A Metric for Reducing False Positives in the Computer-Aided Detection of Breast Cancer from Dynamic Contrast-Enhanced Magnetic Resonance Imaging Based Screening Examinations of High-Risk Women

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Abstract Magnetic resonance imaging (MRI)-enabled cancer screening has been shown to be a highly sensitive method for the early detection of breast cancer. Computer-aided detection systems have the potential to improve the screening process by standardizing radiologists to a high level of diagnostic accuracy. This retrospective study was approved by the institutional review board of Sunnybrook Health Sciences Centre. This study compares the performance of a proposed method for computer-aided detection (based on the second-order spatial derivative of the relative signal intensity) with the signal enhancement ratio (SER) on MRI-based breast screening examinations. Comparison is performed using receiver operating characteristic (ROC) curve analysis as well as free-response receiver operating characteristic (FROC) curve analysis. A modified computer-aided detection system combining the proposed approach with the SER method is also

presented. The proposed method provides improvements in the rates of false positive markings over the SER method in the detection of breast cancer (as assessed by FROC analysis). The modified computer-aided detection system that incorporates both the proposed method and the SER method yields ROC results equal to that produced by SER while simultaneously providing improvements over the SER method in terms of false positives per noncancerous exam. The proposed method for identifying malignancies outperforms the SER method in terms of false positives on a challenging dataset containing many small lesions and may play a useful role in breast cancer screening by MRI as part of a computer-aided detection system.

Keywords Breast cancer · Computer-aided detection · Magnetic resonance imaging · Receiver operating characteristic curve analysis · Free response receiver operating characteristic curve analysis

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Introduction

Regular breast cancer screening has been identified as key for improving survival rates [1]. Genetic mutations on the BRCA1/2 genes can result in up to an 85 % lifetime risk of developing breast cancer [2]. High-risk women who decline prophylactic mastectomy require regular breast screening starting at age 25–30 with the goal of detecting breast cancer at the earliest possible stage. Dynamic contrast-enhanced magnetic resonance imaging is the most sensitive screening methodology for detecting breast cancer in high-risk women [3]. The *American Cancer Society* has recommended that women with a lifetime risk of developing breast cancer of 20–25 % or greater should receive MRI-enabled screening

[4]. MRI screening has also been shown to detect cancers missed by mammography and ultrasound in women who have dense breasts [5]. Thus, magnetic resonance imaging-enabled breast screening is likely to play an important clinical role in the future.

It has been shown that there is a high degree of variability between the sensitivities of trained radiologists in their ability to correctly diagnose lesions from breast MRI examinations [6]. Breast MRI examinations typically involve the acquisition of hundreds of images compared with just four images for typical X-ray mammogram-based screening. This provides motivation for the research, design and development of computer-aided detection systems to assist the breast MRI radiologist in identifying very early stage malignancies in high-risk women. Computer-aided detection and diagnosis systems for breast MRI are the subject of considerable ongoing research [7–11].

When analysing a contrast-enhanced breast MR image set, a radiologist will visually inspect the examination for a number of signs of malignancy. Patterns in the changes in lesion brightness over time (e.g. rapid uptake followed by a washout phase) can be indicative of cancer, and such patterns constitute one of the main features that a radiologist looks for when reading a breast MRI examination. Radiologists also look for spiculated lesions (or generally irregularly shaped lesions), heterogeneous tissue vascularization and diffuse tumour edges, all of which are suggestive of cancer and together influence their final diagnosis according to the Breast Imaging-Reporting and Data System (BI-RADS) lexicon. Assessing tumour characteristics based on the visual assessment of a radiologist is susceptible to human error, which highlights the need for automated methods for characterizing potentially malignant lesions. This has motivated substantial research towards the development of computer-aided detection (CAD) systems. It is common for breast MRI CAD systems to focus on the dynamic information (how a lesion's brightness changes over the course of the examination after the injection of a contrast agent) as well as morphological features (such as lesion shape and margin sharpness).

Invasive malignant tumours tend to exhibit heterogeneous vasculature, which can lead to variable contrast agent concentrations in neighbouring voxels during the examination. Preinvasive cancers, such as ductal carcinoma in situ (DCIS), will often exhibit no vascularization of the tumour; however, the lesions are capable of enhancing in a contrast-enhanced MRI examination due to contrast agent uptake from nearby vasculature. Both heterogeneous vasculature in an invasive tumour as well as a lack of vasculature in an enhancing preinvasive tumour are liable to cause local variations in contrast agent concentration in the extracellular space. These local variations in contrast agent concentration are liable to result in inter-voxel contrast agent diffusion (via Fick's diffusion) provided that no membrane separates neighbouring voxels (i.e.

provided there is no barrier preventing the diffusion of the contrast agent). The computer-aided detection metric presented in this paper does not attempt to fully characterize contrast agent diffusion as this is not possible given the imaging data acquired in a typical contrast-enhanced MR screening examination. Instead, this retrospective analysis evaluates a metric that can be used in a typical MR screening examination and is inspired by inter-voxel Fick's diffusion of the contrast agent used in the exam. It is demonstrated in this paper that the proposed metric has considerable potential towards lowering the false positive rate of computer-aided detection systems, one of this technology's major shortcomings.

Inter-voxel contrast agent diffusion has been the subject of simulation and experimental research that modifies the Tofts pharmacokinetic model [12, 13]. Simulation of diffusion characteristics and contrast agent diffusion's associated effect on capillary permeability has also been the subject of research [14]. The diffusion coefficient has been used to assess the heterogeneity of liver metastases [15]. The diffusion of contrast agent through a polyvinyl alcohol-cryogel has been measured with a novel magnetic resonance imaging method [16]. Diffusion measurements have also been performed in breast tumours in a mouse model [17]. Considerable research has also been focused on the potential use of diffusion imaging for the detection of breast cancer based on MRI technology [18–20]; however, these methods employ an MR pulse sequence that estimates local diffusion of hydrogen protons (typically in the form of water molecules). Unlike the existing work in water diffusion, the proposed method presented in this study computes a measurement inspired by inter-voxel diffusion of the contrast agent and demonstrates that metric's potential as a mechanism for lowering false positives in computer-aided detection systems targeting breast cancer. The main advantage of this approach is that the proposed metric can be computed from traditional MRI examinations and does not require a specialized MR pulse sequence. Although the metric computed is related to inter-voxel contrast agent diffusion, it also has potential as a marker of local vascular heterogeneity.

Materials and Methods

Image Acquisition and Preprocessing

Women at high risk for breast cancer based on family history or a known genetic mutation were recruited consecutively from familial cancer clinics. Participation in screening was offered to all eligible women in the context of genetic counseling. Informed consent was obtained from all participants. Ethics approval for this retrospective study was obtained from the institutional review board of the participating institution (*Sunnybrook Health Sciences Centre*). This retrospective analysis includes 383 examinations, with 44 examinations

containing 50 malignant lesions, and 339 examinations with negative findings. The diagnostic analysis below also included 209 radiologically suspicious benign lesions obtained as part of this screening program. The database from which this dataset was obtained is one of the few available with associated mortality data, with challenging BRCA mutation carriers (who tend to develop aggressive malignancies) having 96 % survival five and a half years after breast cancer diagnosis as part of an MRI-enabled screening exam [21]. Furthermore, the study also includes the examination of patients with X-ray mammography, ultrasound and clinical breast examination. The MRI dataset used in this study includes lesions missed by MRI but caught by any of the other techniques, resulting in many small lesions (2–5 mm) and ductal carcinoma in situ (DCIS), making this a particularly challenging dataset for breast cancer detection.

The screening protocol used is as follows. Simultaneous bilateral magnetic resonance imaging was performed using a 1.5T magnet (GE Signa, version 11.4). Sagittal images were obtained with a phased-array coil arrangement using a dual slab interleaved bilateral imaging method [22]. This provided 3D volume data over each breast obtained with an RF-spoiled gradient recalled sequence (SPGR, scan parameters: TR/TE/angle=18.4/4.3/30°, 256×256×32 voxels, FOV 18×18×6–8 cm). T1-weighted imaging is performed before and after a bolus injection of 0.1 mmol/kg of contrast agent gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA). Each bilateral acquisition was obtained in 2 min and 48 s. Slice thickness was 2 to 3 mm. Ground truth for malignant lesions is based on the analysis of tissue biopsies by a histopathologist. When the histopathologist determines a tissue sample to be noncancerous, a benign diagnosis is accepted. In cases where a suspicious mass did not receive a biopsy but returned to screening without observed changes to the lesion for greater than 1 year, then a benign diagnosis is also accepted.

Image registration is the process of aligning images that vary in position over time. This is performed to compensate for any patient motion that occurs during the examination. For this study, we have used a three-dimensional non-rigid registration technique for magnetic resonance breast images that is applied globally on the breast examination [23] in order to help ensure that suspect tissues are spatially aligned at each time point. An enhancement threshold of 60 % was employed based on the results of a related study [24], forcing benign diagnoses on voxels with low levels of contrast enhancement for both the proposed method, the established signal enhancement ratio (SER) method, and the combined method.

Proposed Contrast Agent Diffusion-Inspired Measurement

The proposed metric is inspired by the laws of diffusion established by Adolf Fick in 1855. Fick's diffusion states that

the change in local molecular concentration in the presence of variable spatial concentrations is proportional to the second-order spatial gradient of the local molecular concentrations multiplied by the diffusion coefficient. The equation governing this process is provided in Eq. 1:

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi \quad (1)$$

where

- ϕ is the local concentration
- D is the diffusion coefficient for the molecule in the given medium
- ∇^2 is the second-order spatial gradient (spatial derivative) operator
- t is the time

The equation denotes the expected change in local molecular concentration due to diffusion.

In our hospital's magnetic resonance (MR) imaging-based screening of breast cancer, the patient is injected with a Gd-DTPA contrast agent. When adapting Fick's diffusion to breast MRI examinations, ideally, we would be able to measure the concentration of contrast agent in the extracellular space. Measuring the concentration of the contrast agent in the extracellular space is possible if the MR acquisition protocol measures the T1 relaxation time of the tissue as well as the tissue's extracellular volume fraction (v_e). While research projects exist that attempt to measure these physiological parameters (v_e and T1 relaxation time), they were not reliable in the MRI-based screening data available for use in this study, nor in standard MRI examinations of the breast. As such, this research study uses a simplistic proxy for contrast agent concentration information (the relative signal intensity) since concentration information is unavailable. As such, we are not measuring diffusion, but we are computing a metric to assist in a computer-aided detection system that is inspired by Fick's law of diffusion and computable from a standard breast MRI examination. The relative signal intensity R_{SI} is related to contrast agent concentration and is used in the calculation of the proposed methodology defined in Eq. 2:

$$\text{Metric} = -\nabla^2 R_{SI}(t) \quad (2)$$

where

- $R_{SI}(t)$ is the relative signal intensity defined as $SI(t)/SI(0)$
- $SI(t)$ is the signal intensity at time t
- $SI(0)$ is the pre-contrast signal intensity
- ∇^2 is the second-order spatial derivative (gradient) operator

The results of Eq. 2 are not physically meaningful—unlike Eq. 1 which can be expressed in moles of diffused molecules per unit time. However, using the R_{SI} as a proxy for

concentration may yield an index of potential interest in the computer-aided detection of breast cancer and as such we hypothesize that Eq. 2 may be of use in MRI-based breast cancer screening. Malignant tumours exhibit an elevated value on this index scale relative to normal tissue. Although the metric proposed in Eq. 2 is related to contrast agent diffusion, it also functions as a measure of heterogeneity of enhancement and thus could be useful as a biomarker of tissue vascular heterogeneity.

Although there are a number of challenges towards making accurate contrast agent diffusion measurements based on MRI and Fick's law, for the purposes of this research study, we have implemented a computer-aided detection method for marking suspect tissues based on applying a threshold to the metric computed in Eq. 2. The computer-aided detection of breast cancer from MRI examinations was implemented by marking tissues as suspicious if the computed metric of Eq. 2 was higher than a given threshold (which is varied for statistical analyses). This metric may imply the possible existence of a change in contrast agent concentration due to Fick's diffusion; however, the metric will also be related to local tissue vascular heterogeneity and the heterogeneity of lesion enhancement.

A modified computer-aided detection system that incorporates both the signal enhancement ratio as well as the metric proposed in Eq. 2 is also included in this analysis. This modified approach involves using the SER method provided that the metric computed from Eq. 2 is above a fixed threshold (0.05). This is discussed in more detail in the discussion.

Validation/Statistical Analyses

The established signal enhancement ratio method, the proposed method and the combined method were evaluated with receiver operating characteristic (ROC) curve analysis [25] and free-response receiver operating characteristic (FROC) curve analysis [26]. ROC analysis evaluates a given method's potential to perform differential diagnosis between malignant lesions and radiologically suspicious benign lesions. ROC analysis was performed on 50 cancers and 209 radiologically suspicious benign lesions all detected as part of the same cancer screening program. For ROC analysis, a 25×25 voxel box was drawn around each radiologically suspicious lesion. A 25×25 patch was chosen as we have many small lesions detected in our highly sensitive screening program and a 25×25 patch allows visual inspection and analysis of our smallest lesions (about 2 to 3 mm across). If a single voxel inside the 25×25 box surrounding a benign lesion is diagnosed as cancer by any of the methods addressed, then that sample is counted as a false positive. All voxels within the 25×25 bounding box surrounding a benign lesion need to be diagnosed as noncancerous for the lesion to be counted as a true negative. This 25×25 bounding box was used in order to make sure that our analysis correctly counts any false positive voxels located

around benign lesions. The same counting scheme (making use of 25×25 bounding boxes) is used for the study's malignant lesions in order to measure true positives and false negatives, respectively.

FROC analysis was performed to measure the robustness of a particular computer-aided detection test by evaluating the tradeoff between the test's sensitivity and the rate at which the test yields false positive markings on noncancerous examinations. In this study, we have elected to evaluate false positive markings on a per voxel basis, as grouping spatially contiguous false positive voxels yields irregular FROC curves on this dataset due to the phenomenon of joining existing false positive regions as the sensitivity is improved. This results in an erratic FROC curve which can mislead the reader into thinking either CAD approach lowers the false positive rate as the sensitivity is increased through changing the threshold for malignancy. As such, in order to avoid misleading the reader, we have elected to perform FROC analysis comparing the tradeoff between the test sensitivity and the rate of false positive voxels per noncancerous examination.

The threshold for predicting cancer was varied for the signal enhancement ratio method, the proposed diffusion inspired method as well as the combined method in order to bias each test along the FROC curve. An atlas-based approach was used to automatically segment each breast volume away from the air as well as from the physiology behind the chest wall [27], thus helping to restrict the false positive counting scheme to breast tissues. The proposed diffusion inspired method's threshold for predicting malignancy was varied from 0 to 2.5 in steps of 0.05. The established signal enhancement ratio method, which flags tissues with suspicious dynamics was used as a baseline comparison for the proposed technique. The signal enhancement ratio (SER) method's threshold for predicting malignancy was varied from 0.0 to 10 in steps of 0.05, where the signal enhancement ratio is based on the examination's signal intensities (SI) based on the following definition: $SER = (SI(t=1\text{st post contrast time point}) - SI(t=\text{pre-contrast})) / (SI(t=\text{final post contrast time point}) - SI(t=\text{pre-contrast}))$. The combined method used the same threshold profile as was used for the signal enhancement ratio, where voxels below a threshold of 0.05 on Eq. 2 are assigned a benign/normal diagnosis.

The paired Wilcoxon sign-rank statistical test was performed to compare the rate of false positives of the signal enhancement ratio method (SER threshold for malignancy = 1.1) with the results of the combined system incorporating both SER and Eq. 2 (threshold for malignancy is 1.1 for SER as well as 0.05 for Eq. 2).

Results

The FROC results for each of the methods addressed is provided in Fig. 1. The proposed method defined in Eq. 2 yielded

Fig. 1 FROC analysis of proposed method, SER method and the combined method

the most robust test via FROC analysis on the first time point post contrast agent injection. This outperformed the established signal enhancement ratio method.

Although the proposed method provides promising results in terms of false positives per noncancerous examination (see FROC analysis), it is not appropriate for the differential diagnosis between malignant tumours and radiologically suspicious benign lesions. Results for the differential diagnosis of radiologically suspicious lesions are provided in the ROC analysis of Fig. 2. Combining the SER approach with the metric from Eq. 2 yields ROC results that match the SER method, while providing a comparatively low false positive rate as measured by our FROC analysis.

The paired Wilcoxon sign-rank statistical test was performed to compare the rate of false positives of the signal enhancement ratio method (SER threshold for malignancy =

Fig. 2 ROC analysis of proposed method, SER method and the combined method

1.1) with the results of the combined system incorporating both SER and Eq. 2 (threshold for malignancy is 1.1 for SER and 0.05 for Eq. 2). The results indicate that the proposed combined method yields a statistically significant reduction in false positives as compared with the SER method ($p < 0.00001$) based on the Wilcoxon sign-rank paired statistical test. This analysis of the proposed method was performed on the first time point post contrast agent injection. If the analysis were repeated on later time points throughout the examination, then the presented results degrade. As such, we have focused on its use as applied to the time point corresponding most closely with the expected peak signal enhancement post contrast agent injection. Example relative signal intensity images extracted from five malignant lesions are provided in Fig. 3 in the left column with the proposed metric's results displayed in the right column.

Discussion

Malignant lesions tend to exhibit elevated values of the proposed metric in Eq. 2. This might imply the existence of inter-voxel contrast agent diffusion towards less vascularized or unvascularized neighbouring tissues. The FROC analysis presented demonstrates that this proposed approach has potential as a computer-aided detection mechanism to assist radiologists in analysing MRI examinations acquired as part of screening high-risk women, particularly as a mechanism to reduce the false positives produced by the computer-aided detection system. Screening via MRI is particularly challenging given the large quantities of data acquired in the examinations. The ROC analysis presented demonstrates that, at present, the proposed metric should not be used for differential diagnosis between malignant and benign lesions, instead the potential utility of the proposed approach is found in the process of marking suspicious tissues (computer-aided detection) as opposed to differential diagnosis (computer-aided diagnosis).

The dataset used in this study contains many small lesions as well as ductal carcinoma in situ (DCIS), all of which exhibited some voxels that may exhibit contrast agent diffusion (based on their computed values for Eq. 2). The technique has been retrospectively evaluated for its potential use as a computer-aided detection system, responsible for marking suspicious tissues as part of a cancer screening program. The SER method's sensitivity for detecting malignancies is moderately low (80 % at the standard operating point where lesions are marked suspicious if they have a computed SER value above 1.1). These findings may help explain why a review of computer-aided breast MRI analysis software has found no sensitivity benefits from the technologies available, while their use was associated with a small decline in test specificity [28].

Fig. 3 Example relative signal intensity malignant lesions from the first post contrast time point (*left column*) and the results of the proposed metric (*right column*)

Many of the hardest to diagnose lesions in this study were very small cancers (2–5 mm across) which typically present on only a single slice based on the imaging protocol employed. Extending the analysis to 3D is not likely to help accurately diagnose these challenging cases as adding 3D analyses to this type of data would add noise to the measurement used by the CAD system as the slice thickness is about four times larger than the in plane spatial resolution. The slice thickness appears to prevent the acquisition of reliable through plane measurements in small lesions.

The combined method integrates the SER method with the proposed method and a threshold of 0.05 was selected as it did

not degrade the ROC results relative to the SER method alone. Raising the threshold substantially will degrade the ROC curve of the combined method while simultaneously improving the FROC results through lower false positives. Lowering the 0.05 threshold results in increased false positives from the combined CAD system and provides no improvements over the SER method's ROC results. At a threshold of 0.05, no degradation of ROC results was observed while simultaneously providing a major improvement in the false positive rate as measured through FROC analysis. The proposed metric is based on the spatial distribution of signal intensity values; as such, it is expected that an imaging examination's spatial resolution will affect the optimum threshold for this metric. Imaging examinations with variable spatial resolutions were not available when preparing this manuscript, and so a detailed assessment of the optimum threshold at varying spatial resolutions is the subject of future work. This technique has potential in screening applications as reduced false positives obtained through the combined approach can potentially assist radiologists in a particularly challenging and time-consuming aspect of the MRI-enabled screening process—scanning for suspect lesions.

An area of future research will be to combine this work with other features that are useful in distinguishing benign from malignant lesions to form a multi-dimensional classifier [29]. Considerable research in the literature is focused on computer-aided detection/diagnosis systems that combine an array of physiologically meaningful measurements. Hopefully, the presented metric will be shown to play a beneficial role in such systems in the future. Additionally, there is potential for variations in the MR acquisition protocol's spatial resolution to affect the appropriate threshold at which tissue is marked as suspicious based on this paper's proposed technique. Analysing this approach on a variety of MR protocol data including examples with varying spatial resolutions is an additional area for future research.

The main limitation of this study is that it was performed on a single dataset. Future work will entail analysing the proposed approach in the context of a challenging independent screening dataset. Furthermore, if we were trying to characterize a physically meaningful measurement of contrast agent diffusion based on Fick's law, we would need to establish what factors affect the diffusion coefficient for the contrast agent in the extracellular space. The extracellular volume fraction and local body temperature variations are examples of factors that will play a role in affecting the true diffusion coefficient for the contrast agent being used in the examination. In an ideal modification of this experiment, we would measure the extracellular volume fraction and would make T1 relaxation measurements so that our measured signal intensity values can be converted into contrast agent concentrations for the tissue. Then, the extracellular volume fraction can be used to estimate the contrast agent concentration in the extracellular

space. The diffusion coefficient of the contrast agent in the extracellular space (as affected by the extracellular volume fraction as well as other factors) would also be established. This could potentially improve on this study substantially, by allowing the diffusion estimation to be based on the contrast agent concentration differentials in neighbouring voxels' extracellular space. In this scenario, estimating a measure of Fick's diffusion would provide a physiologically and physically meaningful measurement (for example in moles of diffused molecules per unit time).

Additional limitations of this study include the assumption of a linear relationship between the relative signal intensity and the concentration of the contrast agent in the tissue. In reality, the relationship between the relative signal intensity and the concentration of the contrast agent in the tissue is nonlinear; however, contrast agent injections are provided at doses whereby the differences between the linear assumption and the true nonlinear relationship are small.

An additional limitation can be found in the assumption that the diffusion coefficient is a constant. The true diffusion coefficient D is not necessarily a constant. An accurate diffusion coefficient for the injected contrast agent in the extracellular space would be needed in order to extract physically meaningful contrast agent diffusion measurements (along with extracellular contrast agent concentrations). The appropriate diffusion coefficient would vary in a typical malignancy as cancerous lesions exhibit heterogeneity of vasculature and heterogeneity of the extracellular volume fraction. It is known that Fick's diffusion in a porous substance results in the diffusion coefficient being affected by a number of factors including the size of the pores and the tortuosity of the medium the molecules diffuse through, indicating that potentially measureable parameters such as the extracellular volume fraction may affect the diffusion coefficient.

Future work will include a detailed analysis combining the proposed tool as part of an overarching computer-aided detection system that is relied upon clinically. A detailed comparison will be performed analysing the radiologist's performance with and without the computer-aided detection tool. Future work will also entail examining this approach's potential based on exams with substantially higher spatial resolution. It is known that DCIS can exhibit enhancement due to what is expected to be diffusion of the contrast agent from high concentration regions near a leaky blood vessel towards lower concentrations within a duct containing a DCIS lesion [30]. At the moment, this approach does not provide discriminating information between malignant and benign lesions; however, it is possible that in the future, once imaging protocols are of higher spatial resolution, that metrics exploiting contrast agent diffusion will play an exciting role in early detection. At present, this paper's proposed method demonstrates considerable potential as a component of a CAD system responsible for lowering the false positives produced by the test. Future work

will look at validating the technique on larger independent datasets.

Conclusions

In this study, we have presented a metric inspired by Fick's diffusion of the contrast agent and demonstrated its potential use as a component of a computer-aided detection system targeting breast cancer from MRI examinations. We have shown that our technique can substantially lower the false positives produced by the test as demonstrated by FROC analysis. These results indicate that the proposed method may be useful as part of a computer-aided detection system assisting in the breast cancer screening process. Our combined system (using both Eq. 2 and SER) results in a substantial improvement in false positive voxels per noncancerous exam as well as providing equal differential diagnosis results as obtained with the established signal enhancement ratio as demonstrated by our ROC analysis in Fig. 2. False positive diagnoses are one of the largest shortcomings of modern computer-aided detection technologies; as such, the approach presented has considerable potential to assist in CAD enabled breast cancer screening.

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