The Self-Overlap Method for Assessment of Lung Nodule Morphology in Chest CT

Joseph N. Stember · Jane P. Ko · David P. Naidich ·
Manmeen Kaur · Henry Rusinek

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Abstract Surface morphology is an important indicator of malignant potential for solid-type lung nodules detected at CT, but is difficult to assess subjectively. Automated methods for morphology assessment have previously been described using a common measure of nodule shape, representative of the broad class of existing methods, termed area-to-perimeter-length ratio (*APR*). *APR* is static and thus highly susceptible to alterations by random noise and artifacts in image acquisition. We introduce and analyze the self-overlap (*SO*) method as a dynamic automated morphology detection scheme. *SO* measures the degree of change of nodule masks upon Gaussian blurring. We hypothesized that this new metric would afford equally high accuracy and superior precision than *APR*. Application of the two methods to a set of 119 patient lung nodules and a set of simulation nodules showed our approach to be slightly more accurate and on the order of ten times as precise, respectively. The dynamic quality of this new automated metric renders it less sensitive to image noise and artifacts than *APR*, and as such, *SO* is a potentially useful measure of cancer risk for solid-type lung nodules detected on CT.

Keywords Computer-aided diagnosis (CAD) · Lung neoplasms · Computed tomography · Surface morphology

Introduction

Lung cancer is responsible for roughly 1.4 million deaths annually as of 2008 [1]. Many potential lung cancers start

out as small pulmonary nodules that show up as incidental findings on chest radiograph or computed tomography (CT) scans. However, a large number of nodules prove to be benign [2]. Imaging and minimally invasive methods are available for further characterization of nodules, such as 18-fluorodeoxyglucose positron emission tomography CT and biopsy, the latter usually involving bronchoscope-guided aspiration, transthoracic CT needle biopsy, or video-assisted thoracoscopic surgical biopsy. However, many of these nodules are too small to characterize via the aforementioned methods, which entail invasive procedures that expose patients to additional risks.

Prior to further evaluation with the aforementioned methods, assessment of nodule features is currently performed to identify features that predict whether a nodule is more likely to be malignant or benign [3]. Additionally, characterizing known malignant nodules—more specifically lung cancer—in terms of the presence and degree of varying complex features such as attenuation, airway dilatation, and margins may prove useful in predicting degrees of aggressiveness and patient prognosis [4–9]. Small nodules detected can appear solid, pure ground glass or part solid/part ground glass in attenuation [10]. Irregular borders have been associated with malignancy in solid nodules. For subsolid nodules, including part solid and pure ground glass lesions, margin features have not been proven significant as of yet in differentiating benign from malignant counterparts [11], although future investigation may elucidate any predictive nature [12]. Therefore, the focus of this investigation will be on solid nodules.

The process of visual morphologic assessment is challenging in terms of predicting malignancy given the overlap of benign and malignant features and due to the heterogeneous appearance of primary lung neoplasia. Therefore, computer-assisted methods of lung nodule characterization have been investigated. Assessment of lung nodules thus far

J. N. Stember (✉) · J. P. Ko · D. P. Naidich · M. Kaur · H. Rusinek
Department of Radiology, School of Medicine, New York
University,
560 1st Avenue,
New York, NY 10016, USA
e-mail: joestember@gmail.com

has focused primarily on growth rate, attenuation, shape, texture, and the use of neural networks [13–19]. Assessing change in a nodule entails evaluating not only the lesion's growth rate but also any alterations in morphology. Currently, in clinical practice, radiologists estimate surface morphology subjectively. A major problem is inter-reader variability and difficulty in expressing textural features and identifying those that are more predictive of invasive properties. A more sensitive and precise method to differentiate benign lesions from those with varying degrees of aggressive behavior is needed and potentially enabled by automatic texture and morphology analysis using CT data.

The establishment of precise automated measures of nodule morphology is key to this ability. A number of methods exist for the automated evaluation of border morphology for various types of lesions in addition to lung nodules [20–23]. To our knowledge, these are all static methods, involving the computation of shape-related quantities such as circularity, eccentricity, and compactness, as expressed by the surface-area-to-volume ratio or, inversely and in two dimensions, the area-to-perimeter-length ratio, which we shall denote as *APR*. However, the *APR* technique in particular and static approaches in general are subject to image noise and partial volume effects that are encountered in CT [24–26], particularly when imaging with low-dose chest CT techniques that are being investigated for cancer screening.

Therefore, in this work, we introduce the self-overlap method, a dynamic metric for automated surface morphology characterization. We compare this approach to a representative static method (area-to-perimeter-length ratio) and show that ours is equally accurate and more precise in the presence of image noise.

Methods

General Approach

We create lung nodule matrices in FireVoxel, cropping around the lesion of interest from a CT slice that roughly traverses the nodule's center. We import the resulting nodule image as a matrix into Matlab (Mathworks, Natick, MA) for all subsequent calculations.

For purposes of our averaging procedure, we add a “ring” of zeros around the i th image matrix $\mu^{(i)}$. Then, we normalize each matrix $\mu^{(i)} \in \{\mu^{(j)}\}_{j=1}^{N_{\text{nods}}}$, where N_{nods} is the number of nodules we are studying, such that $\dim(\mu^{(i)}) = N_{\text{rows}} \times N_{\text{cols}} \forall i \in [1, \dots, N_{\text{nods}}]$. One can normalize each row to length N_{rows} sequentially and then each column to length N_{cols} in turn via the following procedure: let a given row or column be the vector $\vec{v}_a$ of length N_a . This vector can

transform into $\vec{v}_b$ with length N_b via the operation:

$$\vec{v}_b = \bigcup_{i=1}^{N_a} \bigcup_{j=1}^{F(i;N_a,N_b)} v_a(i), \quad (1)$$

where $F(i;N_a,N_b) \equiv \text{Round}\left(\frac{iN_b}{N_a}\right) - \text{Round}\left(\frac{(i-1)N_b}{N_a}\right)$. For our study, we normalize both row and column length to the maximum dimension (row or column) of all the nodule matrices in the set.

We next transform the nodule matrix $\mu^{(i)}$ by a smoothing or blurring procedure that involves a simple averaging of each pixel (not on the matrix border) with each of its nearest neighbors. We thus transform the unblurred matrix $\mu^{(i)}$ to its blurred counterpart $\mu'^{(i)}$ via the transformation B defined by:

$$B(u_{jk}^{(i)}) = \mu'_{jk}{}^{(i)} = \frac{1}{9} \times \sum_{\substack{l \in \{j-1, j, j+1\} \\ m \in \{k-1, k, k+1\}}} \mu_{lm}^{(i)}, \quad (2)$$

for $j \in \{2, \dots, N_{\text{rows}} - 1\}$, $k \in \{2, \dots, N_{\text{cols}} - 1\}$. This averaging procedure is equivalent to a two-dimensional Gaussian blur, which uses the Gaussian distribution

$$G(x, y) \propto \frac{-(x^2 + y^2)}{2\sigma^2} \quad (3)$$

to create a convolution matrix that is applied to $\mu^{(i)}$ with standard deviation $\sigma = \frac{3}{2}$ and nearest integer rounding. Gaussian blurring serves as a low-pass filter, removing high-frequency image components. As such, it is commonly employed to reduce noise in image processing, particularly in segmentation [27, 28]. Blurring can be seen as a decrease in image resolution. As such, a nodule's shape change under blurring reflects its change in detail with varying scale and hence its fractal dimension. Spiculated or lobulated masses are expected to have higher fractal dimensions than smooth masses [29].

The intuition for using a smoothing approach to assess nodule surface morphology is that a lobulated and/or spiculated surface will feature peninsulas with pixels of zero-attenuation neighbors. These pixels, on the edges of the lobulations/spiculations, will get washed out by the blurring process since they will have to be averaged with surrounding attenuation values of zero. On the other hand, smooth surface pixels will be surrounded by a larger number of high attenuation pixels, so that blurring these images will not significantly change the overall image. This is illustrated in Figs. 1 (smooth nodule) and 2 (spiculated nodule). We wish to point out that use of the terms “lobulated” and “spiculated” in this manuscript refers to irregularity of nodule margins as viewed on CT more than pathologic spiculation caused by desmoplasia.

Our procedure will thus be to start with an unblurred or once-blurred (number of blurrings $N_{\text{blur}}^a = 0$ or 1) nodule

Fig. 1 A smooth nodule undergoing successive blurrings or shavings. Due to the high degree of conservation in the face of blurring, this nodule would have a large self-overlap value

image and overlap it with its more blurred ($N_{\text{blur}}^b > 1$) counterpart. To assess this effect formally, we define the matrix self-overlap $SO_i = SO(\mu^{(i)})$ by

$$SO(\mu^{(i)}) = \frac{\text{vec}(\Theta(B_{\text{blur}}^a(\mu^{(i)}))) \cdot \text{vec}(\Theta(B_{\text{blur}}^b(\mu^{(i)})))}{\|\text{vec}(\Theta(B_{\text{blur}}^a(\mu^{(i)})))\| \times \|\text{vec}(\Theta(B_{\text{blur}}^b(\mu^{(i)})))\|}, \quad (4)$$

where Θ is a threshold function that eliminates all but tumor attenuation pixels as defined in Appendix 1, and vec is the vectorization mapping, which allows us to take normalized inner products in the standard manner.

A useful comparison with our method, the APR, is a standard tumor morphology metric and for our purposes represents the broad class of morphology measures that are static in nature. For a two-dimensional nodule cross section

Fig. 2 A spiculated nodule undergoing successive blurrings or shavings. Because of the relatively large degree of nodule lost in the face of blurring, the self-overlap for this nodule would be small

$$\text{APR}_i = \text{APR}(\mu^{(i)}) = \frac{A(\mu^{(i)})}{\text{PL}(\mu^{(i)})}, \quad (5)$$

where $\text{PL}(\mu^{(i)})$ is nodule i 's perimeter arc length and $A(\mu^{(i)})$ is its area.

Patient-Based Comparison

As an initial test of SO and comparison with APR, we apply both methods to $N_{\text{nods}}=119$ small chest nodules identified by CT scan performed for cancer screening. They are from a set of lung nodules used in a previous study in which an average CT follow-up period of 6.4 years was employed to analyze the precision of growth rate measurements [14]. The mean linear dimension of nodules in our set is $5.4 \text{ mm} \pm 3.0$, with a range from 1.9 to 28.5 mm. Six solid nodules displayed unstable growth and were later proven by pathology to be malignancies. The remaining nodules were found to be clinically stable by the Fleischner guidelines, whereby 2-year stability for small ($<8 \text{ mm}$) nodules has been satisfactory to determine benign nature [2]. For comparison to the automated methods, two thoracic imaging-trained radiologists with 14 and 32 years of post-fellowship experience (JPK and DN) assigned each nodule a surface smoothness value sm of 1 or 0. Nodule i has been judged to be smooth when $\text{sm}_i=1$ and irregular when $\text{sm}_i=0$. A consensus set of observer values $\{\text{sm}_i^{\text{OBS}}\}_{i=1}^{N_{\text{nods}}}$ consists of agreed-upon sm values with $\text{sm}_d^{\text{OBS}}=0$ for all solid nodules d for which the two radiologists disagree. The consensus assessment was 104 smooth nodules, with the remaining 15 deemed lobulated or spiculated. By the method discussed in Appendix 2, we generate a set of predicted smooth values $\{\text{sm}_i^{\text{SO}}\}_{i=1}^{N_{\text{nods}}}$ and $\{\text{sm}_i^{\text{APR}}\}_{i=1}^{N_{\text{nods}}}$ from SO and APR, respectively, for comparison with $\{\text{sm}_i^{\text{OBS}}\}_{i=1}^{N_{\text{nods}}}$.

Simulation Nodules

In order to evaluate the resilience of our method to random image noise, we generate artificial nodules whose shapes correspond to two-dimensional slices through spherical harmonics $Y_l^m(\theta, \phi)$, of degree l and order m (Fig. 3), where θ is the polar angle and ϕ is the azimuthal angle. In particular, we produce a set of binary simulation nodules $\{\mu^{(l)}\}_{l=1}^7$ with surfaces defined by $\{Y_l^{m=0}\}_{l=0}^7$. As shown in Fig. 3, the number of lobulations rises with increasing l , so that the shapes become progressively more irregular for larger values of l . As such, we expect in general for $\mu^{(l+1)}$ to have more

lobulations and thus a less regular surface morphology than $\mu^{(l)}$. Applying the two morphological assessment schemes, we find both $\{\text{SO}_l\}_{l=1}^7$ and $\{\text{APR}_l\}_{l=1}^7$ to be monotonically decreasing sets. In other words, both SO and APR decrease as l increases, as shown in Figs. 4 and 5, respectively. We anticipate this trend, since it reflects the fact that the nodule's smoothness decreases as we add more lobulations/spiculations. Hence, the two methods, given appropriate respective cutoff values used to determine $\text{sm}^{\text{SO/APR}}$, should have the same accuracy.

Where our method, which is dynamic in terms of nodule morphology assessment, shows strength over APR is in SO's precision in the presence of random noise. Intuitively, one might expect a static measure such as APR to be rather sensitive to random changes in the nodule's shape, whereas SO, which depends on several rounds of smoothing, should not be as sensitive because small changes in initial structure are likely to get washed out by the smoothing process. And this is indeed what we see, as demonstrated below.

We test for precision by generating sets of nodules with image noise, as detailed in Appendix 3. Producing 1,000 noise-altered nodule images $\tilde{\mu}^{(l)}$ for each value of l yields

$\left\{ \left\{ \tilde{\mu}_m^{(l)} \right\}_{m=1}^{1,000} \right\}_{l=1}^7$. These sets of permuted nodules permit us to ascertain how much SO and APR vary with random noise. Due to a higher mean value of APR than SO, we compute a “weighted variation” λ that scales standard deviation by mean so that the two methods are comparable. Defining λ for the two methods, we have

$$\lambda(\text{SO}_l) = \frac{\sigma(\text{SO}(\tilde{\mu}^{(l)}))}{\langle \text{SO}(\tilde{\mu}^{(l)}) \rangle}, \text{ and} \quad (6)$$

$$\lambda(\text{APR}_l) = \frac{\sigma(\text{APR}(\tilde{\mu}^{(l)}))}{\langle \text{APR}(\tilde{\mu}^{(l)}) \rangle}, \quad (7)$$

where σ is the standard deviation and $\langle \rangle$ denotes the ensemble average.

Results

The percentage agreement with radiologist assessment is 88.2 % for self-overlap (90.8 % when thresholding is

Fig. 3 Simulated nodules generated by spherical harmonic functions

done to the initial image) and 87.4 % with APR (for which thresholding is always done initially). The predictions of these two approaches are nearly the same, with inter-method percent agreements of 97.5 and 95.0 %, depending on when thresholding is performed. Adding APR to the SO computation does not contribute any additional information to our model (i.e., does not

improve the accuracy of the self-overlap method). The SO (initial thresholding) values of the six solid histologically malignant nodules are relatively low, occupying the bottom 20 % of the SO distribution for the full patient nodule set. The mean SO value for proven malignant nodules was 0.9749 (range, 0.9320 to 0.9910, with standard deviation of 0.0240), whereas for benign nodules, the mean was 0.9945

Fig. 4 Self-overlap vs l for simulated nodules

Fig. 5 Area-to-perimeter-length ratio vs l for simulated nodules

(range, 0.9601 to 0.9989, with standard deviation of 0.0046). This is an expected result, since SO (as well as APR) predicts nodule smoothness.

The two methods differ markedly in the comparison of their respective weighted variations for simulated spherical harmonics nodules of order zero and degree $l \in \{0, \dots, 7\}$. We find that SO is significantly more resistant to noise and

image imperfections than APR. Figure 6 shows $\frac{\lambda(\text{APR}_l)}{\lambda(\text{SO}_l)}$ values on the order of ten. This robustness of the self-overlap method represents an important improvement over static methods, since it renders the former approach more useful in the regime of smaller signal-to-noise ratios that characterize lower radiation exposures in chest CT. Overall, our method, from image importation to comparison of the

Fig. 6 Ratio of weighted variation from area-to-perimeter-length ratio to self-overlap vs. l

two methods, requires less than 1 min of computer time for the complete set of nodules running in Matlab v9.

Conclusions

Traditional methods for investigating nodule texture are static in nature. In our investigation, simulation nodules show that both our dynamic method (SO) and a representative static method (APR) for automated lung nodule surface morphology determination show correlation with surface smoothness. Applied to our patient data set, both approaches predict low values for the six solid nodules that were biopsied and pathologically proven to be malignant and were graded as irregular by both radiologists. Overall, SO and APR yield very similar predictions for the entire set when method-appropriate cutoff values are employed. This follows from the fact that both metrics display positive correlation with simulation nodule surface regularity, as we would expect. Hence, both methods can, with proper fitting and cutoff selection, yield predictions that have over 80 % agreement with expert assessment.

However, when the simulation nodules are subjected to random noise, we find that the scaled variability of SO is an order of magnitude less than that of APR. We conclude that SO yields more reproducible results than APR. Since Gaussian blurs are commonly employed to reduce image noise (and detail) in graphics software and image segmentation, it is not surprising that this method applied to CT nodule images affords noise reduction and thus higher precision. Our results stress the importance of employing noise-reducing filters such as Gaussian blurs in order to obtain more precise measurements of nodule morphology.

In our data set, pathological assessment was available only for six solid-type nodules and therefore a small subset of diagnosed malignancy. However, we were able to characterize these nodules as more likely malignant according to margin characterization with our method. SO values for the known malignant subset all fall within the lower 20 % of SO values in the full nodule collection, consistent with SO reflecting margin regularity. Further limitations in our investigation include the fact that analysis was performed on the axial section on which the nodule was largest rather than for the entire nodule volume. However, three-dimensional analysis with the self-overlap method should be straightforward. We chose a sigma value of $\frac{3}{2}$ to remove unwanted noise while not completely obliterating the nodules' essential features (such as smooth nodular contours and lobulations) in our current data sets, so that the SO output does not lose descriptive value. The sigma value may need to be varied depending upon the image noise, which would depend upon different clinical CT protocols and tube current

exposures. Future work would establish appropriate sigma parameter values for differing CT scanning protocols.

The dynamic quality of the new SO automated metric makes it less sensitive to image noise and artifacts than APR and thus a potentially useful measure of cancer risk for lung nodules detected on CT.

Appendix

Appendix 1

We seek a threshold function Θ that turns $\mu^{(i)}$ into a binary matrix $\hat{\mu}^{(i)}$ whose entries $\hat{\mu}_{jk}^{(i)}$ are equal to 1 if they exceed the assigned threshold value and are 0 otherwise, i.e.

$$\hat{\mu}_{jk}^{(i)} = \Theta(\mu_{jk}^{(i)}) = H(\mu_{jk}^{(i)} - T(\mu^{(i)})), \quad (8)$$

where H is the Heaviside step function and $T(\mu^{(i)})$ is the threshold-generating function for blurred nodule i 's image matrix $\mu^{(i)}$. The latter function is defined by

$$T(\mu^{(i)}) = \frac{1}{2} (\text{att}_{\text{high}}^{(i)} + \text{att}_{\text{low}}^{(i)}), \quad (9)$$

where $\text{att}_{\text{low}}^{(i)}$ is the attenuation value below which approximately 10 % of the attenuation values for nodule i lie. In other words, for a frequency distribution $f_i(\text{att}^{(i)})$ of nodule i 's attenuation values, $\text{att}_{\text{low}}^{(i)}$ satisfies

$$\int_0^{\text{att}_{\text{low}}^{(i)}} f_i(\text{att}^{(i)}) d(\text{att}^{(i)}) = \frac{1}{10} \int_0^{\max(\{\text{att}_j^{(i)}\}_{j=1}^{N_{\text{rows}} \times N_{\text{cols}}})} f_i(\text{att}^{(i)}) d(\text{att}^{(i)}), \quad (10)$$

where $\{\text{att}_j^{(i)}\}_{j=1}^{N_{\text{rows}} \times N_{\text{cols}}} = \text{vec}(\mu^{(i)})$ is the set of attenuation values in $\mu^{(i)}$. Similarly, $\text{att}_{\text{high}}^{(i)}$ is the attenuation value above which the highest 10 % of attenuation values for nodule i reside, so that

$$\begin{aligned} \int_{\text{att}_{\text{high}}^{(i)}}^{\max(\{\text{att}_j^{(i)}\}_{j=1}^{N_{\text{rows}} \times N_{\text{cols}}})} f_i(\text{att}^{(i)}) d(\text{att}^{(i)}) \\ = \frac{1}{10} \int_0^{\max(\{\text{att}_j^{(i)}\}_{j=1}^{N_{\text{rows}} \times N_{\text{cols}}})} f_i(\text{att}^{(i)}) d(\text{att}^{(i)}). \end{aligned} \quad (11)$$

The hope is that by using this 10 % margin, the attenuation value $T(\mu^{(i)})$ accurately reflects a typical value characterizing the attenuation distribution for nodule i and is not unduly influenced by aberrantly large or small attenuation values, as these can represent for example pieces of bone or air that are caught in the nodule image slice.

Appendix 2

According to the generalized linear model, we can write any expected value for a dependent variable Y in terms of the independent variable X with parameter set β :

$$E(Y) = g^{-1}(X\beta), \quad (12)$$

where $E(Y)$ is the expected value for Y and g is the link function. In our case, the outcome Y_i is smoothness _{i} , a continuous quantity that expresses the likelihood that nodule i is smooth or not smooth, and X is the self-overlap SO. Since we are interested in predicting whether a given nodule is smooth or not, our distribution is binomial, and we will denote the binary counterpart to smoothness to be “smooth” sm. When sm _{i} =1, we can say that nodule i is smooth, while sm _{i} =0 is a statement that nodule i is not smooth. Thus, the link function is given by

$$g(E(Y)) = \text{sm}_i = X\beta = \ln\left(\frac{E(Y)}{1 - E(Y)}\right), \quad (13)$$

with corresponding mean function

$$\begin{aligned} E(Y) = \text{smoothness}_i &= \frac{1}{1 - \exp(-X\beta)} \\ &= \frac{1}{1 - \exp(-\beta_0 + \text{so}_i \times \beta_1)}. \end{aligned} \quad (14)$$

The smooth values $\{\text{sm}_i\}_{i=1}^{N_{\text{nods}}}$ were assigned by an experienced radiologist (JPK and DN). Together with $\{\text{SO}_i\}_{i=1}^{N_{\text{nods}}}$, we can compute $\{\beta_0, \beta_1\}$ by least squares regression applied to the system of equations

$$\{\text{sm}_i = \beta_0 + \text{so}_i \times \beta_1\}_{i=1}^{N_{\text{nods}}}, \quad (15)$$

called in Matlab as glmfit. Then we can compute $\{\text{smoothness}_i\}_{i=1}^{N_{\text{nods}}}$ via the mean function (Eq. 14). Finally, using a threshold

$$T_{\text{sm}} = \frac{1}{2}(\text{smoothness}_{\text{min}} + \text{smoothness}_{\text{max}}), \quad (16)$$

we can assign a predicted smooth value

$$\text{sm}_i^{\text{SO}} = H(\text{smoothness}_i - T_{\text{sm}}), \quad (17)$$

where H is the Heaviside step function.

Using the same fitting technique, we generate smooth values predicted from area-to-perimeter-length ratio $\{\text{sm}_i^{\text{APR}}\}_{i=1}^{N_{\text{nods}}}$ for comparison with the smooth values $\{\text{sm}_i^{\text{SO}}\}_{i=1}^{N_{\text{nods}}}$ predicted from the self-overlap method.

Appendix 3

We test for robustness by permuting the nodule $\mu^{(i)}$ into $\tilde{\mu}^{(i)}$, which now has noise on top of the simulation image. We introduce noise by generating $N_{rp}=200$ randomly positioned trial points and subjecting them to the probability distribution $p_{\text{flip}} = \exp(-d_{\text{bd}})$, where p_{flip} is the probability of a trial point's being accepted (thus flipping the sign of the pixel in that position), and d_{bd} is the distance of the trial point from the nearest point on the nodule–air interface/boundary. This probability distribution weights noise toward the boundary, so that the added noise affects predominantly surface morphology. For each value of l , we generate $N_{\text{perm}}=1,000$ permuted nodules $\{\tilde{\mu}_m^{(l)}\}_{m=1}^{N_{\text{perm}}}$ by this approach, giving us sets of nodules that are distorted in various places and to various degrees.

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