

Parametric time warping of peaks with the ptw package

Ron Wehrens

Tom Bloemberg

Paul Eilers

January 19, 2022

Note

As of November, 2019, the vignette source code is no longer distributed with the package but can be accessed from

<https://github.com/rwehrens/ptw/tree/master/ptwVignette>.

1 Introduction

In many fields of science one can find examples where similar events are not occurring simultaneously. When comparing these events, one has to make sure that they are matched correctly. In the natural sciences such phenomena occur frequently, especially in techniques employing chromatography as a separation step, e.g., in metabolomics and proteomics. Retention times are variable, more so when samples are measured in different labs, using different equipment or at different points in time. In cases where such retention time differences cannot easily be corrected, e.g., by using internal standards, automatic methods defining the optimal “warping” of the time axis are necessary Bloemberg et al. [2013]. Many different methods have been proposed in literature for warping chromatograms, e.g., Dynamic Time Warping (DTW, Wang and Isenhour [1987]) and a penalized variant of DTW (VPdtw, Clifford and Stone [2012]), and Correlation Optimized Warping (COW, Tomasi et al. [2004]).

Parametric Time Warping (PTW, Eilers [2004]) tackles this issue by finding a polynomial transformation of the time axis that leads to maximal overlap between two samples. Typically, one sample is taken as a reference r , and all others (s_i) are transformed: $s_i(w_i(t)) \approx r(t)$, where $w_i(t)$ signifies the warping function for the i -th signal. The degree of the warping function can be chosen by the user: a zeroth-order warping signifies a constant shift, whereas a first-order function also introduces stretching or compression. Higher-order terms allow for even more complex behaviour. Compared to other approaches, PTW is particularly appropriate for aligning chromatographic signals for a number of reasons:

- it is *simple*; basically, one only has to decide on the degree of the warping function, and on the similarity function.
- it is *fast*; many alternatives, in particular COW, are much slower.

- it is *restricted*; too much liberty in the warping will lead to false matches and erroneous results. For applications in chromatography the restricted nature of the accessible warping space is actually an advantage.
- it presents *explicit warping functions*. This has a number of advantages, mentioned below.

Note that in many fields such as proteomics and metabolomics, often based on mass-spectrometry (MS) detection, dedicated peak-matching algorithms are being used to link features across samples. Typically, these allow for only minor differences in retention time, and are not able to correct for larger ones – in many cases they are very flexible, and allowing too much freedom would lead to many incorrect matches. An example is the retention time correction implemented in the popular R package **xcms**, which fits a smooth curve through the centers of peak groups and in that way iteratively determines what retention time correction to apply [Smith et al., 2006]. Such a procedure works really well to counter the usual small and random deviations in LC-MS data. However, it cannot correct the larger and more systematic effects that occur when comparing retention times to data measured some time before, or measured under different circumstances or in different labs. In these cases, the polynomial warpings provided by PTW can be extremely useful.

The current document describes an extension over the original implementation in the **ptw** R package [Bloemberg et al., 2010] providing the warping of stick spectra, i.e., data where not the profiles over time are recorded, but only the positions and intensities of the features. This leads to a speed improvement of sometimes orders of magnitude, as well as (in some cases) to better warpings. The key idea is that the optimization focuses on only the relevant parts of the data, and that irrelevant areas with high intensities but not constituting regular peaks, as are often encountered in chromatograms, are ignored. The consequence is also that elements like baseline correction, essential in the full-profile version of **ptw**, are now taken care of by the peak picking procedures, which are often domain-specific, and can therefore be much more efficient. The theory of warping sticks is (briefly) described in Wehrens et al. [2015a] – here, we concentrate on the R code and show a more full version of the results. Unfortunately the vignette takes too long to build according to CRAN guidelines, so only the \LaTeX source is included: the Sweave source and the data files can be found on the package github site: <https://github.com/rwehrens/ptw>.

2 Forward and backward warping

The original version of PTW [Eilers, 2004] calculates for a given position, or index, which other index will end up in that particular place [Bloemberg et al., 2013]. Or, to put it differently: for a given time point in the reference, it calculates what time point in the signal should be compared with that: $s_i(w_i(t)) \approx r(t)$. This is somewhat counter-intuitive. A positive zeroth-order warping coefficient, for example, indicates a shift to the *left*. Interpretation, and several other actions, would be easier if the warping

would be implemented in exactly the opposite way, i.e., the warping function would tell where a particular time point would end up. This new functionality is implemented in version 1.9-0 (and later) of **ptw** under the label *forward warping*; the old behaviour is still available as *backward warping*. So for a given point in the signal, forward warping tells you where the corresponding point in the reference is: $s_i(t) \approx r(w_i(t))$. Alignment of sticks is only implemented in forward warping mode: in this way one directly calculates the new time associated with a particular feature. In general, forward and backward warping give the same or at least very similar results, but it may happen that one of the two ends up in a local optimum.

3 Example data

In this tutorial vignette, two data sets are used. The first comes from an investigation of carotenoid levels in grape samples, investigating the influence of tri-ethylamine (TEA) as a conservation agent [Wehrens et al., 2015b]. Data were measured on separate days using diode-array detection coupled to liquid chromatography (LC-DAD). Multivariate curve resolution (MCR, de Juan and Tauler [2006]) was used to finally obtain elution profiles, clustered in 14 groups according to spectral characteristics. Although these samples were analysed in a single batch, retention time differences are appreciable, due to the volatile nature of the solvent and the variable temperature conditions in the lab. This set will be used to explain the principles of warping stick spectra.

The second data set consists of LC-MS measurements of 156 apple extracts. This set is much more complex than the DAD set for a number of reasons: first, the number of features is orders of magnitude larger than in the DAD set. Second, whereas the grape set contained replicate measurements of the same sample, in the apple data set biological replicates from apples of seven different varieties are present, as well as a pooled apple sample that is used as a quality control (QC) sample. This set will be used to show the potential of warping sticks on much larger data sets and on sets containing different classes. Here, particularly severe deviations of retention times occur because of a leaking column.

Both sets are publicly available from the Metabolights repository¹ with identifiers MTBLS85 and MTBLS99, respectively. The raw data can easily be read into R using the **Risa** package [Gonzalez-Beltran et al., 2015] but the sets also contain the RData objects used in this vignette.

4 Analysis of the LC-DAD data from grapes

Here we analyse a subset of the original data from MTBLS85, corresponding to those injections where TEA was added. The data are present in the directory containing the vignette code, and can be loaded with the following code:

¹<http://www.ebi.ac.uk/metabolights>

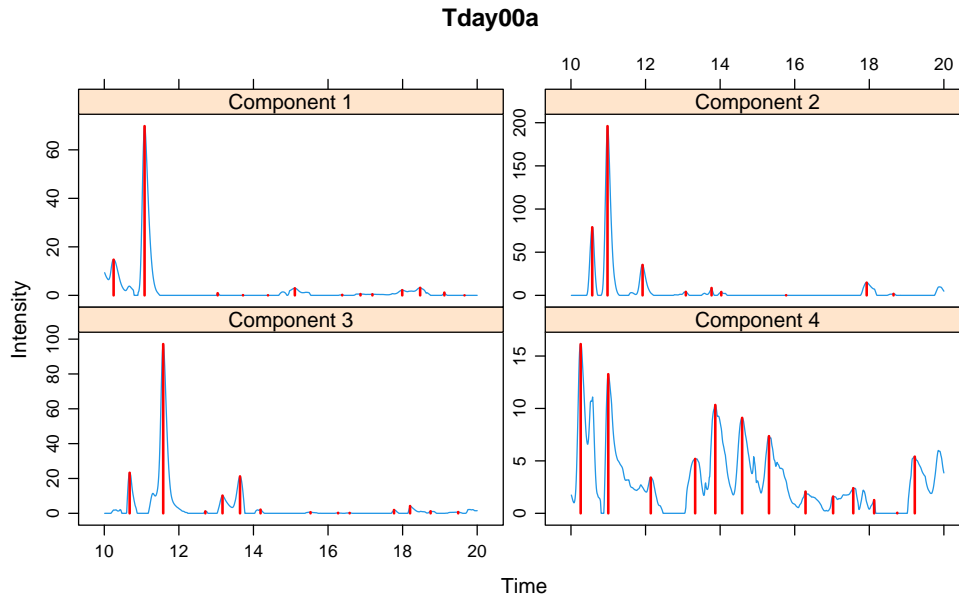


Figure 1: Some elution profiles from the first sample in the grape data set (blue continuous lines). Peaks, obtained after peak picking with a very simple algorithm, are indicated with red vertical lines.

Examples of both the elution profiles, obtained after MCR analysis, and the lists of peaks obtained from these profiles with a very simple peak picking procedure, are shown in Figure 1. Note that some less important peaks are missed, in particular peaks near the edges of the retention time range, and shoulder peaks.

The data are available in two objects, `grape.peaks` and `grape.profiles`, both nested lists, with the samples at the first level and the MCR components at the second level. As the names suggest, the first contains peaks (for each component a number of combinations of retention time and intensity), and the second contains the elution profiles for each of the components at all time points. As an example, the number of peaks in each sample/component combination can be assessed by the following command:

```
> sapply(grape.peaks, function(x) sapply(x, nrow))[1:8, 1:7]
      Tday00a Tday00b Tday01 Tday03 Tday04 Tday09 Tday10
[1,]      13      13      15      12      13      16      13
[2,]       9       9      10      10       7      10       6
[3,]      13      14      18      15      15      14      15
[4,]      13      13      13      13      13      15      14
[5,]      11      14      12      11      12      13      11
[6,]      15      16      16      15      14      16      14
[7,]       9      11       9       7       9      12       8
[8,]       6      11       8       6       8       8       8
```

For reasons of space we restrict the output to the first eight components and the first seven samples. Clearly, there is some difference in the number of peaks, not only for each component, but also over time.

Closer inspection of the peaks in the MCR component over the different samples reveals that there are some differences in retention times. Component 2, for instance, has few peaks and therefore is easy to inspect – the next code shows the retention time of the largest feature in this component across all samples:

```
> sapply(grape.peaks, function(x) {
+   big.idx <- which.max(x[[2]][,"I"])
+   as.numeric(rownames(x[[2]])[big.idx])
+ })
```

Tday00a	Tday00b	Tday01	Tday03	Tday04	Tday09	Tday10	Tday11	Tday13	Tday15
10.98	10.80	10.94	10.91	10.94	10.99	10.94	10.95	11.09	10.67
Tday17	Tday21	Tday24	Tday28						
10.57	10.89	10.89	10.90						

Assuming that the biggest peak is actually the same compound in all cases, we see a maximal retention time difference of almost one minute.

Alignment of the profiles using the `ptw` function is easy, and works pretty well. We choose (rather arbitrarily) the first injection as a reference sample. This is usually not the best choice, since retention time differences are likely to be biggest when comparing the extremes of the sequence – often, a sample from the middle is selected as a reference. Since the retention time deviations here are caused by environmental fluctuations in temperature rather than by a slower process like column degradation, it is expected that the choice of a reference here does not make much of a difference. We will create one single warping function that optimizes the overlap in all fourteen MCR components simultaneously, and use `system.time` to get an impression on the speed of the warping. All parameters have been kept to the system defaults; in particular, a quadratic warping function is fitted.

```
> system.time(grape.profwrap <-
+   lapply(grape.profiles[-1],
+         function(y) ptw(t(grape.profiles[[1]]), t(y), mode = "forward",
+                           warp.type = "global", trwidth = 40)))
```

user	system	elapsed
10.582	0.000	10.583

In comparison, the warping of the peak positions is much faster – note that each profile contains 1,000 time points, whereas the maximal number of peaks in one component is less than 20. So what exactly does “much faster” mean? We can find out by using function `stptw` instead of `ptw`. Note that a few things change in the call. We now use peak lists rather than lists of elution profiles. In stick-based warping, the only possible warping type is the “global” warping, so this argument is no longer needed. Here goes:

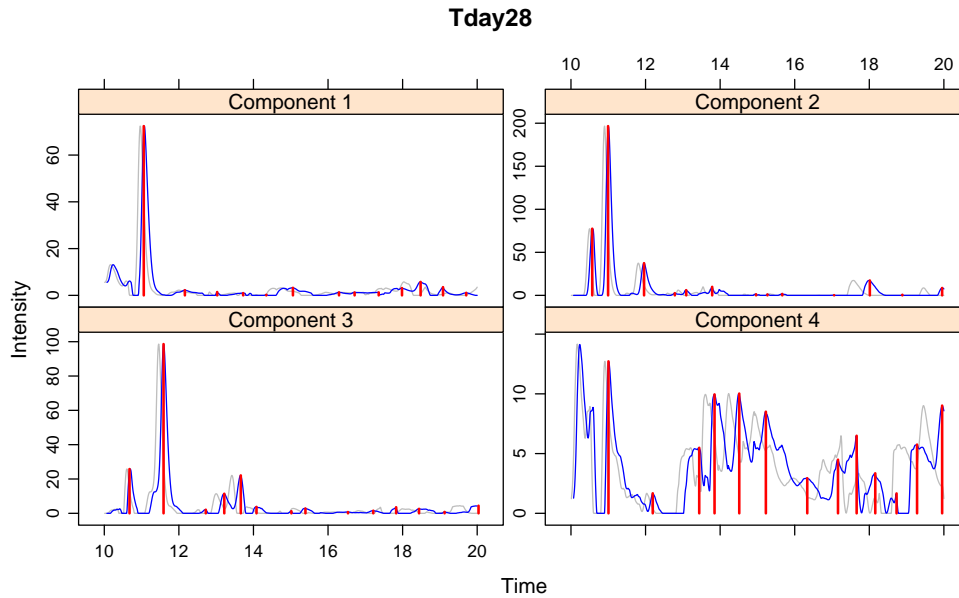


Figure 2: Warped elution profiles and peak positions from the last sample; the figure shows the same components as those in Figure 1. Profiles in gray show the original time profiles, those in blue the profiles after warping. Red vertical segments show sticks after warping.

```
> system.time(grape.stickwarp <-
+   lapply(grape.peaks[-1],
+     function(y)
+       stptw(grape.peaks[[1]], y, trwdth = 40)))
  user system elapsed
 1.29   0.00   1.29
```

That is a speed increase of almost an order of magnitude – not bad!

How good is the agreement between the two types of warping? First of all, we can look at the warped profiles, and the positions of the warped peaks. The same components as seen in Figure 1, but now for the last sample in the sequence, are shown in Figure 2.

The agreement between the peaks in the blue warped profiles and the warped peaks, shown in red, is excellent. There is one case, in component 4, where a major peak is not picked because it is too close to the boundary of the time window – note that in the reference sample, Tday00a, the peak *is* found. This kind of errors can easily be corrected by either more sophisticated peak picking algorithms or simply taking a larger time window.

Apart from the agreement between warped profiles and peak positions, one can also inspect the warping objects to see if both warpings lead to the same result. The values of the WCC quality criterion for profile- and stick-based warpings are not directly

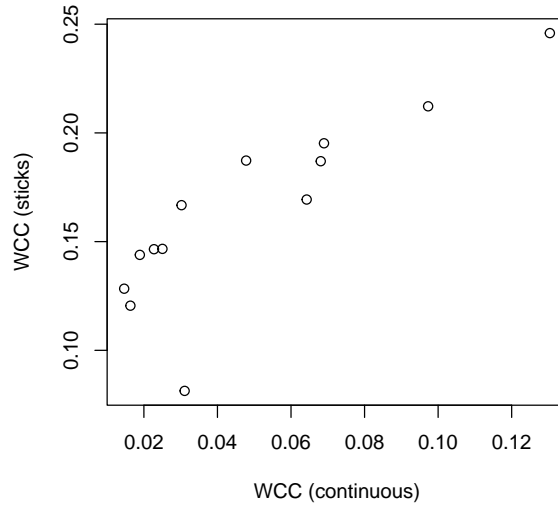


Figure 3: Comparison of WCC values from the continuous warping (x axis) and stick warping (y axis) of the grape DAD data.

comparable, even though they both use the same triangle width. Figure 3 shows this. The reason is that the data are different: in general the profile-based WCC values are lower (indicating more agreement) because they take into account large areas in which there is no or very little signal, which positively contributes to the evaluation criterion.

Luckily, we can use one of the big advantages of parametric time warping here, *viz.*, the existence of an explicit warping function. This means we can directly warp the continuous profiles using the warping function obtained from the sticks. The result can then be compared with the result of the warping of the continuous profiles. In Figure 4 this is done, with the warping functions of the continuous data on the left, and those of the sticks on the right. Clearly, both sets of warping functions are extremely similar.

We can warp the peaks with both sets of warping functions, and compare the WCC values:

```
> ## warp peaks according to continuous warping functions
> grape.warped.peaks <-
+   lapply(2:length(grape.peaks),
+         function(ii)
+           lapply(grape.peaks[[ii]],
+                 function(x) {
+                   new.times <- warp.time(x, "rt",
+                                         t(grape.profwarped[[ii-1]]$warp.coef))
+                   x[, "rt"] <- new.times
+                 }
+               ))
```

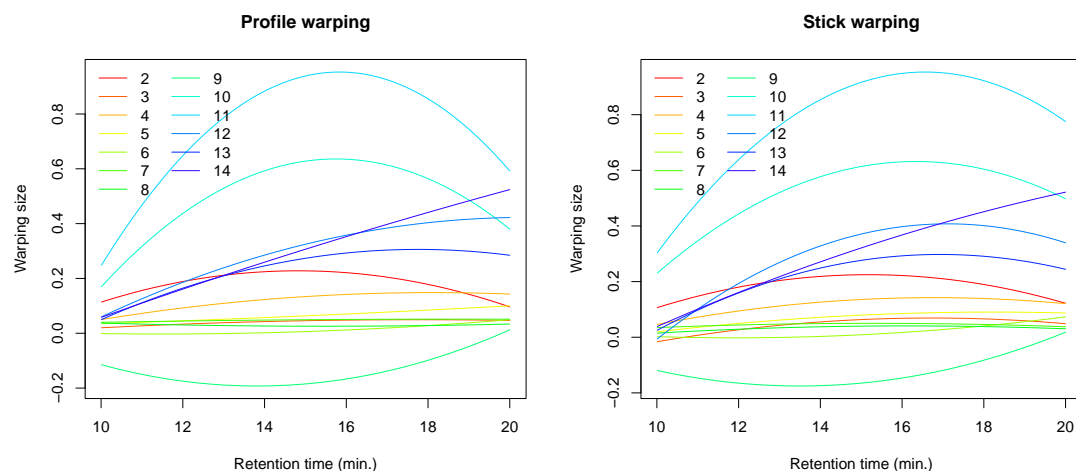


Figure 4: Grape DAD data: the 13 warping functions for continuous data (left) and sticks (right) – the first of the 14 samples is taken as the reference. The x axis presents the time, and the y axis the size of the time correction, where a positive value indicates a shift to the right.

```
> ## calculate WCC values for each sample and each ALS component
> profWCCs <-
+   1-sapply(grape.warped.peaks,
+           function(x)
+             mapply(wcc.st, x, pat2 = grape.peaks[[1]], trwidth = 40))
>
> ## and the result is:
> mean(profWCCs)
[1] 0.1699119
> ## compare that to the WCC value obtained in the stick warping:
> mean(sapply(grape.stickwarp, "[", "crit.value"))
[1] 0.1639269
```

They are virtually equal, indicating that warping the profiles gives the same result as warping the peaks, the latter, of course, being much faster.

5 Analysis of LC-MS data from apples

This section shows a more challenging application of peak-based parametric time warping, coming from the field of untargeted metabolomics. Typically, one sample leads to thousands of peaks, that need to be aligned with the features found in other samples in order to draw any conclusions. A peak is defined by three characteristics: the retention time, the mass-to-charge ratio, and the intensity. All three are subject to experimen-

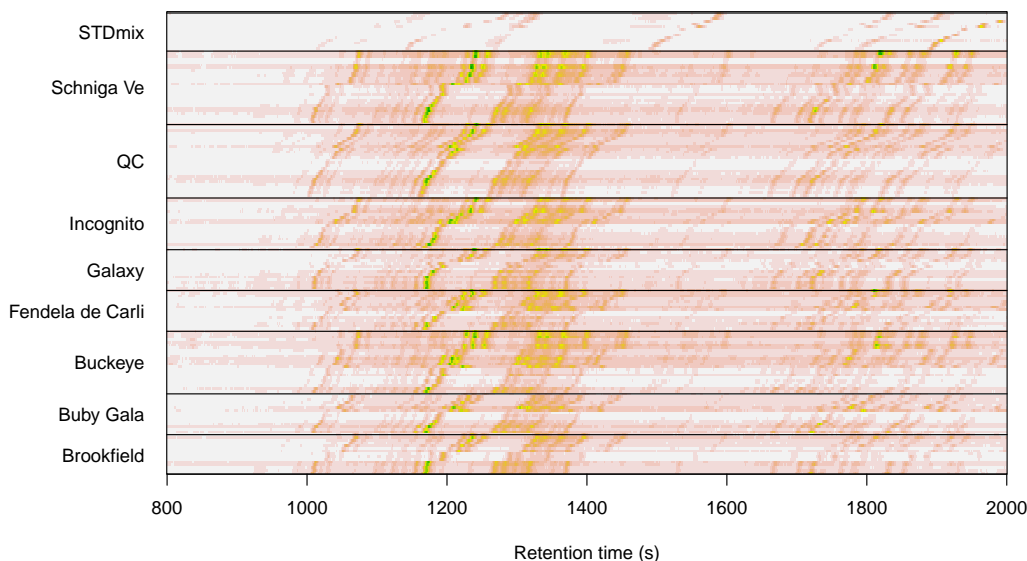


Figure 5: TICs of the LC-MS data – intensities increase from white to brown to yellow to green. Injection classes are shown separately to show the gradual increase in retention times more clearly. The earliest injections are at the bottom of each class panel – retention time shifts are up to one minute in size.

tal error, but the error in retention time is by far the largest and most important, in particular when comparing data that have not been measured in the same batch.

To align peaks, we start by defining m/z bins of a specific width, and construct a peak list for each bin. The result is very similar in structure to the ALS components seen with the DAD data, only more extensive: one can easily define hundreds or even thousands of bins. Choosing a high resolution leads to many bins, but there will be many cases where bins are empty, or contain only very few peaks. Putting all m/z values in one bin corresponds to something like aligning using the total ion current (TIC), something that is not going to be easy [Bloemberg et al., 2010]. On the other hand, having too few peaks in individual bins may make the alignment harder because no information is available for the optimization routine, and one will have to strike a balance between these two effects. Note that this binning process does not mean that mass resolution is lost: individual peaks are merely grouped for the purpose of retention time alignment.

The total-ion current (TIC) chromatograms of these data are shown in Figure 5. To show the deviations in retention times more clearly, the TICs are shown for each class of apples separately, in order of injection. Note how different the peaks in the standard mixture (at the top of the figure) are, compared to the apple data.

5.1 Time warping of QC samples only

For the apple data set, we start by considering only the 27 QC samples. These have been measured at regular intervals, covering the complete injection sequence. First we load the data, and define bins of 1 Dalton (i.e., very broad bins) in which peaks are grouped. We only retain those bins containing peaks for at least half the samples.

```
> QC.idx <- which(metaInf$Variety == "QC")
> QC.pks <- All.pks[QC.idx]
> QC.tics <- All.tics[QC.idx]
>
> ## divide the peak tables for all files into bins of size 1
> mzbins <- lapply(QC.pks, pktab2mzchannel, massDigits = 0)
> ## which bins occur in more than half of the files?
> allmasses <-
+   table(unlist(lapply(mzbins, function(x) unique(names(x)))))
> mymasses <- as.numeric(names(allmasses[allmasses > 13]))
> length(mymasses)
[1] 698
> ## now we can divide the peak tables again, focusing on these masses only
> QC.mzlist <- lapply(QC.pks, pktab2mzchannel,
+                     masses = mymasses, massDigits = 0)
```

The result is a nested list: for each of the 27 samples, 688 m/z bins are considered in defining a warping function. Clearly, this is much more challenging than the 14 DAD samples with 14 components.

Let us define the first QC sample as the reference sample, and calculate warping functions for all 26 other samples:

```
> QCwarpings <-
+   lapply(2:length(QC.mzlist),
+         function(ii)
+           stptw(QC.mzlist[[1]], QC.mzlist[[ii]], trwdth = 50))
```

This step may take some time.

We can visualize the effect of the warping by applying it to the (continuous) total ion chromatogram (TIC) data, summarizing for every time point the total amount of signal across all masses. Here, we concentrate on the middle part of the chromatogram, between 800 and 2000 seconds:

```
> ## create a matrix of tic signals from the individual vectors of the
> ## samples - these are not measured at exactly the same times, so we
> ## use interpolation, one value for each second.
> QCticmat <- sapply(QC.tics,
+                   function(x)
+                     approx(x$scantime, x$tic, tictimes)$y)
```

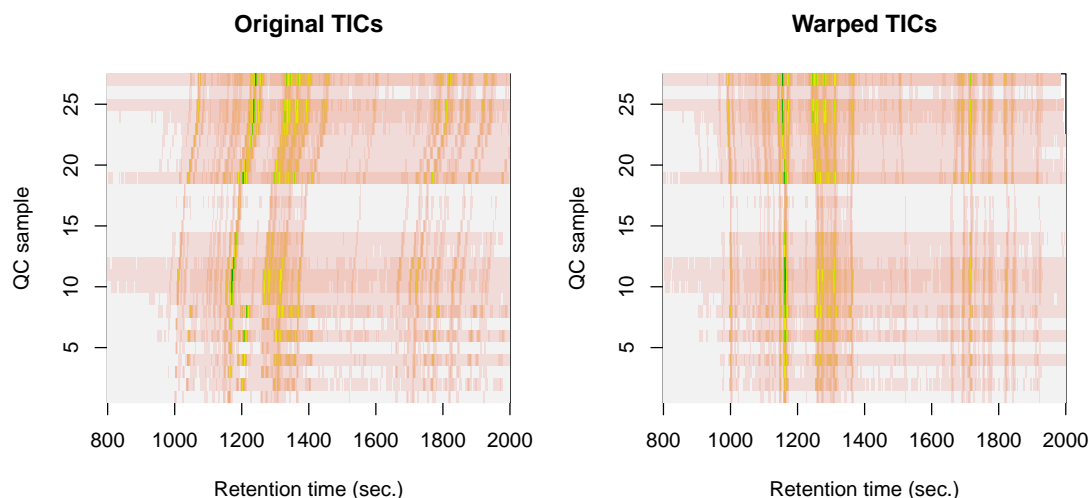


Figure 6: Original TICs of the apple QC samples (left), and TICS warped according to the warping functions from the peak lists (right). The injection order of the samples is from the bottom to the top.

```
> ## Now do the same, but apply the warping to the scantimes
> QCticmat2 <-
+   sapply(seq(along = QC.tics),
+         function(ii) {
+           if (ii == 1) {
+             approx(QC.tics[[ii]]$scantime,
+                   QC.tics[[ii]]$tic,
+                   tictimes)$y
+           } else {
+             new.times <- warp.time(QC.tics[[ii]]$scantime,
+                                   QCwarpings[[ii-1]]$warp.coef)
+             approx(new.times, QC.tics[[ii]]$tic, tictimes)$y
+           })
+ }
```

The result is shown in Figure 6. The left figure clearly shows that peaks elute at later times in later QC samples, whereas this trend is absent in the right figure, showing the PTW-corrected TICs.

5.2 Time warping of non-QC samples

Defining the optimal warping works best if the majority of features is present in all samples. Obviously, in real-life data sets this is very often not the case, and the danger is that the optimization will end up in a suboptimal solution. Two approaches can be

used to remedy this. The first assumes that subsequent injections are similar. That is, in finding the optimal warping of sample $i+1$, one could start from the result of warping sample i . Not only does this decrease the result of false matches and an incorrect warping, it probably also speeds up the procedure since fewer optimization steps are needed to reach convergence.

However, this is not a fundamental solution to the fact that samples may be very different, and that in such a case false matches between peaks can be expected. The second possibility is to use the QC samples mentioned earlier, and interpolate the warping functions of samples injected between two QC samples. This again assumes a smooth shift in retention times over the injection sequence, which usually is the case. The retention times of the peaks in the apple samples can then be warped according to the warping functions found in the QC warping, through a simple process of linear interpolation between the QCs. We can calculate warped retention times for the QC warpings and then interpolate, or directly interpolate the warping coefficients:

```
> interpolate.warping <- function(rt, coef1, coef2, idx,
+                               type = c("coef", "time")) {
+   weights <- abs(idx[2:3] - idx[1]) / diff(idx[2:3])
+   type <- match.arg(type)
+   if (type == "time") {
+     rt1 <- warp.time(rt, coef1)
+     rt2 <- warp.time(rt, coef2)
+     crossprod(rbind(rt1, rt2), weights)
+   } else {
+     coefs <- crossprod(rbind(coef1, coef2), weights)
+     warp.time(rt, coefs[,1])
+   }
+ }
```

First we define the relevant QCs for each of the real samples:

```
> ## sort on injection order
> inj.order <- order(metaInf$InjectionNr)
> metaInf <- metaInf[inj.order,]
> All.pks <- All.pks[inj.order]
> All.tics <- All.tics[inj.order]
>
> ## pick out only the apple samples
> sample.idx <- which(!(metaInf$Variety %in% c("QC", "STDmix")))
> QC.idx <- which(metaInf$Variety == "QC")
> ## store the IDs of the QC samples around each sample
> neighbours.idx <- t(sapply(sample.idx,
+                             function(x) {
+                               c(x,
+                                 max(QC.idx[QC.idx < x]),
+                                 min(QC.idx[QC.idx > x]))}))
```

```
> head(neighbours.idx, 9)
      [,1] [,2] [,3]
[1,]    7    5   14
[2,]    8    5   14
[3,]    9    5   14
[4,]   10    5   14
[5,]   11    5   14
[6,]   12    5   14
[7,]   13    5   14
[8,]   15   14   21
[9,]   16   14   21
```

So now we know what warpings to use for each of the sample. For example, let's look at the fifth sample, injected at position 12. This is flanked by the fourth and fifth QC samples, at positions 5 and 14:

```
> relevant.warpings <- which(QC.idx %in% c(5, 14)) - 1
> ## Original data:
> head(All.pks[[12]][,c("mz", "rt", "maxo", "sn")])
      mz      rt      maxo      sn
[1,] 57.06821 1299.491  7.088608  7.150621
[2,] 60.07875 1368.869 12.151901 10.056416
[3,] 67.05031 1370.171  7.088608  5.346768
[4,] 69.06414 1686.200 14.177216  9.407192
[5,] 69.06279 1845.409 14.177216  6.286520
[6,] 69.06596 1616.806  9.113922  4.191239
> ## the weighted average of the warpings of the 2 QC samples
> interpolate.warping(All.pks[[12]][1:6, "rt"],
+                     QCwarpings[[relevant.warpings[1]]]$warp.coef,
+                     QCwarpings[[relevant.warpings[2]]]$warp.coef,
+                     neighbours.idx[5,],
+                     type = "time")
      [,1]
[1,] 1270.069
[2,] 1338.654
[3,] 1339.941
[4,] 1651.215
[5,] 1807.324
[6,] 1583.025
> ## one warping, obtained by the weighted average of the warping coefs
> interpolate.warping(All.pks[[12]][1:6, "rt"],
+                     QCwarpings[[relevant.warpings[1]]]$warp.coef,
+                     QCwarpings[[relevant.warpings[2]]]$warp.coef,
+                     neighbours.idx[5,],
+                     type = "coef")
[1] 1270.069 1338.654 1339.941 1651.215 1807.324 1583.025
```

Clearly, the results of the two types of warping are the same. Calculating average coefficients is more efficient, so that is the default in our function. Now, let's do this for

all the samples, where we have to remember not only to correct the retention time but also the intervals around the retention times:

```
> corrected.pks <-
+   lapply(1:nrow(neighbours.idx),
+         function(pki) {
+             smp.idx <- which(names(All.pks) ==
+                               metaInf[neighbours.idx[pki, 1], "file.name"])
+             QC1 <- which(QC.idx == neighbours.idx[pki, 2]) - 1
+             QC2 <- which(QC.idx == neighbours.idx[pki, 3]) - 1
+             coef1 <- QCwarpings[[QC1]]$warp.coef
+             coef2 <- QCwarpings[[QC2]]$warp.coef
+
+             cpk <- All.pks[[smp.idx]]
+             cpk[, "rt"] <-
+                 interpolate.warping(cpk[, "rt"], coef1, coef2, neighbours.idx[pki,])
+             cpk[, "rtmin"] <-
+                 interpolate.warping(cpk[, "rtmin"], coef1, coef2,
+                                     neighbours.idx[pki,])
+             cpk[, "rtmax"] <-
+                 interpolate.warping(cpk[, "rtmax"], coef1, coef2,
+                                     neighbours.idx[pki,])
+             cpk
+         })
+ names(corrected.pks) <- metaInf[neighbours.idx[,1], "file.name"]
```

Applying the peak-based warpings to the TICs is done following exactly the same line as earlier. First we correct all apple profiles:

```
> samp.tics <- All.tics[sample.idx] ## only real apple samples
> Corr.tics <-
+   lapply(seq(along = samp.tics),
+         function(ii) { ## no warping for the first sample, the reference
+             if (ii == 1) {
+                 samp.tics[[1]]
+             } else {
+                 QC1 <- which(QC.idx == neighbours.idx[ii, 2]) - 1
+                 QC2 <- which(QC.idx == neighbours.idx[ii, 3]) - 1
+                 coef1 <- QCwarpings[[QC1]]$warp.coef
+                 coef2 <- QCwarpings[[QC2]]$warp.coef
+
+                 new.times <-
+                     interpolate.warping(samp.tics[[ii]]$scantime,
+                                         coef1, coef2, neighbours.idx[ii,])
+                 list(tic = samp.tics[[ii]]$tic, scantime = new.times)
+             }})
```

A part of the time axis of these corrected TICs is shown in Figure 7. This figure should be compared with Figure 5 – again, we can see that within each class the retention time

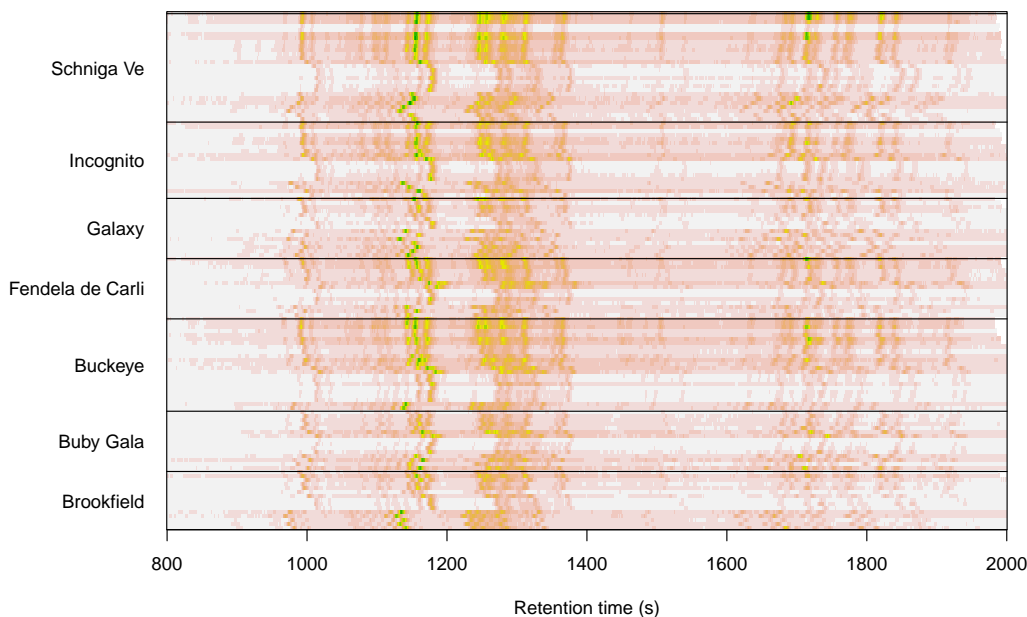


Figure 7: Corrected TICs of the LC-MS data, where the warping functions are obtained from the peak lists.

shift has been corrected very well. There still is some variation, but the large effects of the leaking column have been eliminated, and the remaining variation is probably small enough to be tackled with the usual retention time correction methods present in **XCMS**.

6 Discussion

Alignment can be a lengthy process, especially when many samples with many time points need to be corrected. PTW has always been quite fast, but the new peak-based form decreases computation times by an order of magnitude or more, which significantly enhances its usefulness in modern high-throughput applications. The new functionality could even be used to fit higher-order warping functions with optimization routines that are less likely to end up in local minima (but that need more iterations) – in some cases, we have seen that higher-order warping coefficients can be quite variable, and this effect is significantly reduced when using optimization methods like simulated annealing or genetic algorithms. In practice, this functionality may not be of crucial importance, but the possibility to investigate this is an asset. In the `stptw` function experimental code has been included, accessible through the argument `nGlobal`: this integer indicates the number of global searches to be performed (using function `nloptr` from the package with

the same name, algorithm “NLOPT_GN_CRS2_LM”) prior to the normal steepest-descent optimization. By default, `nGlobal` = 0 when the polynomial degree is three or smaller, and `nGlobal` = 5 when higher-order polynomials are used. Note that this takes quite a bit of computing time.

In this vignette we show that the peak-based warpings are very similar to the original profile-based ones, and that forward and backward warping modes can both be used for alignment of chromatographic signals. We explicitly indicate how to use interpolated warpings, based on QC samples, for aligning real samples, as already indicated in Eilers [2004]. This is a real bonus in cases where samples of a quite different nature need to be warped: when comparing cases with controls, for example, it may happen that large differences in features lead a classical warping astray and that regular shift corrections such as DTW or COW, that do not yield functional descriptions of the optimal warpings, cannot be used.

We already mentioned the simple form of the PTW paradigm, requiring the user only to choose a polynomial degree and the similarity function. The latter choice is absent in the peak-based form of PTW, which is only implemented for the WCC criterion (shown to outperform the other criterion, Euclidean distance, in any case – see Bloemberg et al. [2010]). When analysing the peak lists in LC-MS data, it will be necessary to aggregate the peaks into m/z bins² of a certain width. This *is* an extra step that requires some attention from the user. Luckily, the choice of bin width is not crucial. Wider bins lead to more peaks per bin and fewer alignment steps, and are therefore faster; narrow bins contain few peaks, but then there are more bins to process. In general, as long as there are not too many empty bins, and there is not too much overlap within individual bins, peak-based PTW will have no problems. In this vignette, for example, we have not optimized the bin width at all.

²For nominal-mass GC data, this step is not even necessary.

References

- T.G. Bloemberg, J. Gerretzen, H. Wouters, J. Gloerich, H.J.C.T. Wessels, M. van Dael, L.P. van den Heuvel, P.H.C. Eilers, L.M.C. Buydens, and R. Wehrens. Improved parametric time warping for proteomics. *Chemom. Intell. Lab. Syst.*, 104:65–74, 2010.
- T.G. Bloemberg, J. Gerretzen, A. Lunshof, R. Wehrens, and L.M.C. Buydens. Warping methods for spectroscopic and spectrometric signal alignment: a tutorial. *Anal. Chim. Acta*, 781:14–32, 2013.
- D. Clifford and G. Stone. Variable penalty dynamic time warping code for aligning mass spectrometry chromatograms in R. *J. Stat. Softw.*, 47(8):1–17, 2012.
- A. de Juan and R. Tauler. MCR from 2000: progress in concepts and applications. *Crit. Rev. Anal. Chem.*, 36:163–176, 2006.
- P.H.C. Eilers. Parametric time warping. *Anal. Chem.*, 76:404–411, 2004.
- A. Gonzalez-Beltran, S. Neumann, E. Maguire, P. Rocca-Serra, and S. Sansone. The Risa R/Bioconductor package: integrative data analysis from experimental metadata and back again. *BMC Bioinformatics*, 15(Suppl 1):S11, 2015.
- C. A. Smith, E. J. Want, G. O’Maille, R. Abagyan, and G. Siuzdak. **XCMS**: Processing mass spectrometry data for metabolite profiling using nonlinear peak alignment, matching, and identification. *Anal. Chem.*, 78:779–787, 2006.
- G. Tomasi, F. van den Berg, and C. Andersson. Correlation-optimized warping and dynamic time warping as preprocessing methods for chromatographic data. *J. Chemom.*, 19:231–241, 2004.
- C.P. Wang and T.L. Isenhour. Time-warping algorithm applied to chromatographic peak matching gas chromatography / Fourier Transform infrared / Mass Spectrometry. *Anal. Chem.*, 59:649–654, 1987.
- R. Wehrens, T.G. Bloemberg, and P.H.C. Eilers. Fast parametric time warping of peak lists. *Bioinformatics*, In press, 2015a. doi: 10.1093/bioinformatics/btv299.
- R. Wehrens, E. Carvalho, and P. Fraser. Metabolite profiling in LC-DAD using multivariate curve resolution: the alsace package for R. *Metabolomics*, 11:143–154, 2015b. doi: 10.1007/s11306-014-0683-5.

7 Technical details

```
> sessionInfo()
R version 4.1.2 (2021-11-01)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 20.04.3 LTS

Matrix products: default
BLAS:   /usr/lib/x86_64-linux-gnu/openblas-pthread/libblas.so.3
LAPACK: /usr/lib/x86_64-linux-gnu/openblas-pthread/liblapack.so.3

locale:
 [1] LC_CTYPE=en_GB.UTF-8      LC_NUMERIC=C
 [3] LC_TIME=nl_NL.UTF-8      LC_COLLATE=en_GB.UTF-8
 [5] LC_MONETARY=nl_NL.UTF-8  LC_MESSAGES=en_GB.UTF-8
 [7] LC_PAPER=nl_NL.UTF-8     LC_NAME=C
 [9] LC_ADDRESS=C             LC_TELEPHONE=C
[11] LC_MEASUREMENT=nl_NL.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] stats      graphics  grDevices  utils      datasets  methods   base

other attached packages:
[1] ptw_1.9-16      lattice_0.20-45 knitr_1.36

loaded via a namespace (and not attached):
 [1] RcppDE_0.1.6    compiler_4.1.2 magrittr_2.0.1 tools_4.1.2     Rcpp_1.0.7
 [6] stringi_1.7.5  highr_0.9       grid_4.1.2     stringr_1.4.0  xfun_0.26
[11] evaluate_0.14
```