Non-Parametric Image Subtraction for MRI

P. A. Bromiley*, N.A. Thacker and P. Courtney

Imaging Science and Biomedical Engineering, Stopford Building,
University of Manchester, Oxford Road, Manchester, M13 9PT.

Abstract. Image subtraction is used in many areas of machine vision to identify small changes between equivalent pairs of images. Often only a small subset of the differences will be of interest. For example, MS lesions can be detected by subtraction of MRI scans taken before and after the injection of GdDTPA contrast agent. The contrast agent highlights the lesions, but also results in global changes in the post-injection scan. Simple image subtraction detects all differences regardless of their source, and is therefore problematic to use. Superior techniques, analogous to standard statistical tests, can isolate localised differences due to lesions from global differences. We introduce a new non-parametric statistical measure which allows a direct probabilistic interpretation of image differences. We expect this to be applicable to a wide range of image formation processes. Its application to medical images is discussed.

1 Introduction

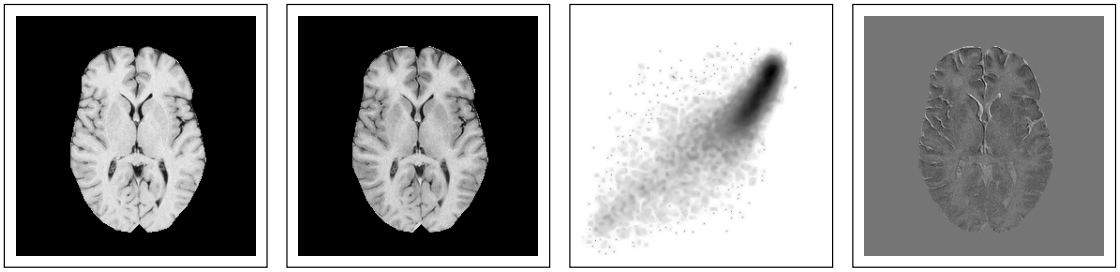
Image subtraction is a common tool for the analysis of change in pairs of images, used in a wide range of circumstances [1]. Most researchers will already be familiar with the difficulties of interpreting the resulting difference image [2]. Taking a simple subtraction between two images and identifying regions of change using a threshold is directly equivalent to forming a null hypothesis test statistic, with the assumption of a single distribution for the expected level of change due to uniform noise. In order for the technique to be used successfully great care has to be taken to ensure that the only differences between the two images are due to the physical mechanisms of interest. This may require realignment or pre-processing of the data in order to remove gross changes before a subtraction can be performed. The result can always be used immediately to identify regions of maximal change, but ultimately we would also like to be able to put a quantitative statistical interpretation on the significance of the observed change. The formation of such an interpretation using conventional statistics is generally prevented by the lack of a known statistical model of the expected scene contents or perhaps even the imaging process. However, most images contain a sufficient data that in theory we might extract sensible models of data behaviour from the data itself. This approach has been used widely in recent image registration techniques [3], particularly in medical applications [4]. The technique generally referred to as maximisation of mutual entropy is in fact a boot-strap approach to the construction of a maximum-likelihood statistic [5]. It therefore seems reasonable to attempt to adapt these measures, and equivalent approaches, to the problem of image subtraction in order to investigate the possibility of getting quantitative and statistically well-defined measures of difference for arbitrary image pairs.

2 Methods

The idea behind the new subtraction technique, one of four developed [1], was to try to construct a probability value that reflected how likely it was that each grey level had been drawn from the same generation process as the rest of the data. A scattergram produced from a sample of image data was used as a basis for a statistical model. In order to construct the scattergram $S(g_1, g_2)$ from a pair of images, corresponding pixels were taken and their grey levels g_1, g_2 were used to define co-ordinates for entries in the scattergram. The two images are referred to below as the first image, plotted on the abscissa of the scattergram, and the second image, plotted on on the ordinate. A vertical cut on the scattergram $F(g_1 = const, g_2)$ isolates a set of pixels in the first image with the same grey level. The distribution of this data then gives the relative frequency of grey levels for those pixels in the second image. Iterated tangential smoothing [1] was applied to the scattergram to ensure that the surface in grey-level space was smooth and continuous. Furthermore, the scattergram was normalised along all vertical cuts $g_1 = k$ to give a probability distributions, so that each graph pixel corresponded to the probability of obtaining a particular grey level value at a pixel in the second image given the grey level value of the same pixel in the first image.

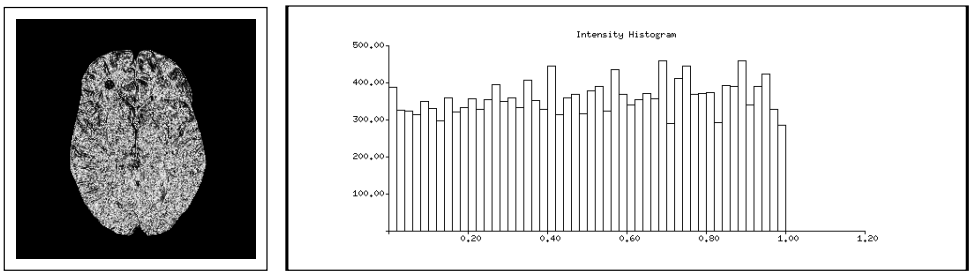
The grey levels of a pair of pixels from the original images were used as co-ordinates in the normalised scattergram. An integration was then performed along the vertical cut passing through this point, summing values **smaller** than

* E-mail: paul.bromiley@talk21.com



(a) (b) (c) (d)

Figure 1. The original MRI brain images (a,b), scattergram (c), and simple subtraction difference image (d), with a 2σ offset added to a small region of image (b).



(a) (b)

Figure 2. The difference image produced by the new method (a) showing the altered region in the upper left. The histogram of this difference image (b) is by definition flat.

that of this pixel. This total was used as the grey level value for the relevant pixel in the difference image[1].

$$D(x,y) \;=\; \sum_{c} \delta(\; F(x,c) > F(x,y)\;) F(x,c).$$

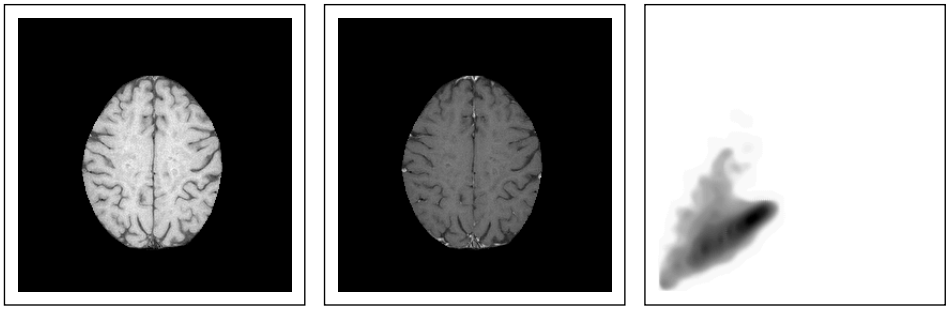
This integration is identical to the construction of a confidence interval, using the original definition due to Neyman [6], utilizing an ordering principle which guarantees the shortest possible interval [7]. The result is the probability of the pairing of grey levels at corresponding pixels in the original images. The distribution of grey levels in the difference image is by definition flat and therefore **honest** [8], i.e. a 1% probability implies that data will be generated worse than this only 1/100 th of the time. The measure has the same interpretation as the conventional "chi-squared probability" but is essentially non-parametric. Low probabilities indicate that the pairings of pixels are expected to be uncommon. This is exactly the type of measure needed in order to identify outlying combinations of pixel values in an automatic manner. The distribution of grey levels in the difference images produced using this method can also act as a self-test. Any significant departure from a flat distribution indicates inappropriate behaviour of the two data sets and therefore unsuitability of the statistic for that comparison.

3 Results

MS lesions in the brain can be difficult to detect in an MRI scan, but can be highlighted using an injection of gadolinium (GdDTPA), which concentrates at the lesion sites. Scans taken before and after the injection can be subtracted to help identify lesions, but the gadolinium also alters the global characteristics of the scan, so a simple pixel-by-pixel subtraction will not remove all of the underlying structure of the brain from the image. The new image subtraction method should ignore the global changes, and so produce an image that shows only the lesions.

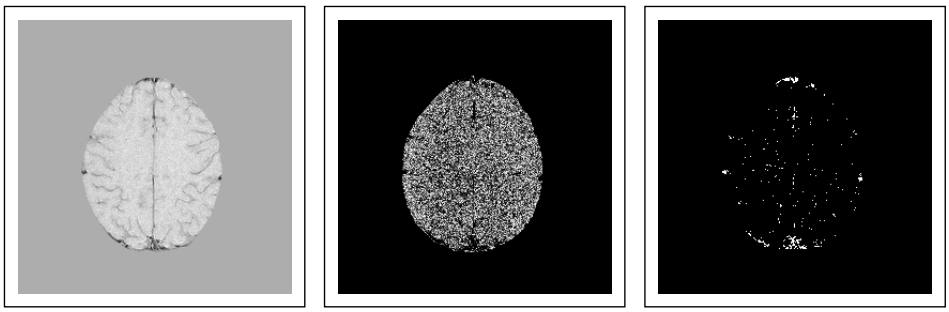
Obtaining a gold standard for this work is difficult without extensive hystological investigation. In order to simulate the imaging process, two T2 scans with slightly different echo train times (TE) of the same slice of a brain were used. This simulates the effects of repeat scanning on different scanners after a significant time interval, and the small quantitative changes which occur in the signal due to the presence of a contrast agent. The background was removed from the image so that our statistical model (scattergram) was estimated using only the tissues in which we were interested. It was expected that, under many circumstances, corrections for intensity non-uniformities in the data would need to be applied [9], but this was not found to be neccessary with these images. A grey-level offset too small to be detected visually was then added to a small circular region of one of the brain images, simulating lesions in a testable manner. The magnitude of the offset was based on the noise in the original images. The subtraction routine was applied to this data in an attempt to detect the change. Fig. 1 shows the brain images

[1] δ represents the Kronecker delta function.



(a) (b) (c)

Figure 3. MRI brain scans from an MS patient before (a) and after (b) GdDTPA injection, and the scattergram (c).



(a) (b) (c)

Figure 4. The difference images produced by simple subtraction (a) and the new method (b) from the MRI brain scans of an MS patient, and the result of thresholding the image at the 1% level (c).

with an offset of 2σ added to a small region of one image, together with the scattergram and the results of a simple subtraction. The altered region cannot be detected visually in the original images, and is barely visible in the pixel-by-pixel difference image. Fig. 2 shows the difference image generated using the new method, and the altered region shows up clearly. The altered region ceased to be detectable when the magnitude of the offset was reduced below around 1σ. Fig. 2 also shows a histogram generated from the difference image and, as expected, this method produced an honest probability distribution, confirming the applicability of this statistical measure to this MR data.

The new subtraction technique was also applied to genuine MRI data, in the form of a pair of scans of the brain of an MS patient, taken before and after the injection of the GdDTPA contrast agent used to highlight MS lesions. Fig. 3 shows the two scans, together with the scattergram. The larger lesions can easily be seen in both the second scan, as the lighter regions, and the results of the simple subtraction, as the darker regions. The result of both a simple subtraction and the new image subtraction method are shown in Fig. 4. As in the previous example, the new method removed all of the underlying brain structure from the image, leaving only the lesions as darker regions against a background of random noise with a flat probability distribution. Fig. 4 also shows the result of thresholding the difference image at the 1% level to highlight the lesions. The lesion sites detected by the new technique matched those identified by the radiologist. In these images the lesions were easily visible, and so visual inspection of the simple subtraction results by the radiologist was sufficient to identify the lesion sites. In this case the main advantage of the new subtraction technique was that it produced results in terms of a well-defined statistical quantity. This would allow further processing of the images to be conducted in a quantitative manner.

4 Discussion and Conclusions

Pixel-by-pixel image subtraction, when considered as a statistical test, can be shown to rely on many assumptions regarding the information contained in a pair of images. These assumptions are rarely valid and, as a consequence, simple image subtraction cannot be used reliably [2]. The new image subtraction technique described here used a scattergram of the grey levels in a pair of images as a model of the global variations between the images, avoiding such assumptions, and allowing the new technique to focus only on localised variations. The technique was shown to be superior in detecting abnormalities in medical images. In addition the grey levels in the new technique difference image correspond to a probability, a well-defined quantity. The new technique can be considered as the definition of new non-parametric statistical test, with theoretically predictable properties. As such, the method is firmly grounded in the existing body of statistical decision theory and can be used in combination with more restrictive parametric techniques for hypothesis testing. This fact makes extensive quantiative analysis redundant,

though the results presented here demonstrate the applicability of these measures to the subtraction of MR datasets.

The new technique produces an output image where the probability distribution is flat, which provides a mechanism for self-test. Such statistical methods also permit data interpretation using only the single model of interest. In contrast, Bayesian techniques for computing the probability $P(C_i|D)$ that a given model C_i explains the data D require prior knowledge of models representing all the distributions present in the data,

$$P(C_i|D) = \frac{P(C_i)P(D|C_i)}{\sum_i P(C_i)P(D|C_i)}.$$

This difference can be important in some data interpretation tasks. In addition, a standard technique exists for combining and re-flattening independent flat probability distributions [10]. If n probabilities P drawn from a flat distribution are multiplied to produce a combined probability, the combined probability can be re-flattened using

$$P' = P\sum_{j=0}^{n-1}\frac{(-lnP)^j}{j!}.$$

This process is potentially nestable, allowing region-based data fusion to produce a principled statistical test of whether the data are drawn from the mean distribution. These measures could also be used in the analysis of co-occurence of spatially distributed values and may thus also have a role in the analysis of texture.

The technique as described here produces an output image with a flat probability distribution, and so thresholding at some level n will extract the lowest-probability $100n\%$ of the pixels from the image. However, if the scattergram is generated from regions of the images where the differences are due solely to noise, then the distribution in the difference image will be flat only for pixels drawn from the mean distribution. Localised differences between the images not due to noise will generate a peak at low probability in the probability distribution of the difference image. Thresholding at some probabiltiy higher than this peak will therefore extract all the pixels due to the differences, together with some known percentage of pixels from the rest of the images. Since the proprotion of normal tissue pixels extracted is known, volumetric analysis of the lesions can be performed. The issues of enhancing the contrast of MS lesions in MRI scans and of volumetric analysis of the lesions are important areas, in relation to both tracking the progression of the subclinical disease, and to theraputic trials [11].

Acknowledgements

The authors would like to acknowledge the support of the MEDLINK programme, grant no. P169, in funding part of this work. All software is freely available from the TINA [12] website www.niac.man.ac.uk/Tina.

References

1. P.A. Bromiley, N.A. Thacker, & P. Courtney. “Non-parametric Image Subtraction using Grey Level Scattergrams.” In *Proceedings of the British Machine Vision Conference 2000*, pp. 795-804. BMVA, 2000.
2. J.V. Hajnal, I.R. Young, & G.M. Bydder. “Contrast Mechanisms, Functional MRI of the Brain.” In *Advanced MR Imaging Techniques*, pp. 195-207. Martin Dunitz Ltd, London, 1997.
3. P. Viola. *Alignment by Maximisation of Mutual Information.* PhD. Thesis, Artificial Intelligence Laboratory, MIT, 1995.
4. J. West, J. Fitzpatrick, M. Wang, et al. “Comparison and Evaluation of Retrospective Intermodality Image Registration Techniques.” In *Journal of Computer Assisted Tomography* **21**(4), pp. 554-566, 1997.
5. A. Roche, G. Malandain, N. Ayache, et al. “Towards a Better Comprehension of Similarity Measures Used in Medical Image Registration.” In *Proc. MICCAI 1999*, pp 555-565. Cambridge, 1999.
6. J. Neyman, “X-Outline of a Theory of Statistical Estimation Based on the Classical Theory of Probability.”, *Phil. Trans. Royal Soc. London* **A236**, pp. 333-380, 1937.
7. G.J. Feldman and R.D. Cousins, “A Unified Approach to the Classical Statistical Analysis of Small Signals”, *Phys. Rev.* **D57**, pp. 3873, 1998.
8. A.P. Dawid. “Probability Forecasting.” In *Encyclopedia of Statistical Science 7*, pp 210-218. Wiley, 1986.
9. E. Vokurka, N.A. Thacker, and A. Jackson. “A Fast Model Independant Method for Automatic Correction of Intensity Non-Uniformity in MRI Data. ” *Journal of Magnetic Resonance Imaging* **10**(4), pp. 550-562, 1999.
10. ALEPH Collaboration. “A Precise Measurement of $\Gamma_{Z\to b\bar{b}}/\Gamma_{Z\to hadrons}$.” *Physics Letters* **B313**, pp. 535-548, 1993.
11. L.J. Wolansky, J.A. Bardini, S.D. Cook et al. “Triple-Dose Versus Single Dose Gadoteridol in Multiple Sclerosis Patients.” *Journal of Neuroimaging* **4**(3), pp. 141-145, 1994.
12. N.A. Thacker, A. Lacey, E. Vokurka, et al. “TINA an Image Analysis and Computer Vision Application for Medical Imaging Research.” In *Proceedings of the European Congress on Radiology*, 24-003, pp. s566. Vienna, 1999.