A Method for Objective Evaluation of Functional Images

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A method is described for characterizing functional maps by means of a frequency distribution function (DF) of pixels. The method makes use of a map of the standard deviation of the functional parameter. By use of this map the method (a) becomes less sensitive to imprecise definition of the organ borders, (b) compensates for random fluctuations in the functional map, and (most importantly) (c) permits spatial information to be included in the DF. This spatial information is included by performing spatial cluster weighting—a procedure that emphasizes regional dysfunction over global dysfunction. The method is illustrated by applying it to phase maps of the left ventricle. In this example, it is shown that analysis of the DF permits detection of regional abnormalities of LV wall motion and that an improvement in detectability is obtained with cluster weighting.


Functional images are usually created in an attempt to portray some aspect of organ behavior as a single image. Many such functional images have been described for a variety of organs. These images permit easy subjective assessment of function, and provide numeric data describing function on a regional basis. Despite their quantitative nature, functional images are still frequently evaluated subjectively—by observation of the image. This paper describes an objective method for assessing functional images. It can be used to produce a single number that may be a descriptor of overall organ function. The method is based on producing a distribution function of pixels (i.e., a histogram of the number of pixels possessing a certain value plotted against that value). The distribution function (DF) is produced in a unique way that overcomes the three principal objections associated with such analyses: (a) The method is insensitive to selection of the precise organ borders; (b) it compensates for random fluctuations due to the small number of pixels in each “bin” (i.e., range of functional value) of the DF, and the method is also independent of this bin width; and (c) most importantly, it allows spatial information to be included in the DF. That is, the method can be used to emphasize regional dysfunction as opposed to global dysfunction.

In order to illustrate the application of the technique and its advantages, an example of its use is given. The example chosen is the analysis of Fourier “phase” maps of the left ventricle (I–7) produced from gated equilibrium cardiac studies.

METHODS

Calculational. To apply the proposed method for calculating the distribution function of values within a functional image, two images are required—the functional image itself and an error image. The latter consists of an image in which each pixel contains an estimate of the error of the corresponding point in the functional image. Usually the error image will be calculated by applying standard error propagation relations. This is quite straightforward (albeit tedious) for ejection-fraction maps, phase maps, stroke-count maps, etc. If other (not counting-rate-limited) sources of error are known, they also should be included in the error image.

Given the functional map and its associated error image, a region of interest (ROI) is drawn around the
organ of interest. The DF is then calculated on pixels within the ROI. To understand the method used here best, consider first the conventional way of computing the distribution function of pixels within the functional image. One would first examine the range of functional values within the ROI of the map (they might range, for example, from 1 unit to 100 units). This range would then be divided into an arbitrary number of intervals or "bins" (for example, 50 bins of two units each). Then one would simply tabulate the number of pixels (within the ROI) possessing a value of either 1 or 2 for the first bin, 3 or 4 for the second bin, and so on.

The new method described here differs from this conventional technique. No "bin" interval range is chosen. Instead, the value of each pixel in the functional image is considered to represent the mean of a normal distribution function of values. The width \( \sigma \) of this distribution function is given by the corresponding point in the error image. Each pixel in the functional image, then, has no definite value, but rather a range of possible values with the most probable being the measured value and with less-probable values occurring further from the measured value. That is, the single pixel itself can be thought of as possessing a Gaussian distribution function of values. If \( P_{x,y}(I) \) is the probability that this single pixel at \((x,y)\) possesses a value \( I \), then we assume:

\[
P_{x,y}(I) = \frac{1}{\sqrt{2\pi \sigma_{x,y}}} \exp\left[-\frac{(I - \text{measured})^2}{2\sigma_{x,y}^2}\right],
\]

where \( \text{measured} \) equals the measured value of the pixel and \( \sigma_{x,y} \) is the estimated error in that measured value.

The distribution function of values in the whole ROI is then just the sum of all the single-pixel distribution functions:

\[
\text{DF}(I) = \sum_{x,y, \text{ROI}} P_{x,y}(I),
\]

where \( \text{DF}(I) \) is the "number" of pixels possessing a functional value \( I \). The word "number" is in quotes because the number of pixels will be nonintegral. Each pixel contributes some fraction of "itself" to every possible functional value, as given by Eq. (1). The overall distribution function \( \text{DF}(I) \) is simply a sum of Gaussians. Pixels with low errors contribute strongly to their corresponding measured functional value (a peaked Gaussian), whereas pixels with large errors contribute weakly to both the measured value and a range of nearby values (a broad Gaussian). The DF described by Eqs. (1) and (2) will henceforth be referred to as the error-corrected DF.

In order to emphasize regional abnormalities, the distribution function can be "cluster-weighted." That is, if several pixels all possessing similar values are grouped together spatially in a small region of the organ, these pixels can be counted more heavily in the distribution function than if these same pixels were spread out over the whole organ. Figure 1 illustrates this concept.

To implement the spatial-clustering algorithm, the distribution function is weighted by the reciprocal of the spatial variance of the pixels. That is, for each value of the functional parameter \( I \), all pixels possessing that value are examined, and their spatial variance computed. In Eq. (1), every pixel possesses some "amount" of every possible value of the functional parameter. Thus in computing the spatial variance of pixels possessing value \( I \), every pixel within the ROI must be used, and in computing this variance the "number" of pixels is derived from Eq. (1):

\[
\text{SV}(I) = \sum_{x,y, \text{ROI}} P_{x,y}(I) \cdot [(x - x_0)^2 + (y - y_0)^2],
\]

where \( \text{SV}(I) \) is the spatial variance of pixels possessing a value \( I \).

The distribution function of Eq. (3) can then be re-computed as:

\[
\text{DF}'(I) = \text{DF}(I)/\text{SV}(I),
\]

where \( \text{DF}'(I) \) is the "cluster-weighted" distribution function.

Illustrative example. Fourier "phase" maps of the cardiac left ventricle (LV) have been chosen to illustrate the use of the error-corrected distribution function and to demonstrate the effects of cluster weighting. Cluster weighting should be most useful when applied to a functional parameter possessing localized, regional abnormalities. Cardiac LV wall-motion abnormalities are frequently regional in nature, especially in subjects with coronary artery disease. There are many functional parameters that may be descriptors of wall motion. There is evidence that Fourier phase maps are influenced by the presence or absence of regional wall-motion abnormalities. Their presence or absence was therefore chosen.
as the functional parameter to illustrate the effects of cluster weighting, and Fourier phase was chosen as a parameter that might be descriptive of wall motion. Phase maps of LV cardiac function were chosen not because they necessarily represent a "good" or "useful" functional parameter, but because they may be familiar to the reader. The phase maps were obtained from the first harmonic of the temporal Fourier expansion of the single-pixel time-activity curves (TAC), in the usual way (1-6). The temporal resolution of each TAC was 20 msec. An error map was also calculated. For Fourier phase, the standard deviation of each phase value may be computed as:

\[
\sigma_{x,y} = \frac{1}{1 + (A/B)^2} \cdot \left( \frac{A}{B} \right) \cdot \text{SQRT} \times \left[ \frac{\sum f(t) \sin^2(2\pi t/T)}{A^2} + \frac{\sum f(t) \cos^2(2\pi t/T)}{B^2} - 2 \cdot \frac{\sum f(t) \sin(2\pi t/T) \cos(2\pi t/T)}{A \cdot B} \right],
\]

where \( A \) and \( B \) are the first harmonic coefficients of the sine and cosine, respectively, in the single-pixel TAC Fourier expansion, \( f(t) = \) LV time-activity curve, and \( T = \) period of the cardiac cycle. \( \sum \) = sum over all \( t \). SQRT represents the square root. This calculation takes only a small amount of additional computer processing (CPU) time when performed during calculation of the phase values, and is easily implemented.

We desired to compare the cluster-weighted with the noncluster-weighted distribution function. To this end, phase maps were produced from two groups of subjects: 40 normal volunteers (NV) and 70 subjects having angiographically demonstrated coronary artery disease (CAD). The NVs (aged 18-66) each had a normal history, treadmill ECG, chest radiograph, and echocardiogram. Coronary arteriography was not performed on the NVs. The 70 CAD subjects each had >50% stenosis in one or more of the three major vessels as determined by coronary arteriography. Both groups underwent ECG-gated equilibrium blood-pool scintigraphy at rest. Three observers independently assessed each subject's cardiac LV wall motion from the cinematic display of the scintigraphic images. Each reader made a simple binary "normal" or "abnormal" assessment. A CAD subject was considered to have "normal" or "abnormal" wall motion on the basis of agreement between two or more of the observers. On this basis, 37 of the 70 CAD subjects had normal wall motion at rest.

**Analysis of distribution function.** The error-corrected distribution function (cluster-weighted or not) can be analyzed in several ways. Many well-known measures, such as variance, skew, kurtosis, etc., may be calculated to give a single number that describes the distribution function. Which of these measures has the most physical meaning will depend to some extent on the application.

For the distribution function of phase values described above, the relatively simple measure of symmetry illustrated in Fig. 2 was chosen. Each subject, a "reflected" curve was created by reflecting the left portion of the distribution function about the maximum. From this reflected curve a "reflected area" was calculated, defined as the difference in area between this reflected curve and the measured distribution function, expressed as a percentage of the whole area under the measured curve.

The "reflected area" parameter is not necessarily the best or most sensitive measure of curve symmetry. Nor is it even known that curve symmetry is the most sensitive descriptor of the distribution function. Reflected area was chosen simply to illustrate the application of cluster weighting using one of the many possible parameters calculable from the distribution function.

**RESULTS**

Figure 3 shows a typical Fourier phase map (panel A) from the heart of a normal subject, and its associated error map calculated from Eq. (5) (panel C). The images were acquired in a 40° modified left anterior oblique view. Figure 4A shows the distribution function (after
applying an LV ROI to Fig. 3A) as it is usually calculated. Figure 4C shows the same distribution function after applying Eq. (2) and using the errors determined from the error map of Fig. 3B. Applying the cluster-weighting operation to this normal volunteer’s distribution function, we obtain Fig. 4B.

Figure 5 presents the same kind of data as in Fig. 4 but from a CAD subject with a wall-motion abnormality. Panel 5A is the error-corrected distribution function, while panel 5C represents the cluster-weighted DF. Panel 5B represents a milder form of cluster weighting in which SV(I) of Eq. (4) is replaced with its square root, the spatial standard deviation.

The error-corrected DFs of phase, with and without cluster weighting, were used to try to detect visually determined wall-motion abnormalities in the group of 40 NVs and 70 CAD subjects. The previously described “reflected area” parameter was used as the descriptor of the distribution function. The ability of this parameter to detect wall-motion defects was evaluated using receiver operating characteristics (ROC) curve analysis. Figure 6 shows the ROC curves obtained with and without cluster weighting. Sensitivity, as used in Fig. 6, is defined as true positives divided by total number of subjects with wall-motion abnormalities (as described previously). Specificity, as used in Fig. 6, is defined as number of false positives among the normal volunteers divided by the total number of NVs. It is again emphasized that the goal was not to determine sensitivity–specificity relationships carefully from phase maps, but only to illustrate the effects of cluster weighting.

**DISCUSSION**

Frequency functions have been used previously in attempts to evaluate functional images (1–3, 5, 6). There are several objections associated with such analyses—objections that are partially overcome by the use of Eqs. (1) through (3). Figure 3 illustrates the first of these objections and how it is overcome. Panel A of this figure shows the phase map from the cardiac chambers. Values of phase are calculated everywhere in the image. Outside the cardiac structures, the values of phase fluctuate nearly randomly over the entire range of 360°. If an ROI is drawn slightly too large, the resulting raw distribution function will include pixels from these nonmeaningful regions. Such pixels will distort any measurements made (e.g., variance, skew, etc.) on the raw DF. One might think that the amplitude image (Fig. 3B) could be used to overcome this problem. By choosing only those pixels in the phase map that have large amplitudes, one indeed
avoids including nonmeaningful phase values accidentally. By so doing, however, one also excludes akinetic and poorly moving regions of the LV—the very regions one is attempting to detect. A large Fourier amplitude, while usually a sufficient condition for a meaningful phase value, is not a necessary condition. Poorly moving regions of the LV may have quite low amplitude; yet if they possess high count densities, these regions may possess statistically reliable values of phase. It is the statistical reliability, then, that must be used as the criterion for inclusion of a pixel within the distribution function. Figure 3C illustrates a typical error map, showing the statistical reliability of phase at each pixel. The errors are, in general, low inside the cardiac structures and high outside of them. Equations (1) and (2) essentially allow creation of a weighted distribution function (the “error-weighted” DF) in which each pixel is weighted with its reliability. Even if the ROI is drawn so as accidentally to include noncardiac (time-independent) structures, such structures will not contribute heavily to the error-corrected DF, since they have low reliability (a high error value).

Figures 4A and 4C illustrate the application of Eqs. (1) and (2) to the case of a phase map of a normal LV. Figure 4A shows the raw distribution function. The horizontal-axis resolution (i.e., the bin width) is one degree. The phase distribution function in a normal LV is typically a narrow, symmetric, approximately Gaussian bell-shaped curve. Although this general behavior can be appreciated from Fig. 4A, note the large fluctuations of pixels within each bin and the many bins in which the DF is zero, due to the sharp horizontal-axis resolution (i.e., small bin width) chosen. Note also that there are a few pixels in the DF considerably to the right of the main peak. These pixels probably result from a slightly oversized LV region of interest. They might easily be interpreted as an abnormality. In reality, these pixels have high errors associated with them. When Eqs. (1) and (2) are applied, Fig. 4C results. The extraneous points are no longer noticeable owing to their high error. Figure 4C is obviously much more amenable to analyses such as the “reflected area” calculation illustrated in Fig. 2. Note that for some calculations Eq. (2) is not necessary. For example, if the variance or skew of the distribution function were desired, they could be computed in the usual way from the raw DF, but weighting each point inversely with the square of the standard deviation as determined from the error map. In general, however, applying Eq. (2) to produce the error-corrected DF as shown in Fig. 4B is useful.

A major disadvantage of using a distribution function of pixels to characterize an image is that all spatial information is lost. Cluster weighting (illustrated in Figs. 4B and 4D and in Fig. 5) attempts to put regional, spatial information back into the distribution function. Figure 4B shows the cluster-weighted DF from a normal volunteer. It was produced by applying cluster weighting to the error-corrected DF of Fig. 4C. Note that for this normal subject, cluster weighting does not appreciably alter the shape of the DF. The DFs with and without cluster weighting are shown in Fig. 4D. In this case cluster weighting actually narrows the DF. In general, the distribution functions of phase in normal subjects do not change greatly with cluster weighting. In CAD subjects with wall-motion defects, on the other hand, cluster weighting frequently produces dramatic effects. Figure 5 demonstrates this. Panel A of this figure illustrates the error-corrected DF. The distribution is slightly skewed to high phase values (right-hand side), but an asymmetry of this magnitude is occasionally also seen in normal individuals. After cluster weighting [Eq. (4)], this asymmetry is markedly emphasized (Fig. 5C), indicating that a regional defect caused it. Figure 5B is similar to 5C but uses a weaker cluster weight. This weaker weighting may be useful with very noisy data.

It is clear from Fig. 5 that cluster weighting can emphasize regional abnormalities. It is also possible to define the regional phase abnormality (the smaller peak in Fig. 5C) and determine which pixels from the original map caused this abnormality. This may possibly be useful in visually emphasizing the location of regional abnormalities in the original image.

Note that without the error-corrected DFs, as described in Eq. 2, cluster weighting would be quite difficult to perform. When using the raw DF, there are so few pixels in each bin that one often cannot compute the spatial variance. In the raw DF of Fig. 4A, for example, many bins have two or fewer pixels. A wider bin improves the situation, but at the expense of worsened resolution on the phase axis. The scheme described by Eqs. (1) and (2) avoids these problems. The equations allow each single pixel to possess a distribution of phase values [as in Eq. (1)]. Thus all pixels contribute to some extent to every value of phase, making calculation of spatial variance, and hence clustering, possible.

In order to investigate the effects of cluster weighting more quantitatively, we studied distribution functions of phase with and without weighting. The ability to discriminate between normal and abnormal left-ventricular wall motion was used as the criterion of comparison. The group of normal volunteers, and subjects with CAD described previously, allowed ROC curves to be constructed with and without cluster weighting. The ROC curves of Fig. 6 illustrate the sensitivity–specificity relations obtained with and without cluster weighting. Cluster weighting is seen to result in a slight (but visually apparent) increase in sensitivity at high specificity values. The choice of reflected area as the parameter for this comparison is completely arbitrary. It was simply one of several possible parameters, and was chosen for its simplicity. It is certainly not (we have since discovered) the most sensitive or specific parameter for detection of
LV wall-motion abnormalities. It does illustrate, however, the improvement that may be gained by cluster weighting. Other descriptors of the DF, or DFs of functional parameters other than phase, may respond differently to cluster weighting, depending on the extent to which such descriptors or parameters are regional in nature.

There are several computational difficulties in implementing Eqs. (1)–(4). First, the process is slow unless floating-point hardware is available. A minicomputer* with floating-point hardware typically required 30 sec to produce cluster-weighted DFs from a 150-pixel ROI. Second, if single-precision variables are used to perform the cluster weighting, consideration must be given to round off errors. Such errors may occasionally cause the cluster-weighted DF to increase without bound at phase values far from the main peak. Use of double-precision variables and/or care in implementing the algorithm will minimize this problem. Third, in Eqs. (1)–(3), integrals have been replaced by sums. Proper computer integration must be utilized.

The analysis embodied by Eqs. (1)–(3) can in principle be applied to any functional image for which an error map has been created. In many cases the functional parameter of interest is spatially uniform, approximately, over the organ of interest in normal individuals. This is true for the phase maps considered here as well as for maps of LV time to minimum counts, EF maps, and many others. This approximate spatial uniformity of function over normal organs facilitates analysis of the DF, permitting simple descriptors such as “reflected area” to be used. There are, however, classes of functional maps for which normal function is not even approximately uniform over the organ of interest. In such cases different methods of describing the DF may be necessary. Also, if large spatial inhomogeneities are expected to be present even in normal maps, cluster weighting may be of less value.

Finally, note that many descriptors of the DF do not require creation of the error-corrected DF [Eq. (2)]. Variance, skew, kurtosis, etc., may all be calculated directly, not from the raw DF but from the functional map and its associated error map. The error map must be used in order to weight properly the contribution of each pixel to the value of the parameter being calculated (variance, skew, etc.).

**CONCLUSION**

By use of Eqs. (1) and (2), we are able to produce distribution functions from functional images. The method used to produce the distribution functions, by using the error image, alleviates the usual statistical problems associated with raw DFs. In addition, a cluster-weighting scheme is proposed that should allow enhanced detection of regional abnormalities.

Application of the proposed method to phase maps verifies that the cluster-weighting scheme has value in emphasizing regional LV wall-motion abnormalities. We also demonstrate that use of the error-corrected DF permits an entire image to be characterized by one (or a few) descriptive parameters. For the case of phase images, the arbitrarily chosen parameter of “reflected area” gave a reasonably good sensitivity–specificity relationship. By more careful selection of parameters characterizing the DF, or by combining several such parameters, still better results may be hoped for. Although the method has been tested only on phase images of the LV, it is in principle applicable to nearly any organ from which a functional map can be produced.

**FOOTNOTE**

* Hewlett Packard HP-1000 F Series.

**REFERENCES**


