Classifying Symmetrical Differences and Temporal Change in Mammography Using Deep Neural Networks

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Abstract. Neural networks, in particular deep Convolutional Neural Networks (CNN), have recently gone through a renaissance sparked by the introduction of more efficient training procedures and massive amounts of raw annotated data. Barring a handful of modalities, medical images are typically too large to present as input as a whole and models are consequently trained with subsets of images or cases, representing the most crucial bits of information. When inspecting a scene to identify objects, humans take cues from not just the article in question but also the elements in its vicinity: a frisbee is more likely to be a plate in the presence of a fork and knife. Similar principles apply to the analysis of medical images: specialists base their judgment of an abnormality on all available data, harnessing information such as symmetrical differences in or between organs in question and temporal change, if multiple recordings are available.

In this paper we investigate the addition of symmetry and temporal context information to a deep CNN with the purpose of detecting malignant soft tissue lesions in mammography. We employ a simple linear mapping that takes the location of a mass candidate and maps it to either the contra-lateral or prior mammogram and Regions Of Interest (ROI) are extracted around each location. We subsequently explore two different architectures (1) a fusion model employing two datastreams were both ROIs are fed to the network during training and testing and (2) a stage-wise approach where a single ROI CNN is trained on the primary image and subsequently used as feature extractor for both primary and symmetrical or prior ROIs. A `shallow’ Gradient Boosted Tree (GBT) classifier is then trained on the concatenation of these features and used to classify the joint representation. Results shown a significant increase in performance using the first architecture and symmetry information, but only marginal gains in performance using temporal data and the other setting. We feel results are promising and can greatly be improved when more temporal data becomes available.

Keywords: Deep Learning, Convolutional Neural Networks, Machine Learning, Computer Aided Diagnosis, Breast Cancer.

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1 Introduction

Breast cancer screening in the form of annual or biennial breast X-rays is being performed to detect cancer at an early stage, which has been shown to increase chances of survival significantly. Studies suggest a reduction in breast cancer mortality of up to 40%. Manual reading of screening data is time consuming and error prone and to aid interpretation, Computer Aided Detection and Diagnosis (CAD) systems are developed. For mammography, CAD is already widely applied as a second reader but effectiveness of current technology is disputed. Several studies show no increase in sensitivity or specificity with CAD for masses or even a decreased specificity without an improvement in detection rate or characterization of invasive cancers.

During a mammographic exam, images are typically recorded of each breast and absence of a certain structure around the same location in the contra-lateral image will render an area under scrutiny more suspicious. Conversely, the presence of alike tissue less so. Additionally, due to the annual or biennial organization of screening, there is a temporal dimension and similar principles
apply: the amount of fibroglandular tissue is expected to decrease with age and therefore, novel structures that are not visible on previous exams, commonly referred to as \textit{priors}, spark suspicion.

In medical literature, an asymmetry denotes a potentially malignant density that is not characterized as a mass or architectural distortion. Four types are distinguished: (1) a plain \textit{asymmetry} refers to a density lacking convex borders, seen in only one of the two standard mammographic views, (2) a \textit{focal asymmetry} is visible on two views but does not fit the definition of a mass, (3) a \textit{global asymmetry} indicates a substantial difference in total fibroglandular tissue between left and right breast, (4) a \textit{developing asymmetry} refers to a growing asymmetry in comparison to prior mammograms.\textsuperscript{11,12} These types are generally benign, but have been associated with an increased risk\textsuperscript{13} and are sometimes the only manifestation of a malignancy. To the best of our knowledge, no relevant work has been done that compare readers performance of malignancies with and without left and right comparisons, but asymmetry is often mentioned by clinicians as an important clue, also to detect malignancies that are classified as a mass. The merit of temporal comparison mammograms on the other hand has been well studied and is generally known to improve specificity without a profound impact on sensitivity for detection.\textsuperscript{14–18}

Burnside et al.\textsuperscript{15} analyzed a set of diagnostic and screening mammograms and concluded that in the latter case, comparison with previous examinations significantly decreases the recall rate and false positive rate, but does not increase sensitivity. Varela et al.\textsuperscript{16} compared the reading performance of six readers and found the performance drops significantly when removing the prior mammogram, in particular in areas of high specificity, relevant for screening. Roelofs et al.\textsuperscript{17} also investigated the merit of prior mammograms in both detection and assessment of malignant lesions. Their results show performance was significantly better in the presence of a prior exam, but no more lesions are found. They subsequently postulate priors are predominantly useful for interpretation and less so for initial detection. Yankakis et al.\textsuperscript{18} additionally investigate the effect of noticeable change in tissue in mammograms. They generated separate sets of current-prior examination pairs with and without noticeable change and observed that recall rate, sensitivity and Cancer Detection Rate (CDR) are higher when change is noted, but specificity is lower, resulting in a higher false positive rate.

Symmetry is often used as a feature in traditional CAD systems detecting pathologies such as lesions in the brain,\textsuperscript{19} prostate cancer\textsuperscript{20} and abnormalities in the lungs.\textsuperscript{21} Most research on mammographic asymmetries involves the classification of a holistic notion of discrepancy rather than the incorporation of this information in a CAD system.\textsuperscript{22,23} Published work on temporal analysis typically relies on the extraction of features from both current and prior exams which are combined into a single observation and fed to a statistical learning algorithm.\textsuperscript{24,25} For detection, an additional registration step is performed.\textsuperscript{26} This has been shown to significantly increase performance of the traditional, handcrafted feature based systems.

Recent advances in machine learning, in particular deep learning\textsuperscript{27–30} signified a breakthrough in Artificial Intelligence (AI) research and heralded in a new ’AI summer’. Several pattern recognition applications are now claiming human or even super human performance\textsuperscript{31–34} and progress is still being made at an astounding pace. Development for vision based systems benefited substantially from large scale challenges such as ImageNet\textsuperscript{35} where deep Convolutional Neural Networks
CNNs) are currently dominating leader boards on all sub tasks and have become the de-facto standard for object detection. Rather than relying on engineers and domain experts to design features, the systems learn feature transformations from data, saving enormous amounts of time in development and preventing any human bias imposed on the descriptors.

The adoption of deep neural architectures in medical image analysis was initially reluctant, but the community has recently seen a surge of papers denunciating the classical tenets of feature extraction and shallow learning algorithms, making way for deep systems fed with large amounts of raw data. Recent work showed significant improvements upon the state-of-the art and claimed top ranks on benchmarks and challenges bolstering their status as a new paradigm.

The vanilla CNN architecture facilitates a rather generic problem solver for many signal processing tasks but is still limited by the constraint that a single tensor needs to be fed to the front-end layer if no further adaptations in the network are made. Medical images provide an interesting new data source, warranting adaption of methods successful in natural images. Several alternative architectures that go beyond the patch level and work with multi-scale or video have been explored for natural scenes. In these settings, multiple datastreams are employed, where each datastream represents, for instance, a different scale in the image or frames at different time points in a video. Similar ideas have been applied to medical data, most notably the 2.5D simplification of volumetric scans.

In this paper we extend previous work and investigate the addition of symmetry and temporal information to a deep CNN with the purpose of detecting malignant soft tissue lesions in mammography. We employ a simple linear mapping that takes the location of a mass candidate and maps it to either the contra-lateral or prior mammogram and Regions Of Interest (ROI) are extracted around each location. We subsequently explore two different architectures

1. A fusion model employing two datastreams were both ROIs are fed to the network during training and testing, an illustration is provided in figure 4.

2. A stage-wise approach where a single ROI CNN is trained on the primary image and subsequently used as feature extractor for both primary and symmetrical or prior ROIs. A ‘shallow’ Gradient Boosted Tree (GBT) classifier is subsequently trained on the concatenation of these features and used to classify similar concatenations of features in the test set.

Examples of symmetry pairs are show in figure 1. Figure 2 shows several examples of temporal pairs.

To the best of our knowledge, this is the first CAD and deep learning approach incorporating symmetry as a feature in a CAD system and the first CAD paper exploring deep neural networks for temporal comparison. Even though the methods are applied to mammography, we feel results may be relevant as well for other medical image analysis tasks, where classification of anomalies that occur unilaterally or develop over time are sought, such as lung, prostate and brain images.

The rest of this paper is divided into 5 sections. In the following section, we will outline the data pre-processing, candidate detector and registration method used. In section 3 the deep neural
Fig 1: Examples of symmetry pairs. **Top row:** Very suspicious malignant lesion, regardless of its contra-lateral counterpart.

**Middle row:** Malignant lesion that is more suspicious in the light of its contra-lateral image.

**Bottom row:** Normal structure that is less suspicious in the light of its contra-lateral image.

Fig 2: Examples of temporal pairs. The right column represents the current and the left column the prior image it is compared with, using the mapping described in section 2.2
architectures will be described followed by a description of the data and experimental setup in section 4. Results will be discussed in section 5 and we will end with a conclusion in section 6.

2 Data Preparation

2.1 Candidate Detection

We generally follow the candidate detection setup described in Kooi et al.\textsuperscript{38} To get potential locations of lesions and extract candidate patches, we make use of a popular candidate detector for mammographic lesions.\textsuperscript{51} It employs five features based on first and second order Gaussian kernels, two designed to spot the center of a focal mass and two looking for spiculation patterns, characteristic of malignant lesions. A final feature indicates the size of optimal response in scale-space. We subsequently apply a random forest\textsuperscript{52} classifier to generate a likelihood map on which we perform non-maximum suppression. All optima are treated as candidates and patches are extracted around each. Since many candidates are too close to the border to extract full patches, we pad the image with zeros. After candidates have been generated, locations are mapped to the same point in the contra-lateral image or the prior.

2.2 Mapping Image Locations

Finding corresponding locations between two mammograms is a challenging problem due to two main factors: (1) apart from the nipple and chest wall, which may not always be visible, there are no clear landmarks to accommodate feature based registration and (2) the transformation is highly non-linear. Before the mammogram is recorded the breast is deformed strongly: viewing area is optimized and dose is minimized by stretching the breast. Additionally, the compression plates may not always touch the breast at the same location causing some movement of tissue within the breast.

A comparative study between several commonly applied registration methods by Van Engeland et al.\textsuperscript{53} found a simple linear approach based on the position of the nipple and center of mass alignment outperformed more complex methods such as warping. In light of this, we propose a similar approach based on two landmarks. The row location of the front of the breast (an approximation of the nipple location) $p_1$ is estimated by taking the largest distance to the chest wall and a column point in the chest wall $p_2$ is taken as the row location of the center of gravity of a breast segmentation mask, generated by simple thresholding. The lesion center $q'$ in the secondary image is estimated according to:

$$q' = q - p + p'$$  \hspace{1cm} (1)

with $p = (p_1, p_2)^T$, i.e., we simply clamp the x-distance to the chest wall and the y-distance to the estimated location of the nipple. An example is provided in figure 3.

Since most CNN architectures induce a decent amount of translation invariance, the mapping does not need to be very precise. To further mitigate mapping errors, we introduce a form of data augmentation by mapping each location in the image in question to 64 different points in the comparison mammogram by sampling the location from a Gaussian with zero mean and 10 pixel standard deviation.
Fig 3: To incorporate symmetry and temporal information, we make use of a simple mapping, based on two coordinates indicated by the end points of the yellow line. (a) A Region Of Interest (ROI) represented by the green box is extracted around a potential malignant lesion location, indicated by the green dot, found by a candidate detector. The location is subsequently matched to either the prior (b) or the contra-lateral image (c). We explore two deep Convolutional Neural Network (CNN) fusion strategies to optimally capture the relation between contra-lateral and prior images.
3 Deep Convolutional Neural Networks

The CNN architecture exploits structure of the input by sharing weights at different locations in the image, resulting in a convolution operation, the main workhorse of the CNN. The main difference between deep models and conventional statistical learning methods is the nested non-linear function the architecture represents. At each layer, the input signal is convolved with a set of $K$ kernels $W = (W_1, W_2, \ldots, W_K)$, each generating a new set of feature maps $X_k$. These features are subjected to an element-wise non-linear transform $\sigma(\cdot)$ and the same process is repeated for every convolutional layer $l_0, l_1, \ldots, l_L$:

$$X_k^l = \sigma(W_k^{l-1} \otimes X^{l-1} + b_k^{l-1})$$  \hspace{1cm} (2)

Convolutional layers are generally alternated with pooling layers that subsample the resulting feature maps, generating some translation invariance and reducing the dimensionality as information flows through the architecture. After these layers, the final tensor of feature maps is flattened to a vector $x^l$ and several fully connected layers are typically added, where weights are no longer shared:

$$x^l = \sigma(W^l x^{l-1} + b^l)$$  \hspace{1cm} (3)

The posterior distribution over a class variable $y_i$, given input patch $X^0$ is acquired by feeding the last level of activations $x^L$ to either a logistic sigmoid for single class or a softmax function for multi class:

$$P(y_i | X^0; \Theta) = \text{softmax}(x^L | W, b) = \frac{e^{w_i^T x^L + b_i^L}}{\sum_{k=1}^K e^{w_k^T x^L + b_k^L}}$$  \hspace{1cm} (4)

with $\Theta$ the set of all weights and biases in the network and $w_i$ the vectorized set of weights leading to the output node of class $i$. The whole network can be seen as a parameterized feature extractor and classifier, where the parameters of the feature transformation and classifier are learned jointly and optimized based on training data.

The parameters in the network are generally learned using Maximum Likelihood Estimation (MLE) or Maximum A-Posteriori (MAP), when employing regularization and default backpropagation. Increasing depth up to some point, seems to improve efficiency and reduces the amount of parameters that need to be learned, without sacrificing performance or even increases overall performance.\textsuperscript{54–56} The gradient of the error of each training sample is dispersed among parameters in every layer during backpropagation and hence becomes smaller (or in rare cases explodes), which is referred to as the fading gradient problem. Common tricks to quell this phenomenon are smart weight initialization,\textsuperscript{57, 58} batch normalization\textsuperscript{33} and non-saturating transfer functions such as Rectified Linear Units (ReLU) or recently Exponential Linear Units (ELU).\textsuperscript{59}

3.1 Fusion Architectures

Partly inspired by the work of Karpathy et al.,\textsuperscript{45} we propose to add the symmetrical and (first prior) temporal counterparts of a patch as separate datastreams to a network. In principle, the datastreams can be merged at any point in the network, with simply treating the additional patch as a second channel the extreme case. Neverova et al.\textsuperscript{46} postulate the optimal point of fusion pertains to the degree of similarity of the sources, but to the best of our knowledge no empirical or theoretical work exists that investigates this. We evaluate two architectures:
1. A two-stream network were kernels are shared and datastreams are fused at the first fully connected layer. Figure 4 provides an illustration of this network.

2. A single patch, single stream network is used as a feature extractor by classifying all samples in the train and test set and extracting the latent representation of each patch from the first fully connected layer \( x^{fc1} \) of the network. This feature representation of the primary and either contra-lateral or prior ROI are concatenated and fed to a 'shallow' GBT classifier to generate a new posterior that captures both symmetry or (first prior) temporal information.

The second approach is far easier to train, since it does not entail re-optimizing hyperparameters of a deep model, which is tedious and time consuming. A downside is that the kernels effectively see less data and are therefore potentially less adjusted to the task. Additionally, the second setup is more prone to overfitting. We will elaborate on this in the discussion.

In general, there are a lot less temporal than symmetry samples because they require two rounds of screening and symmetry samples only one. To compare these architectures, we could simply take a subset of the data where each current exam has both a symmetrical and prior counterpart. Unfortunately, this yields a relatively small subset of the data and in early experiments, we found the (base) performance to be very marginal and not sufficient to provide a fair comparison. We therefore view missing prior exams simply as missing data. Although missing data has been well studied in the statistics community,\(^{60}\) relatively little has been published with respect to discriminative models.

In the context of Recurrent Neural Networks (RNNs),\(^{61–63}\) several imputation methods have been explored.\(^{64, 65}\) Lipton et al.\(^{65}\) investigate two imputation strategies: zero-imputation, where missing samples are simple set to zero and forward-filling that sets the missing value to the value observed before that. Their results show zero imputation with missing data indicators works best, but no significance analysis is performed. In a similar spirit we propose to use a black image when no prior is available. When women skip a screening, we map the image to the exam four years ago or add a black image if this is absent.

To add symmetry and temporal information simultaneously, both architectures can trivially be extended with a third stream. However, this requires some additional engineering and we therefore restrict this study to learning two separate models and will propose ways to extend this in the discussion.

4 Experiments

4.1 Data

Our data was collected from a mammography screening program in The Netherlands (Screening Mid-West) and was recorded with a Hologic Selenia mammography device. Before presentation to the human reader, the image is typically processed to optimize contrast and enhance the breast periphery. To prevent information loss, we work on the raw images instead and only apply a log transform which results in a representation in which attenuation and pixel values are linearly related. Further details on processing can be found in Kooi et al.\(^{38}\)
To learn differences between left and right breast and temporal change around a candidate location, we use a two-stream Convolutional Neural Network (CNN). The first stream has as input a patch centered at a candidate location, the second stream a patch around the same location in either the contra-lateral image or the prior, using the mapping depicted in figure 3. All weights are shared across streams and feature maps are concatenated before the first fully connected layer.

Table 1: Overview of the data used for training, validation and testing. Findings refers to the amount of candidates (before data augmentation). Number are separated by '/' where the first number indicates the amount for training, the second the amount for validation and the third the amount for testing.

| Findings | Cases |
|----------|-------|
| Masses   | 869/210/470 | 796/189/386 |
| Normal   | 200982/54566/74799 | 3111/1482/1137 |

Our dataset consists of 18366 cases. We generated train, validation and test set by splitting on a case level, i.e., samples from the same patient are not scattered across sets. We took 65% for training, 15% for validation and 25% for testing. An overview of the data is provided in table 1.

4.2 Learning Settings and Implementation Details

The networks were implemented in TensorFlow and generally follow the architecture used in Kooi et al. Hyperparameters of all models were optimized on a separate validation set using random search. For the deep CNNs, we employed VGG-like architectures with 5 convolutional layers with \{16, 16, 32, 32, 64\} kernels of size 3 × 3 in all layers. We used ‘valid’ convolutions using a stride of 1 in all settings. Max pooling of 2 × 2 was used using a stride of 1 in all but the final convolutional layer. Two fully connected layers of 512 each were added. Weights were initialized using the MSRA weight filler, with weight sampled from a truncated normal, all biases were initialized to 0.001. We employed ELU’s as transfer functions in all layers. Further parameters for each network were optimized individually. Learning rate, dropout and L2 norm coefficient were optimized per architecture. On top of the ‘alignment augmentation’ described in section 2.2, we used the data augmentation scheme described in Kooi et al.

Since the class ratio is in the order of 1/10000, randomly sampling minibatches will result in very poor performance as the network will just learn to classify all samples as negative. We therefore applied the following scheme. We generated two separate datasets, one for all positive and one for all negative samples. Negative samples are read from disk in chunks and all positive samples
are loaded into host RAM. During an epoch, we cycle through all negative samples and in each minibatch take a random selection of an equal amount of positives, which are subsequently fed to GPU where gradients are computed and updated. This way, all negative samples are presented in each epoch and the class balance is maintained. Each configuration trained for roughly 10 days on a TitanX 12 GB GPU.

For the shallow model, we employ Gradient Boosted Trees (GBT) using the excellent XGBoost implementation. We cross-validated the shrinkage and depth using 16 folds. Further parameters were tuned on a fixed validation set using a coordinate descent like scheme.

4.3 Results

Given the results from clinical literature regarding the merit of priors, we focus our results on the classification of candidates and therefore only present ROC curves, rather than FROC curves that are commonly used for detection. To obtain confidence intervals and perform significance testing, we performed bootstrapping using 5000 bootstraps. All curves shown are the mean curve from these bootstrap samples using cubic interpolation. The baseline obtained an AUC of 0.87 with confidence interval $[0.853, 0.893]$. The first architecture where both patches are presented during trained obtained an AUC of 0.895 with confidence interval $[0.877, 0.913]$ and the second architecture where a new classifier is retrained on the concatenation and AUC of 0.88 with confidence interval $[0.859, 0.9]$. Figure 5 shows the results of the single ROI baseline, and the fusion architectures as described in section 3.1. We find significant difference at high specificity on the interval $[0.2, 1]$, $p = 0.02$ between the first architecture and the baseline, but no significant difference on the full AUC. For the second architecture we did not find a significant difference between either the baseline or the first architecture.

For the temporal comparison, the first architecture where both patches are presented during trained obtained an AUC of 0.884 with confidence interval $[0.865, 0.902]$ and the second architecture where a new classifier is retrained on the concatenation and AUC of 0.879 with confidence interval $[0.858, 0.898]$. We did not find a significant difference between any of the architectures, but again improvements were found to be consistent during early experiments. Figure 6 shows
5 Discussion

From the curves in figure 5 and 6 we can see both symmetry and temporal data improve performance, but only see marginal improvements with temporal data. The curves also show the scheme where both ROIs are fed to a single network (architecture (1) in section 3.1) works best. As mentioned in section 3.1, architecture (2) has the advantage that no new networks need to be trained which can take several months to do properly for large datasets. Two disadvantages, however, are that (1) the kernels in the network (parameters up to the first fully connected layer) effectively see less data. In the first architecture, even though the kernels are shared, they are trained one both the primary and either symmetry or prior patch and therefore better adjusted to the task. (2) Overfitting is a much bigger issue: since the features are learned on most of the data the models are trained on, the cross-validation procedure of the GBT often gave a strong underestimate of the optimal regularization coefficients (depth, shrinkage in the case of the GBT), resulting in strong gaps between train and test performance. Optimizing this on a fixed validation set did not result in much better performance. We have tried extracting features from deeper in the network to mitigate this effect but found lower performance.

As mentioned in section 3.1, we have added a black image where no prior was available. From the curves in figure 6 we can see that the prior ROI does add some information and therefore this approach is at least not detrimental to performance. Additionally, one possible advantage of this approach is that it carries some additional information: the number of tumours found in the first screening round is often higher, when using imputation methods mentioned by Lipton et al.63 this information is effectively lost.

In clinical practice, radiologists sometimes look back two studies instead of one, when comparing the current to the prior. Since this requires three screening rounds, this reduces the size of our dataset again if we want to emulate this and more prior ROIs need a black image. Ideally, the
neural network architecture should accommodate a varying set of priors. In early experiments, we have explored the use of Recurrent Neural Networks,\textsuperscript{61–63} a model designed for temporal data that can be trained and tested on varying input and output sizes. We did not see a clear improvement in performance, but plan to explore this idea more in future work.

In this study, we have trained all networks from scratch. Since the rudimentary features that are useful to detect cancer in one view are expected to be almost as useful when combining views, a better strategy may be to initialize the symmetry or temporal two-stream network with the weights trained on a single ROI. Similarly, since we expect similar features are useful to spot discrepancies between left and right breast as to spot differences between time points, the temporal network could be initialized with the network trained on symmetry patches or the other way around. Due to time constraints this was left to future work, but we suspect an increase in performance.

We have compared two different fusion strategies. As mentioned in section 3.1, the datastreams can in principle be fused at any point in the network, as done by Karpathy et al.\textsuperscript{45} However, there is no guarantee that different architectures perform optimal using the same hyperparameters. For instance, the weight updates of lower layers change if fusion is performed at different points higher in the network. In particular, the learning rate is often found to be important and we feel comparison rings somewhat hollow if no extensive search through the parameter space is done. Since a model typically trains for roughly a week, this is infeasible in our current hardware and we have decided to focus on the two presented models.

Since the focus of this paper is the presentation of two fusion schemes for adding symmetry and temporal information to a deep CNN, we have presented separate results for each. In practice, when using a CAD system to generate a label for a case, these should be merged into one decision. As mentioned in section 3.1, extending the network with a third datastream is trivial. However, this limits the application to cases where both prior and contra-lateral image are available. In our method, we have added a black image, where priors where not available and a similar approach could be pursued in this setting. Another option would be to train a third classifier on top of the latent representation from separate CNNs or the posterior output by separate CNNs, possibly using a missing data model. Since training deep neural networks and optimizing hyperparameters takes a lot of time, we have left this for future work.

6 Conclusion

In this paper we have presented two deep Convolutional Neural Network (CNN) architectures to add symmetry and temporal information in a Computer Aided Detection (CAD) system for mass candidates in mammography. To the best of our knowledge, this is the first approach exploring deep CNNs for symmetry and temporal classification in a CAD system. Results show improvement in performance for both symmetry and temporal data. Though in the latter case gain in performance is still marginal, it is promising and we suspect that when more data becomes available, performance will significantly increase. Although the methods are applied to mammography, we think results can be relevant for other CAD problems were symmetrical discrepancies within or between organs is sought, such as lung, brain and prostate images or CAD tasks where temporal change
needs to be analyzed, such as lung cancer screening.

Disclosures

Thijs Kooi has no potential conflicts of interest. Nico Karssemeijer is co-founder, shareholder, and director of ScreenPoint Medical BV (Nijmegen, The Netherlands), co-founder of Volpara Health Technologies Ltd. (Wellington, New Zealand), and QView Medical Inc. (Los Altos, CA).

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References

1. L. Tabar, M.-F. Yen, B. Vitak, et al., “Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening,” The Lancet 361, 1405–1410 (2003).
2. M. L. Giger, N. Karssemeijer, and S. G. Armato, “Computer-aided diagnosis in medical imaging,” IEEE Transactions on Medical Imaging 20, 1205–1208 (2001).
3. K. Doi, “Computer-aided diagnosis in medical imaging: historical review, current status and future potential,” Computerized Medical Imaging and Graphics 31, 198–211 (2007). PMID: 17349778.
4. K. Doi, “Current status and future potential of computer-aided diagnosis in medical imaging,” British Journal of Radiology 78 Spec No 1, S3–S19 (2005).
5. B. van Ginneken, C. M. Schaefer-Prokop, and M. Prokop, “Computer-aided diagnosis: how to move from the laboratory to the clinic,” Radiology 261(3), 719–732 (2011).
6. V. M. Rao, D. C. Levin, L. Parker, et al., “How widely is computer-aided detection used in screening and diagnostic mammography?,” Journal of the American College of Radiology 7, 802–805 (2010).
7. A. Malich, D. R. Fischer, and J. Böttcher, “CAD for mammography: the technique, results, current role and further developments,” European Radiology 16, 1449–1460 (2006).
8. P. Taylor, J. Champness, R. Given-Wilson, et al., “Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography,” Health Technology Assessment 9, iii, 1–iii,58 (2005).
9. J. J. Fenton, L. Abraham, S. H. Taplin, et al., “Effectiveness of computer-aided detection in community mammography practice,” Journal of the National Cancer Institute 103, 1152–1161 (2011).
10. C. D. Lehman, R. D. Wellman, D. S. M. Buist, et al., “Diagnostic accuracy of digital screening mammography with and without computer-aided detection.,” JAMA Intern Med 175, 1828–1837 (2015).
11. E. A. Sickles, “The spectrum of breast asymmetries: imaging features, work-up, management,” 45(5), 765–771 (2007).
12. J. H. Youk, E.-K. Kim, K. H. Ko, et al., “Asymmetric mammographic findings based on the fourth edition of bi-rads: Types, evaluation, and management 1,” 29(1), e33–e33 (2009).
13 D. Scutt, G. A. Lancaster, and J. T. Manning, “Breast asymmetry and predisposition to breast cancer,” 8(2), 1 (2006).
14 M. G. Thurfjell, B. Vitak, E. Azavedo, et al., “Effect on sensitivity and specificity of mammography screening with or without comparison of old mammograms,” Acta Radiologica 41(1), 52–56 (2000).
15 E. S. Burnside, E. A. Sickles, R. E. Sohlich, et al., “Differential value of comparison with previous examinations in diagnostic versus screening mammography,” American Journal of Roentgenology 179(5), 1173–1177 (2002).
16 C. Varela, N. Karssemeijer, J. H. C. L. Hendriks, et al., “Use of prior mammograms in the classification of benign and malignant masses,” European Journal of Radiology 56, 248–255 (2005).
17 A. A. J. Roelofs, N. Karssemeijer, N. Wedekind, et al., “Importance of comparison of current and prior mammograms in breast cancer screening,” Radiology 242, 70–77 (2007).
18 B. C. Yankaskas, R. C. May, J. Matuszewski, et al., “Effect of observing change from comparison mammograms on performance of screening mammography in a large community-based population,” Radiology 261(3), 762–770 (2011).
19 S. X. Liu, “Symmetry and asymmetry analysis and its implications to computer-aided diagnosis: A review of the literature,” 42(6), 1056–1064 (2009).
20 G. Litjens, O. Debats, J. Barentsz, et al., “Computer-aided detection of prostate cancer in MRI,” IEEE Transactions on Medical Imaging 33, 1083–1092 (2014).
21 B. van Ginneken, Computer-aided diagnosis in chest radiography. PhD thesis, Utrecht University, The Netherlands (2001).
22 R. J. Ferrari, R. M. Rangayyan, J. E. Desautels, et al., “Analysis of asymmetry in mammograms via directional filtering with gabor wavelets,” IEEE Transactions on Medical Imaging 20, 953–964 (2001).
23 P. Casti, A. Mencattini, M. Salmeri, et al., “Analysis of structural similarity in mammograms for detection of bilateral asymmetry,” 34(2) (2015).
24 L. Hadjiiski, B. Sahiner, H. P. Chan, et al., “Analysis of temporal changes of mammographic features: computer-aided classification of malignant and benign breast masses,” Medical Physics 28, 2309–2317 (2001).
25 S. Timp, C. Varela, and N. Karssemeijer, “Temporal change analysis for characterization of mass lesions in mammography,” IEEE Transactions on Medical Imaging 26, 945–953 (2007).
26 S. Timp and N. Karssemeijer, “Interval change analysis to improve computer aided detection in mammography,” Medical Image Analysis 10, 82–95 (2006).
27 Y. Lecun, L. Bottou, Y. Bengio, et al., “Gradient-based learning applied to document recognition,” Proceedings of the IEEE 86, 2278–2324 (1998).
28 G. E. Hinton, S. Osindero, and Y.-W. Teh, “A fast learning algorithm for deep belief nets,” Neural Computation 18, 1527–1554 (2006).
29 Y. Bengio, A. Courville, and P. Vincent, “Representation learning: A review and new perspectives,” IEEE Transactions on Pattern Analysis and Machine Intelligence 35(8), 1798–1828 (2013).
30 J. Schmidhuber, “Deep learning in neural networks: an overview,” Neural Networks 61, 85–117 (2015).
31 D. C. Ciresan, U. Meier, J. Masci, et al., “Multi-column deep neural network for traffic sign classification,” Neural Networks 32, 333–338 (2012).
32 V. Mnih, K. Kavukcuoglu, D. Silver, et al., “Human-level control through deep reinforcement learning,” Nature 518, 529–533 (2015).
33 S. Ioffe and C. Szegedy, “Batch normalization: Accelerating deep network training by reducing internal covariate shift,” arXiv:1502.03167 (2015).
34 D. Silver, A. Huang, C. J. Maddison, et al., “Mastering the game of go with deep neural networks and tree search,” Nature (2016).
35 O. Russakovsky, J. Deng, H. Su, et al., “ImageNet large scale visual recognition challenge,” International Journal of Computer Vision 115(3), 1–42 (2014).
36 G. Litjens, T. Kooi, B. E. Bejnordi, et al., “A survey on deep learning in medical image analysis,” arXiv:1702.05747v1 (2017).
37 H. Roth, L. Lu, J. Liu, et al., “Improving computer-aided detection using convolutional neural networks and random view aggregation,” IEEE Transactions on Medical Imaging (2016).
38 T. Kooi, G. Litjens, B. van Ginneken, et al., “Large scale deep learning for computer aided detection of mammographic lesions,” Medical Image Analysis 35, 303–312 (2016).
39 A. A. A. Setio, F. Ciompi, G. Litjens, et al., “Pulmonary nodule detection in CT images: false positive reduction using multi-view convolutional networks,” IEEE Transactions on Medical Imaging 35(5), 1160–1169 (2016).
40 M. J. P. van Grinsven, B. van Ginneken, C. B. Hoyng, et al., “Fast convolutional neural network training using selective data sampling: Application to hemorrhage detection in color fundus images,” IEEE Transactions on Medical Imaging 35(5), 1273–1284 (2016).
41 D. Cireşan, A. Giusti, L. M. Gambardella, et al., “Mitosis detection in breast cancer histology images with deep neural networks,” in Medical Image Computing and Computer-Assisted Intervention, Lecture Notes in Computer Science 8150, 411–418 (2013).
42 O. Ronneberger, P. Fischer, and T. Brox, “U-net: Convolutional networks for biomedical image segmentation,” in Medical Image Computing and Computer-Assisted Intervention, Lecture Notes in Computer Science 9351, 234–241 (2015).
43 D. Wang, A. Khosla, R. Gargeya, et al., “Deep learning for identifying metastatic breast cancer,” (2016).
44 C. Farabet, C. Couprie, L. Najman, et al., “Learning hierarchical features for scene labeling,” IEEE Transactions on Pattern Analysis and Machine Intelligence 35(8), 1915–1929 (2013).
45 A. Karpathy, G. Toderici, S. Shetty, et al., “Large-scale video classification with convolutional neural networks,” in Computer Vision and Pattern Recognition (CVPR), 2014 IEEE Conference on, 1725–1732, IEEE (2014).
46 N. Neverova, C. Wolf, G. W. Taylor, et al., “Multi-scale deep learning for gesture detection and localization,” in European Conference on Computer Vision, (2014).
47 K. Simonyan and A. Zisserman, “Two-stream convolutional networks for action recognition in videos,” (2014).
48 A. Prasoon, K. Petersen, C. Igel, et al., “Deep feature learning for knee cartilage segmentation using a triplanar convolutional neural network,” Medical Image Computing and Computer-Assisted Intervention 16, 246–253 (2013).
49 H. R. Roth, L. Lu, A. Seff, et al., “A new 2.5D representation for lymph node detection using random sets of deep convolutional neural network observations,” in Medical Image Computing and Computer-Assisted Intervention, Lecture Notes in Computer Science 8673, 520–527 (2014).

50 T. Kooi and N. Karssemeijer, “Deep learning of symmetrical discrepancies for computer-aided detection of mammographic masses,” in Proceedings of the SPIE, (2017).

51 N. Karssemeijer and G. te Brake, “Detection of stellate distortions in mammograms,” IEEE Transactions on Medical Imaging 15, 611–619 (1996).

52 L. Breiman, “Random forests,” Machine Learning 45(1), 5–32 (2001).

53 S. van Engeland, P. Snoeren, J. Hendriks, et al., “A comparison of methods for mammogram registration,” IEEE Transactions on Medical Imaging 22, 1436–1444 (2003).

54 R. K. Srivastava, K. Greff, and J. Schmidhuber, “Training very deep networks,” (2015).

55 K. Simonyan and A. Zisserman, “Very deep convolutional networks for large-scale image recognition,” arXiv:14091556 (2014).

56 K. He, X. Zhang, S. Ren, et al., “Deep residual learning for image recognition,” arXiv:1512.03385 (2015).

57 X. Glorot and Y. Bengio, “Understanding the difficulty of training deep feedforward neural networks,” in International conference on artificial intelligence and statistics, 249–256 (2010).

58 K. He, X. Zhang, S. Ren, et al., “Delving deep into rectifiers: Surpassing human-level performance on imagenet classification,” Computer Vision and Pattern Recognition, 1026–1034 (2015).

59 D.-A. Clevert, T. Unterthiner, and S. Hochreiter, “Fast and accurate deep network learning by exponential linear units (elus),” (2015).

60 P. D. Allison, MIssing Data, Sage Publications (2001).

61 A. Graves, Supervised Sequence Labelling with Recurrent Neural Networks. PhD thesis (2012).

62 K. Greff, R. K. Srivastava, J. Koutnìk, et al., “Lstm: A search space odyssey,” arXiv:1503.04069 (2015).

63 Z. C. Lipton, J. Berkowitz, and C. Elkan, “A critical review of recurrent neural networks for sequence learning,” arXiv:1506.00019 (2015).

64 Z. Che, S. Purushotham, K. Cho, et al., “Recurrent neural networks for multivariate time series with missing values,” in arXiv:1606.01865, (2016).

65 Z. C. Lipton, D. C. Kale, and R. Wetzel, “Modeling missing data in clinical time series with rns,” (2016).

66 M. Abadi, A. Agarwal, P. Barham, et al., “Tensorflow: Large-scale machine learning on heterogeneous distributed systems,” arXiv:1603.04467 (2016).

67 J. Bergstra and Y. Bengio, “Random search for hyper-parameter optimization,” Journal of Machine Learning Research 13(1), 281–305 (2012).

68 J. H. Friedman, “Greedy function approximation: a gradient boosting machine,” Annals of Statistics, 1189–1232 (2001).

69 T. Chen and C. Guestrin, “Xgboost: A scalable tree boosting system,” (2016).

70 B. Efron and R. J. Tibshirani, An introduction to the bootstrap, vol. 57, CRC press (1994).