency of automated polyp detection across different types

of CTC cases.⁶ In the present study, we tested the effect of the correction on automated polyp detection in cases where all polyps were covered partially or completely by high-density tagging material. The correction yielded a 33% improvement in detection sensitivity and a significant improvement in the overall detection accuracy. The resulting detection sensitivity of 96% is high, especially considering that all of the polyps were affected by tagging and that there was only one CT scan per patient.

The improvement in the accuracy of automated polyp detection was not statistically significant for large polyps ($p=0.08$). This can be attributed to the relatively small number of large polyps ($n=10$) in the study and to the fact that pseudoenhancement has a lesser effect on large polyps than on smaller lesions. The pseudoenhancement effect is likely more severe on small polyps and flat lesions; thus, the pseudoenhancement correction may be more important for the detection of small (6–9 mm) polyps or flat lesions than for the detection of large polyps. Although small polyps are less likely to represent advanced adenomas or cancers than larger lesions, their presence can affect patient management.²⁰ However, clinical studies indicate that the detection sensitivity and specificity of CTC is lower for the 6–9 mm polyps than for the detection of larger lesions.²¹

In this study, a downhill simplex method rather than brute-force optimization as in our previous study was used to optimize the pseudoenhancement correction scheme. The advantage of brute-force optimization would be that it can find a globally optimal solution, whereas optimization algorithms based upon mathematical heuristics could be caught in a local minimum. However, the high-performance results of this study indicate that downhill simplex method was able to find an appropriate solution. Therefore, we expect that even if a brute-force optimization was used, the results would not differ significantly from those of this study.

Our study had some limitations. First, the purpose of this study was not to compare different pseudoenhancement correction methods but to develop a method that directly corrects observed pseudoenhancement by minimizing the observed errors between spatially matched pseudoenhanced and unenhanced materials. Second, the number of clinical cases and clinically significant polyps was not very large. Nevertheless, the method was optimized by use of independent phantom data, and our results indicated statistically significant improvements. Third, for large-scale application of the method, it would be desirable to explore the effect of pseudoenhancement over a wider range of CT scanner models and CT acquisition parameters. Although our experiments did not indicate significant difference in the pseudoenhancement effect when CT scan parameters were varied (Fig. 9), we believe that the use of isotropic scanning could reduce the pseudoenhancement effect. Fourth, a clinical observer study should be performed that explores the practical benefits of the applications of pseudoenhancement correction in CTC. Addressing these issues remains for future study.

V. CONCLUSION

We developed a nonlinear regression-based method for retrospective image-based correction of the pseudoenhancement of CTC data due to positive-contrast tagging agents. The method was optimized by minimizing the difference of pseudoenhanced and actual CT numbers of soft-tissue regions in an anthropomorphic phantom based upon a scheme that involved spatial registration, virtual tagging, and introduction of regularization terms in the objective function of the optimization step. The optimized method was shown to minimize the difference in CT numbers between tagged and untagged phantoms. It was also shown to improve the accuracy of the size measurement of polyps affected by tagging in a soft-tissue CT display window in phantoms and in clinical cases and to improve the accuracy of automated detection of polyps covered by tagging in clinical CTC cases. The correction does not affect CTC data when positive-contrast tagging is not present.²² Therefore, the results indicate that the proposed correction method is a useful preprocessing step for image processing applications in CTC.

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