Improved automatic filtering methodology for an optimal pharmacokinetic modelling of DCE-MR images of the prostate

S. Vázquez Martínez[1], I. Bosch Roig[1], R. Sanz Requena[2]

[1] Communications Department, Universitat Politècnica de València, Valencia, España, igbosroi@dcom.upv.es

[2] Biomedical Engineering / Radiology, Hospital Quirónsalud Valencia, Valencia, España, roberto.sanz@quironsalud.es

Abstract

In Dynamic Contrast-Enhanced Magnetic Resonance (DCE-MR) studies with high temporal resolution, images are quite noisy due to the complicate balance between temporal and spatial resolution. For this reason, the temporal curves extracted from the images present remarkable noise levels and, because of that, the pharmacokinetic parameters calculated by least squares fitting from the curves and the arterial phase (a useful marker in tumour diagnosis which appears in curves with high arterial contribution) are affected. In order to solve these limitations, an automatic filtering method was developed by our group. In this work, an advanced automatic filtering methodology is presented to further improve noise reduction of the temporal curves in order to obtain more accurate kinetic parameters and a proper modelling of the arterial phase.

1. Motivation

These days, the radiologist qualitative diagnosis combined with researcher quantifications offers a complete and detailed report, which helps to locate small areas of complicate detection and customize patient treatment [1]. This article is focused in DCE-MR studies and the study tissue is the prostate. From every pixel of these images, signal intensity curves versus time can be extracted. The kinetic parameters can be computed from these curves by means of non-linear least square fitting. However, images are quite noisy [2], causing incorrect fitting, wrong calculated parameters and a poor characterization of the arterial phase (signal peak which appears after contrast agent injection) in curves that show high arterial contributions. A filtering methodology was designed in order to reduce the noise and solve all those issues [1,2]. Other methods have been used in order to remove the noise of the images [3], instead of the noise of curves. Nevertheless, the current methodology presented some limitations, as the lack of curve classification, which is required to test the filter in different curve types. The objective of this article is to present an improved automatic filtering methodology, with some advances, as the new limit positioning, an improved interpolation and a curve classification method.

2. Methodology

In this work, an advance and new results in the Automatic Filtering Methodology (AFM) detailed in [1,2] have been developed to provide a more exact fitting of DCE-MR uptake curves, which provides more reliable quantitative parameters and a proper characterization of any tissue.

2.1. Pharmacokinetic modelling

The two-compartment model is used, based in the contrast exchange between vascular space and interstitial space. The pharmacokinetic parameters of the two-compartment model are [4]:

- Transfer constant K^{trans} (min^{-1}): relation between blood flow contribution, endothelial surface (interior of blood vessels) and capillary permeability.
- Rate constant k_{ep} (min^{-1}): contrast return between Extracellular Extravascular Space (EES) and vascular space.
- Intravascular extracellular volume fraction (blood plasma) v_p: tissue vascular contribution.

The Arterial Input Function (AIF) is also an important element in this model. It represents the tissue-feeding artery concentration. The iliac arteries are commonly used as AIF for the prostate.

2.2. Automatic Filtering Methodology

As in the previous methodology, the intensity curves are divided into three stages using two temporal limits, t_{lower} and t_{upper}, following the physiological standards of vascular contribution to the tissues. In this work, a new processing pipeline is presented to improve the determination of the temporal position of the limits, also taking into account the arrival times of the AIF and the uptake curves.

- In the first stage (before contrast arrival), all values become zero, because initially contrast does not exist.
- In the second stage (arterial phase), new samples are added between the original ones by means of linear interpolation. The number of samples is controlled by the interpolation degree (for instance, if the interpolation degree is 2, a new sample is inserted between two previous samples, thereby duplicating the existing number of samples between both temporal limits).
- In the third stage (washout), different linear filters have been tested (moving averages, lowess and rlowess) with maximum span (i.e. maximum filtering) to reduce the noise drastically in that part, maintaining the tendency of the original curve.

The lower limit t_{lower} is defined as the contrast arrival time, and the upper limit t_{upper} is set after the purely arterial uptake of the tissue of interest. The contrast arrival time is the temporal instant when the contrast

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arrives at a certain area (blood vessels, organs and so on), which is reflected in the curves as an enhancement of the signal and a fast upslope. In order to obtain it, the average curve of all prostate uptake curves, *x(t)*, has to be calculated. Then, the time when an intensity value *I* exceeds the mean + 3 Standard Deviation (SD) of the initial 6 dynamic values (i.e. baseline) of *x(t)*, t_I, is obtained:

$$t_I > mean\big(x(t_1{:}t_6)\big) + 3 * SD(x(t_1{:}t_6))$$

Finally, t_{lower} is set just before t_I. The chosen number of dynamics is an empirical value, based on the experience of the radiologist. To ensure more accuracy in the pharmacokinetic modelling process, the AIF arrival time and the uptake curves arrival time (t_{lower}) must be re-allocated, ensuring that the onset instant is the same for both curves. As for the upper limit, the temporal difference between the AIF arrival time and the AIF maximum time, Δt_{AIF}, is calculated. Then, the upper limit t_{upper} is obtained as the sum of the lower limit t_{lower} plus 3 times Δt_{AIF}:

$$t_{upper} = t_{lower} + 3 * \Delta t_{AIF}$$

The number of times which Δt_{AIF} is multiplied is also an empirical value. In the 17 studies used in this work, the arterial phase of the intensity curves was contained in both limits. In Figure 1 there is a diagram which summarises the whole workflow. From the DCE-MR images, AIF and uptake curves are extracted. Non-linear least squares are applied to fit every extracted uptake curve in order to obtain the pharmacokinetic parameters. With the AFM, the uptake curves are processed to achieve more accurate and reliable biomarkers by means of non-linear least squares fitting. The same linear filter to smooth the washout part of the uptake curves is used in the washout part of the AIF.

2.3. Case classification

The implemented filtering methodology is oriented towards intensity curves with high arterial contributions. To better focus the analysis on these kind of curves, the principal component that resembles an arterial-like curve and its coefficients from Principal Components Analysis (PCA) have been used. The principal component has been identified applying the Pearson's linear correlation coefficient to every component with respect to the AIF. This component has associated coefficients which represent the arterial contribution value of every enhancement curve. Sorting these coefficients in decreasing order, a group of curves with high arterial contribution can be taken. As a criterion, the first 25 and last 25 coefficients are chosen, associated with 25 arterial-like curves and 25 non arterial-like curves, respectively. With the knowledge of the 3 type of curve patterns traditionally localized in DCE-MR studies (type 1, progressive; type 2, plateau; and type 3, washout [5]), 17 prostate studies have been classified. The patterns are represented in Figure 2. The cases are classified as washout-progressive, washout-plateau and plateau-progressive. That means that if the case 1 is washout-progressive, its 25 first curves show the washout pattern and its 25 last curves the progressive pattern.

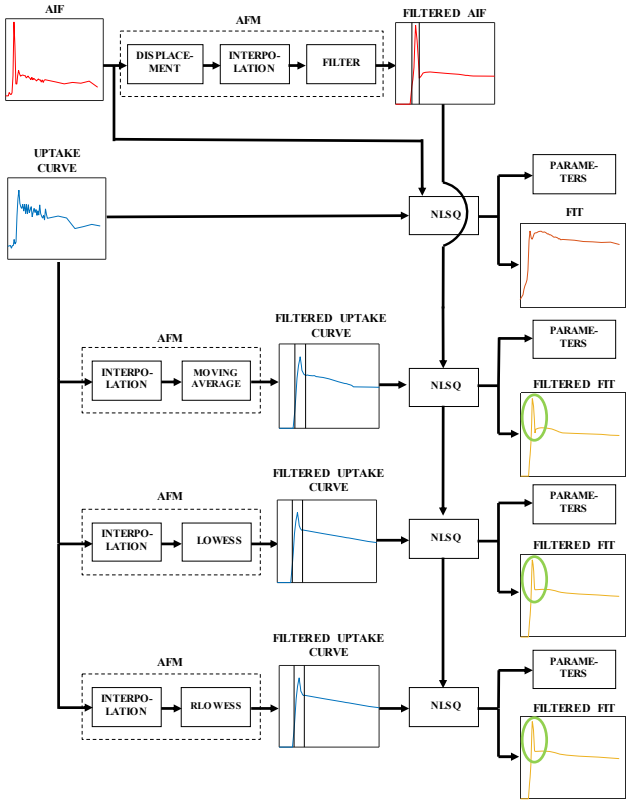

Figure 1. *Diagram describing the whole workflow of the automatic designed filter. It can be seen the good fit in the arterial phase (marked with green ellipses in the filtered fit) from filtered curves (interpolation + moving average/lowess/rlowess), as opposed to the fit from non-filtered curves. Note: NLSQ means non-linear least squares.*

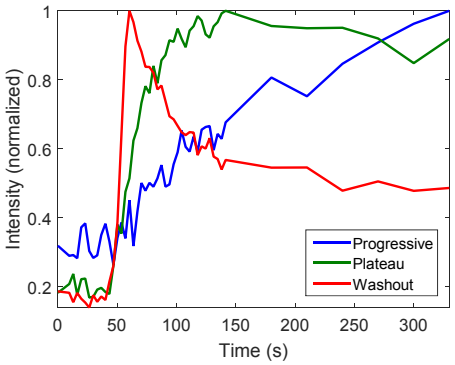

Figure 2. *The three patterns of the washout phase: type 1, progressive (blue); type 2, plateau (green) and type 3, washout (red).*

The cases 1 (washout-progressive), 9 (washout-plateau) and 10 (plateau-progressive) are selected in order to show the obtained results in filtered curves and non-filtered curves, and their results can be extrapolated to the same case types. Once the classification is established, the difference between the fit of filtered and non-filtered curves has to be measured in the three model cases, both

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qualitatively and quantitatively. The qualitative analysis has been performed by the comparison between the average fitted curve from non-filtered (fit in Figure 1) and filtered curves (filtered fit in Figure 1).

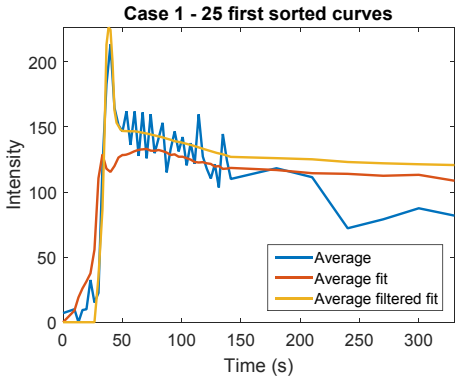
The quantitative analysis is performed by the calculation of the parameter Mean Square Error (MSE), by calculating the difference between an intensity curve (uptake curve or filtered uptake curve in Figure 1) and its fitted curve (fit or filtered fit in Figure 1) :

$$MSE = \frac{1}{N}\sum_{k=1}^{N}(fitted\ curve(k) - \ intensity\ curve(k))^2$$

Furthermore, kinetic parameters are calculated from filtered (filtered uptake curve in Figure 1) and non-filtered curves (uptake curve in Figure 1) and ANOVA tests are performed to study statistical differences between them.

3. Results

As for the results, the qualitative improvement between fits is discussed at first place. It should be noted that an interpolation degree of 2 and a moving average filter have been used in this section, because globally they offer the best results in comparison to the other linear filters options and other interpolation degrees. Besides, due to the good results in the previous articles [1,2], this time new DCE-MR studies are included, in order to validate the proposed methodology, and no simulations are needed. In Figure 3, it can be seen that the average fit from the filtered first 25 curves in case 1 (washout-progressive) is more accurate in the arterial phase than the average fit from the non-filtered first 25 curves. Therefore, the obtained parameters are more reliable. In the last 25 curves, both fits are quite similar. It is also worth noting that in both fits, there are 2 small peaks, related with the modelling assumption that there may be arterial contributions.



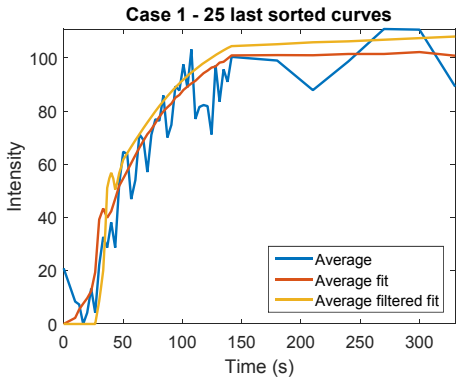


Figure 3. *Comparison of average fit curves from non-filtered curves and average fit curves from filtered curves from case 1.*

In case 9 (washout-plateau), in the first sorted curves there is a precise adjustment in the arterial phase and an approximate fit in the washout part. In the last curves, the average fit from the filtered curves is more exact than the fit from non-filtered curves. This can be analysed in Figure 4.

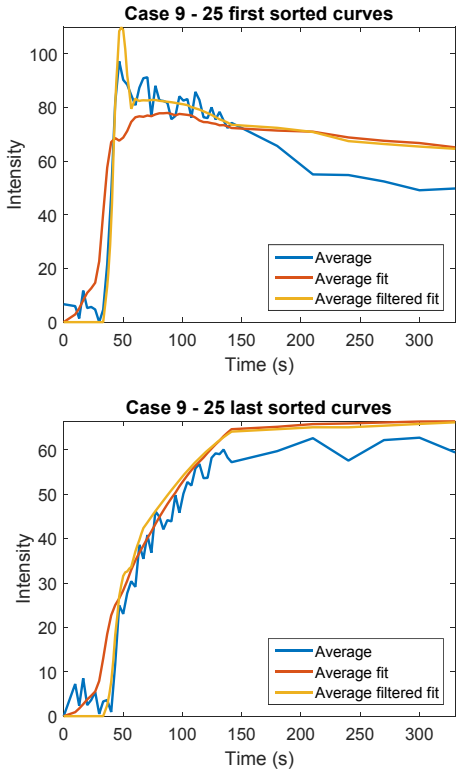


Figure 4. *Comparison of average fit curves from non-filtered curves and average fit curves from filtered curves from case 9.*

In case 10 (plateau-progressive), an undesired peak appears in the average fit from the filtered first curves, due to the AIF influence and the increment of samples in the arterial phase of the AFM. A relatively good agreement is obtained between the non-filtered and filtered adjustment, as it can be seen in Figure 5.

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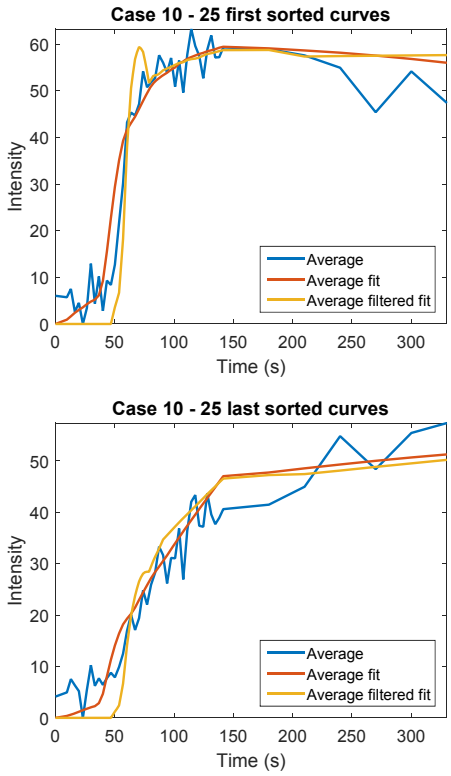

Figure 5. *Comparison of average fit curves from non-filtered curves and average fit curves from filtered curves from case 10.*

Once qualitatively analysed the fit goodness of filtered and non-filtered curves, the last step is to measure it quantitatively with the MSE, kinetic parameters and ANOVA test. In Table 1, it can be checked that mean and standard deviation MSE values are reduced in filtered curves, which implies a more exact fitting and more accurate and reliable kinetic parameters. The mean and standard deviation kinetic markers values show that greater v_p values, smaller K^{trans} values and similar k_{ep} values are obtained in comparison to the values from non-filtered curves. In the ANOVA tests, the p-values are lower than 0.001, which means that there are statistical significant differences between the filtered and non-filtered kinetic marker values and that the null hypothesis of the ANOVA test (all group means are equal) is rejected. As mentioned previously, the results from these cases are comparable to those with the same classification. The same analysis was performed in every case, in order to confirm that statement, obtaining similar values and fits.

4. Conclusions

Qualitatively, the curve fitting results are more accurate in filtered curves than in non-filtered curves. The arterial phase is properly respected and fitted with the proposed algorithm. Concerning the MSE, it can be seen that the designed AFM gives a better least square fitting, due to the reduced MSE values in filtered curves. Analysing the fit information, MSE values, marker values and ANOVA results, it can be assumed that the better fit of the curve provided by the proposed filter presents higher v_p values, lower K^{trans} values and similar k_{ep} values, in comparison to the standard approach without filtering. It can be concluded that the temporal automatic filter allows obtaining more accurate and reliable parameters, both qualitatively and quantitatively, preserving the arterial phase information in the least square fitting, solving one of the limitations of this technique. Furthermore, a better modelling in high arterial contributions from the prostate is obtained. Therefore, the results with the AFM are very satisfying.

		Case 1	Case 9	Case 10
MSE	**All curves, no filter**	427.04 ±171.67	78.23 ± 40.81	117.92 ± 66.57
	All curves, with filter	132.60 ± 77.87	27.33 ± 21.49	71.54 ± 35.64
	First 25 sorted curves, no filter	923.55 ±184.75	184.47 ± 60.66	98.61 ± 37.48
	First 25 sorted curves, with filter	249.67 ± 93.45	63.90 ± 23.82	88.19 ± 32.64
	Last 25 sorted curves, no filter	303.86 ± 82.31	55.72 ± 19.86	124.82 ± 77.41
	Last 25 sorted curves, with filter	164.94 ± 90.52	10.01 ± 2.93	56.31 ± 34.04
v_p	**All curves, no filter**	0.009 ± 0.016	0.008 ± 0.018	0.022 ± 0.018
	All curves, with filter	0.062 ± 0.022	0.058 ± 0.028	0.063 ± 0.019
K^{trans}	**All curves, no filter**	0.035 ± 0.016	0.024 ± 0.013	0.011 ± 0.005
	All curves, with filter	0.021 ± 0.018	0.015 ± 0.009	0.004 ± 0.002
k_{ep}	**All curves, no filter**	0.037 ± 0.014	0.021 ± 0.009	0.010 ± 0.006
	All curves, with filter	0.033 ± 0.018	0.019 ± 0.010	0.002 ± 0.004

Table 1. *Comparison between MSE values from filtered and non-filtered curves from the representative cases.*

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