Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
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CHAPTER 2

Pixel-by-Pixel analysis of DCE-MRI curve patterns and an illustration of its application to the imaging of the musculoskeletal system

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ABSTRACT
Dynamic contrast enhanced (DCE) MRI is a widespread method that has found broad application in the imaging of the musculoskeletal (MSK) system. A common way of analyzing DCE-MRI images is to look at the shape of the time–intensity curve (TIC) in pixels selected after drawing an ROI in a highly enhanced area. Although often applied to a number of MSK affections, shape analysis has so far not led to a unanimous correlation between these TIC patterns and pathology. We hypothesize that this might be a result of the subjective ROI approach.
To overcome the shortcomings of the ROI approach (sampling error and inter-user variability, among others), we created a method for a fast and simple classification of DCE-MRI where time-curve enhancement shapes are classified pixel-by-pixel according to their shape. The result of the analysis is rendered in multislice, 2D color-coded images. With this approach, we show not only that differences on a short distance range of the TIC patterns are significant and cannot be appreciated with a conventional ROI analysis but also that the information that shape maps and conventional standard DCE-MRI parameter maps convey are substantially different.
CHAPTER 2  

Pixel by pixel TIC shape analysis of DCE-MRI

INTRODUCTION

The use of dynamic contrast enhanced (DCE) MRI has been advocated by an increasing number of investigators studying physiological processes that involve neoangiogenesis, such as cancer and inflammatory processes. It has been proposed as a mirror of capillary permeability and membrane viability and as a marker for tissue response to antiangiogenic drugs [1–3]. Clinical DCE-MRI studies that address pathologies of the musculoskeletal (MSK) system have increased considerably in recent years, emphasizing the potential of this technique in the differential diagnosis of many soft tissue tumours [4–6].

Data from these DCE-MRI studies have been analyzed and presented in either a qualitative [5,7–9] or a quantitative way [10,11]. In qualitative analysis, measures such as maximum (relative) enhancement ($ME$) [5], rate of early enhancement ($REE$) [7,8], area under the curve ($AUC$) [9], time to peak ($TTP$) [12] or initial slope of increase [13] are directly derived from the measured signal intensity. They are, therefore, sensitive to variations between acquisition protocols and dependent on other factors such as the sequence parameters (e.g., TR and flip angle), hardware settings, the amount of administered contrast agent and scan duration [14]. Quantification of DCE-MRI data by means of pharmacokinetic models, proposed initially by Tofts, Brix and Larsson independently [15], aims at calculating absolute measures that are directly related to the tissue physiology such as vessel permeability. Because of this, these absolute measures lend well to longitudinal studies as well as to comparison between studies. Nevertheless, compartmental analysis also suffers from large output variability, which is a consequence of the large variety of models used [16,17]. An alternative “halfway” analysis method has been targeted by some authors who have investigated uptake curve shape (or pattern) and who tried to relate them to pathological findings. This approach is based on the observation “by eye” of the time–intensity curve (TIC) generated from an ROI chosen in the lesion by the radiologist [18–21]. Although not quantitative, this approach is less sensitive to variations in the MRI protocol (although still dependent on the duration of the scan and on the injection procedure), making it more suitable for a comparative (meta-) analysis. Furthermore, as shown in the simulations in Tofts et al. [22], curve shapes represent a mirror of those physiological parameters (e.g., the capillary permeability) that can be extracted by means of the abovementioned analysis using compartmental models ($K_{\text{trans}}$ or permeability surface area product [15]). In fact, increased tumor angiogenesis has
often been associated with a specific TIC pattern with rapid wash-in and washout [23], which is described by a large $K^{\text{trans}}$ in these compartmental models. TIC analysis has, therefore, been often used as a surrogate for quantitative analysis [24]. Hawighorst et al. [18] and Verstraete and Lang [21] have presented a broad overview of the TIC findings in various benign and malignant MSK tumors where there appears to be a significant overlap between curve types in benign and malignant tumors [18]. This classification uncertainty can have physiological origins and can also be influenced by the heterogeneity of the DCE protocol. Another important cause could be the location of the selected ROI, which, in general, is selected based on the (postcontrast) anatomical scan. The radiologist’s decision making is based on the area of largest enhancement, an area that can, in principle, contain pixels with different enhancement patterns. For this reason, as variation can occur between neighboring pixels/voxels, the radiologist might benefit from a 2D pixel-by-pixel overview of the TIC behaviour. Whereas 2D or 3D pixel-by-pixel rendering has already been proposed for qualitative (enhancement or slope) [6,25–27] and quantitative ($K^{\text{trans}}$) analysis [23,28], to our knowledge, shape analysis has been so far only presented in an ROI fashion. In this study, we present a method where the shape of the TIC is calculated on a pixel-by-pixel basis. Each curve shape is assigned a unique color (Fig. 1), which is then displayed in the “shape maps”. In this way, we create multislice, 2D color-coded maps that provide a high resolution description of the TIC shape in the whole imaged area. We investigate the reliability of the classification scheme by checking the output of the automatic classification against the classification by eye. We then explore the variability of the TIC shape behaviour within the imaged area of interest and see how the shape maps compare to ME maps. Furthermore, we provide some examples of this method as applied to some MSK affections to illustrate the advantage of using curve shape analysis.

MATERIALS AND METHODS

2.1. MRI protocol

We investigated peripheral joints (ankle, knee, wrist) and feet of adult patients with various MSK diseases. All patients underwent a DCE-MRI scan as part of a standard clinical protocol. The DCE-MRI dynamic protocol (3D T1-w fast spoiled gradient echo) was performed on a 1.5-T clinical scanner (Signa Horizon
Echospeed, LX 9.0, General Electric Medical Systems, Milwaukee, WI) using a dedicated quadrature detection knee coil.

The 3D volume covered the whole affected joint and included the feeding artery. The MRI protocol parameters were as follows: FOV=18×16.4×8 cm, matrix=256×232×24, TR/TE/α = 8.1ms/3.4ms/30. Based on the observation in Ref. [29], we have decided to deliver the contrast agent as a quick bolus. The contrast agent (Magnevist, Shering) was injected at a speed of 5 ml/s using an injection pump (Spectris, Medrad) in the antecubital vein through a 20-gauge needle. The dynamic scan consisted of 20 consecutive scans acquired with a temporal delay of Δt = 21 s, for a total scan duration of 7 min 20 s. The contrast agent was injected 1 min after the start of the scan.

![Classification of TICs](image)

**Figure 1.** Classification of TICs. type 1 (grey): no enhancement; type 2 (green): slow enhancement, maximum of the curve is reached after half scan; type 3 (blue): quick enhancement, followed by a signal plateau; type 4 (magenta): fast enhancement and quick wash-out; type 5 (yellow): quick enhancement followed by a slow constant enhancement); type 6 (red): artery; type 7 (white/light grey): all others.

### 2.2. Analysis of time curves (curve classification)

From the dynamic series, TICs are generated per pixel. We plot the signal intensities S against the index tp (time points of the dynamic scan).

The characteristic patterns of the TICs encountered are described in Fig. 1. They include the five types described in Refs. [19,24] and two other curve types: artery or Type 6 (characterized by a quick uptake and a very quick decay, followed by a
slowly decaying plateau) and undefined or Type 7 (all others, see Fig. 2). The
definition of Curve 4 as proposed in Ref. [20] can be ambiguous as the presence of
a visible washout within the observed temporal window is dependent on the length
of the scan and can comprise, in fact, two types of curves: curves with a quick
uptake (same as in Type 3 or Type 5) followed by a quick washout and curves with
a slower uptake followed by washout that is still visible within the imaging window
(Fig. 1, striped green line). We have decided to classify the former as Type 4 and
include the latter within the Type 2 class. This is to underline the fact that Type 4
curves are associated with a high vascularization.

Figure 2. Examples of curve shapes encountered and classified as type 7. Although all the
types described above were observed experimentally, these curves only occur rarely, so
that none of them deserved to become a class in itself.

2.3. Preprocessing
A signal threshold is applied to a postcontrast image to exclude from the analysis
all pixels outside the imaged joint or those pixels whose signal is too low to provide
significant statistics. Furthermore, all pixels that presented a noisy TIC (i.e., with
significant intensity oscillations in time) through a white noise filter were excluded.
In this way, we make sure that noise does not affect the quality of the classification.
Noisier images result, therefore, in less pixels being classified.
Images were not smoothed, TICs were not interpolated and the actual resolution of
the acquisition was retained for the classification procedure. No assumptions were
made regarding a relation between signal (or signal enhancement) and contrast
agent concentration, and only the values of signal intensities were used for this
analysis.
An artery was first identified in the FOV automatically by looking at the pixels with
the highest ME. Based on the arterial TIC, the time point (tp=0) of the injection was
determined from the last point before the positive slope of the arterial
enhancement. Then, the signal baseline (SB) was calculated per pixel, as the
average signal intensity for all time points \((tp<0)\). The tail of the curves (by tail, it was arbitrarily chosen to take the second half of the TIC after \(tp=0\)) was fitted to a line and the intercept \((a)\) and the tangent \((b)\) of this line with the axis crossing the time axis at the injection time \(tp=0\) (Fig. 3).

![Diagram](image)

**Figure 3:** Parameters used for the features definitions: \(SB\), signal Baseline, \(MSD\), Maximum Signal Difference, \(TTP\), Time to Peak, \(MSI\), Maximum Slope of Increase, \(SM\), signal maximum; \(\alpha\) and \(\beta\) are the intercept and tangent of the line fitting the tail of the curve, respectively.

### 2.4. Classification features

In order to classify the pixels, a number of features were identified, which, combined with appropriate thresholds, determine the classification univocally. For the present implementation, we make use of five features. Three of these are derived from the parameters often used in DCE analysis: \(ME\) (sometimes referred to as relative enhancement) \([7]\), \(TTP\) and maximum slope of increase \((MSI)\) \([5,13]\). Furthermore, we identified two more derived features: relative final slope \((RelFS)\) and initial signal excess \((ISE)\). These features are described below and in Table 1.

1. \(ME\) is defined as maximum signal difference \((MSD)/SB\), where \(MSD\) is the difference between the signal intensity at its maximum \(S(\text{max})\) and \(SB\).
2. \(TTP\): \(TTP=tp(S(\text{max}))x\Delta t\), where \(\Delta t\) is the time interval between two consecutive scans. It is the time difference (in minutes) between the moment where the \(ME\) occurs and the moment of the beginning of the arterial enhancement \((tp=0)\) as obtained from the artery TIC. For increase-only TICs, the \(TTP\) is the last time point in the scan.
3. \(MSI\) or steepest slope. This is the largest positive signal difference between two successive scans. As the interval between the time points is 1, \(MSI\) represents the maximum positive tangent of each TIC.
4. *ISE* is the ratio between the *MSD* and the distance $\alpha$-$SB$. This classifier is introduced to detect whether the TIC changes in its curvature (steady decrease vs. initial fast decrease and late slow decrease). This is needed in order to distinguish Type 4 from Type 6 curves (see also Fig. 4A and B).

5. *RelFS*. It is defined as $RelFS = \beta / MSD$. This parameter is introduced to describe the behaviour of the curves in the last part of the scan: whether it is flat ($RelFS=0$), declining ($RelFS<0$) or increasing ($RelFS>0$). The scaling factor *MSD* is used to take into account the fact that the tangent of the curve is not significant in itself but relative to the *MSD* taking place after contrast injection (see Fig. 4).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Maximum (<em>SM</em>)</td>
<td>Maximum signal intensity of the TIC</td>
</tr>
<tr>
<td>Signal Baseline (<em>SB</em>)</td>
<td>Average signal intensity at $tp&lt;0$</td>
</tr>
<tr>
<td>Maximum Signal Difference (<em>MSD</em>)</td>
<td>$SM-SB$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Intercept of the line fitting the TIC’s tail with the axis $tp=0$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Tangent of the line fitting the TIC’s tail</td>
</tr>
<tr>
<td>$aT$</td>
<td>$\alpha$-$SB$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classifiers</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Enhancement (<em>ME</em>)</td>
<td>$MSD / SB$</td>
</tr>
<tr>
<td>Time to Peak (<em>TTP</em>)</td>
<td>$t(S_{max})$ where $t=tpx\Delta t$</td>
</tr>
<tr>
<td>Maximum Slope of Increase (<em>MSI</em>)</td>
<td>$\max(S(i)-S(i-1))$</td>
</tr>
<tr>
<td>Initial Signal Excess (<em>ISE</em>)</td>
<td>$MSD/(\alpha$-$SB$)</td>
</tr>
<tr>
<td>Relative Final Slope (<em>RelFS</em>)</td>
<td>$RelFS = \beta x MSD$</td>
</tr>
</tbody>
</table>

**Table 1.** Definition of the parameters and classifiers used.

### 2.5. Pixel classification

The classification of the different curve types is obtained by placing each pixel in one category based on the decision making as described in Table 2. The different classes are defined by a combination of these features and threshold values.

As the *ME* values can, in principle, be protocol dependent, the *ME* threshold is not a fixed value but is inferred from the distribution of *ME* values in the image. A histogram of all positive *ME* values reveals a characteristic pattern with an initial peak followed by a shoulder. The *ME* threshold is chosen to be a value that cuts off the initial peak and the shoulder of the histogram (Fig. 5). Applying this threshold to
the ME creates an image mask where fat, bone and other little enhancing structures are left out.

**Figure 4**: Graphical explanation of the parameters ISE and relFS. (a and b), ISE, defined as $MSD/aT$ where $aT = (\alpha - SB)$ highlights a change in the curve slope. In type 6 curves (artery) $SM$ is larger than $a$, thus $ISE > 1$. In type 4 curves $aT$ is larger than $MSD$, leading to a $ISE < 1$. (c): relFS is defined as $\beta/MSD$ to take into account that it is the relative, not the absolute slope that is significant. Curves 1 (- - -), 2(---) and 3(-- - ) have all the same $\beta$ values. Curves 1 and 3 have also the same relFS values, whereas curve 2 has a lower relFS.

**2.6. On the thresholds used for classification (Table 2)**

Type 1: no or low enhancement: all pixels whose enhancement is lower than the ME threshold obtained as described above. Type 1 also includes curves that do enhance but which present noisy TICs.

Type 2: low initial slope ($MSI < MSD/2$), RelFS positive or only slightly negative and large $TTP$.

Type 3: defined by a very quick enhancement (it is required that the signal increase in the beginning ($MSI$) be at least one-half of the ME of that curve) and final slope within a restricted window about 0. Here, the choice of $-0.015 < relFS < 0.015$ is somehow arbitrary, but back testing revealed that this threshold matched well the operator’s as well as the independent reader’s “by-eye” interpretation.

Type 4: characterized by a medium to fast uptake and a signal decay that is visible within the dynamic imaging time window, which is determined by a RelFS lower
than 0.015. The initial slope can either be quick or have intermediate value \((MSI > MSD/3.0)\).

Type 5: characterized by a quick uptake (same as Shape 3) but with markedly positive final slope. A large \(TTP\) is a condition that is set to exclude shapes of the type as in Fig. 2a.

After the classification, a filter (2D median filtering with a 3x3 neighbourhood matrix filter) was applied to the shape maps for rendering purposes in order to eliminate isolated pixels.

<table>
<thead>
<tr>
<th>type</th>
<th>ME threshold</th>
<th>TTP</th>
<th>MSI</th>
<th>RelFS</th>
<th>ISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; ME</td>
<td>&gt;3 min</td>
<td>&lt;MSD/2.0</td>
<td>&gt;-0.15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt; ME</td>
<td>&gt;3 min</td>
<td>&lt;MSD/2.0</td>
<td>&gt;-0.15</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt; ME</td>
<td>&gt;3 min</td>
<td>&gt;MSD/2.0</td>
<td>&lt;0.015 &lt;FS&lt;0.015</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>4</td>
<td>&gt; ME</td>
<td>&lt;3 min</td>
<td>&gt;MSD/3.0</td>
<td>&lt;-0.015</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>5</td>
<td>&gt; ME</td>
<td>&gt;3 min</td>
<td>&gt;MSD/2.0</td>
<td>&gt;0.015</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&gt; ME</td>
<td>&lt;40 sec</td>
<td>&gt;MSD/2.0</td>
<td>&lt;-0.015</td>
<td>&gt;1.3</td>
</tr>
</tbody>
</table>

Table 2: Classification chart. Threshold used for each feature to classify TICs of type 1 to 6. The ME threshold is calculated as explained in figure 5. Not all features are needed to discriminate each curve type. There is no overlap between these 7 categories, so that the order in which the thresholds are applied is irrelevant.

2.7. Testing of the classification algorithm
To test how well the classification scheme matches the operator’s eye, samples of image pixels were randomly chosen by the computer from the images, with each class having the same number of pixels. Sixty pixels (10 per shape type) were chosen randomly by the computer, 10 from each type of TIC from 10 different patients, and presented to a reader blind to the computer’s classification. Matches and mismatches were then computed.

RESULTS
3.1. Clinical applications
We investigated several patients with arthritis and patients with bone and soft tissue tumors. From this population, we have chosen four patients to illustrate the new analysis technique: (a) a patient with arthritis of the knee, (b) a patient with a pathologically proven osteoblastoma of the fifth metatarsal, (c) a patient with a suspected chondrosarcoma of the ankle and (d) a patient with a pathologically proven Grade 1 chondrosarcoma.
In Fig. 6, $ME$ images, shape map images and histograms of the distribution of the shape types for these patients are shown. The diffuse inflammation of the synovial tissue in the patient with arthritis (Fig. 6A) appears to be inhomogeneous in its response to the inflow of gadolinium (Types 2, 3 and 4), often presenting isolated spots of rapid washout (Type 4), which are not highlighted by an $ME$ map. In a patient with osteoblastoma (Fig. 6B), the shape map reveals a striking behavior, where the core of the lesion presents an artery-like curve shape. This seems to be in accordance with the highly vascularized nature of this benign tumor. In a patient with a suspected chondrosarcoma (Fig. 6C), shape maps help identify the part of highly enhanced areas that behaves as Type 2 or Type 5 and a few spots presenting the rapid washout typical of Type 4 curves. In a patient with Grade 1 chondrosarcoma (Fig. 6D), the shape map reveals the heterogeneity of this tumor, which may be of help in identifying the malignant degeneration of the cartilage cap.

This could be seen as a supplementary diagnostic aid, in addition to the thickness of the cartilage, which is, presently, the only parameter used for this differentiation. It should be noted that, in all the analyzed patients, the homogenous areas within the $ME$ are not homogeneous in the corresponding shape images and vice versa.

The analysis through $ME$ and shape maps reveals, in fact, that the information the two convey is substantially different. This can be better elucidated by looking at the distributions of the $ME$ values separately for each shape type. In Fig. 7, the distributions of $ME$ values are reported from a patient with osteoblastoma.
In these histograms, it is seen that for each shape type, the ME values are distributed over a wide range. TICs of Types 2 and 3 are both mainly seen in low enhancing areas. Type 4 curves are more spread around higher ME values, and Shape 5 is only seen in pixels with low enhancement. In general, we observed that Type 5 curves are rarely seen in most of the analyzed patients, usually in isolated unclustered voxels; only in the patient with osteoblastoma was this type present in small clusters. The artery type (Shape 6) is, as expected, only observed in pixels with a very high enhancement. The “undefined” TICs (Type 7) are predominantly seen in low-enhancing pixels that are not clustered together.

3.2. Results of the classification test.

The classification test was performed by a blind reader, and judgement matches (averaged over all the readers) per image type are reported in Table 3. The test showed that the largest agreement between the computer and the reader is with the Type 4 curve (match=90.0%) and the Type 6 curve (match=82.8%). Types 2 (match=78.6%) and 5 (match=67.1%) are more easily confused, as they only differ
by a slope threshold, which cannot be easily appreciated by the reader’s eyes. Types 3 and 5 are also only distinguished by a threshold, namely, the final slope, which, again, makes it more prone to a classification mismatch between user and computer.

<table>
<thead>
<tr>
<th>Type</th>
<th>matches (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>78.6 %</td>
</tr>
<tr>
<td>3</td>
<td>78.6 %</td>
</tr>
<tr>
<td>4</td>
<td>90.0 %</td>
</tr>
<tr>
<td>5</td>
<td>67.1 %</td>
</tr>
<tr>
<td>6</td>
<td>82.8 %</td>
</tr>
<tr>
<td>7</td>
<td>28.0 %</td>
</tr>
<tr>
<td>all types</td>
<td>70.5 %</td>
</tr>
</tbody>
</table>

Table 3: Results of the classification test. Matches between computer-estimated curve shape and “by eye” reading, divided per shape type

The computer is more “cautious” in classifying pixels than the reader, resulting in a low match score for Type 7. Because we observed that the total amount of pixels classified as Type 7 is very low (see histograms in Fig. 6), the effect of the mismatch between user and computer is not substantial.

Figure 7. Distribution of ME displayed for each shape type in a patient with osteoblastoma. The x-axes represents the ME values, the y-axes the pixel counts.
Figure 8. Shape type distribution in selected ME ranges. Large ME (ME larger than 1.4), medium ME (ME comprised between 1.0 and 1.4), and low ME (ME < 1.0). Type 2, 5 and 7 (undefined) appear predominantly in low-enhanced regions, whereas pixels with a high signal enhancement are populated with all shape types.

DISCUSSION

In the technique described in this article, the dynamics of the enhancement are analyzed and presented in the whole lesion volume, and the color coding of the different enhancement curve shapes enables the radiologist to perform a fast and visual determination of the enhancement characteristics of the whole lesion. This overcomes the operator dependency of ROI-based TIC analysis and may also be advantageous in follow-up studies (e.g., to determine tumour response to chemotherapy or radiotherapy).

We have applied this method to a number of soft tissue pathologies, including arthritis and bone tumours. The shape maps obtained revealed that the method helps appreciate the variability of the tissue response in different pathologies. It has shown that each shape encompasses a large range of ME values (Fig. 7) and that a large shape variability is seen even in areas where ME is uniform (Fig. 8). This observation has confirmed the fact that ROI selection based on highly enhanced areas is not equivalent to choosing the area with the most interesting TIC shapes. Although analysis through TIC shape is not strictly quantitative (it simply represents the response of tissues to a particular input), it poses some advantages over quantitative (model based) methods. Quantification is a complex and computationally demanding task where the signal analysis relies on the assumption
that a certain model is able to describe the physiology of the phenomenon observed [30,31]. The result of the analysis is, thus, model dependent [17]. Moreover, the image processing required (involving nonlinear fitting) puts rather high requirements on the quality of the MRI data, such as a high SNR. Besides, the knowledge of intrinsic $T1$ of the tissue and of the arterial input function (AIF) is required, conditions often not met in many clinical settings. TIC analysis is, conversely, computationally not demanding: there is no fitting involved (except linear fitting), and it does not rely on any model-based assumption. This makes shape analysis feasible also in areas or pixels where these conditions are not met. The output of DCE data through TIC analysis is a pure description of the tissue response to a certain input (the contrast agent delivery) and, thus, provides simple “facts” that can be easily read, compared and used by others. At the same time, this type of analysis is not as sensitive to changes in MR sequence parameters and scanner calibrations, as are the enhancement values. Nevertheless, it should be stressed that results of the TIC classification can only be compared between patients if the same total scan length and the same injection technique (bolus/infusion) are chosen. For instance, if TICs are acquired only for a very short time, only the early curve enhancement will appear, leaving the washout part outside the imaging time window and leading to the absurd conclusion that all curves are of Type 2 (i.e., increase-only curves). Furthermore, the classification is dependent on the contrast injection technique (bolus or infusion) as tissues responding as “Type 4” curves on a bolus injection method may appear as “Type 3” when a bolus infusion is used [14].

As the analysis is done pixel-by-pixel, it should be emphasized that an appropriate noise threshold should be applied before running the classification to avoid incurring low SNR. The classification is not particularly sensitive to small changes in MR parameters (data not shown), as we were able to show by changing the flip angle in the MR protocol. A large change in MR protocol, injection protocol and analyzed tissue pathology may require an adjustment of the classification thresholds used in the classification step. Although the main target of this study was to overcome the dependency of shape classification on the user’s choice of the ROI, the scope of the pixel-by-pixel analysis goes beyond overcoming sampling errors. By providing an overview of the tissue behaviour in the whole imaged area, it is possible to gather information on the appropriateness of the MRI protocol. If increase-only curves are observed in a particular disease, it should be suspected...
that data are not sampled long enough. By providing volumetric shape maps, we can define in what time range the interesting part (the time range with the largest range of shapes) of the contrast uptake is observable, what sort of shapes are encountered, with what frequency (as seen in the shape histograms) and how these shapes compare with the ME maps.

Furthermore, coexistence of more types of tissue response within the affected area, as highlighted with this approach, can help make an appropriate choice of the compartmental model a priori. The presence of TIC shapes of Types 3 and 5 (which were always present in the patients we analyzed), where a quick initial uptake is followed by a plateau or signal increase, points toward the necessity of including a vascular compartment in the generalized model [15] as well as the necessity of modelling the short time scale rise up and decay of the AIF [11].

CONCLUSIONS

Our results draw attention to the fact that analyses through ME and shape maps are substantially different, that a large variability in TIC shapes takes place in areas of constant signal enhancement and that an ROI analysis is therefore often not sufficient to correctly identify areas of abnormal enhancement. Although TIC analysis cannot replace quantification, it helps decision making in choosing appropriate models for quantification. In addition, 2D color-coded rendering of TIC shape analysis is not computationally demanding, is insensitive to model-related artefacts and allows, therefore, a quick overview of the tissue behavior where quantification by means of a compartmental model is not feasible.

REFERENCES


