July 26, 2022

Editor
The R Journal

Dear Professor Urbánek,

Thank you again for editing our manuscript "Analysis of the Results of Metadynamics Simulations by metadynminer and metadynminer3D". Below are our answers to your questions (questions are in bold).

The code for replicating results in the paper should be included as supplementary material. The original submission has some such in the figures directory, the the revision did not. Also the code did not match the paper: Fig 2 does not match the output listed in the paper, the listing in the paper would produce 1d-hill, whereas the the shown figure uses 2d hill from acealanme and not the HILLS file. Further Fig-2 should be improved to be more meaningful, such as plot(acealanme, xlab="phi", ylab="psi", pch=19, cex=0.5, col=gray(0, 0.1))

We apologize for the omission of this supplementary material. In the revised version we included it in a similar form as in the first submission.

We also double checked that the code in the manuscript matches the figures.

We decided to include all input files (*HILLS*, *HILLS3d* and *COLVAR*) into supplementary material rather than using identical in-package data (*acealanme*, *acealanme3d*). Our motivation is to attract the metadynamics and molecular simulation community to use R. Therefore we wanted to show how to load and then analyze the output of their simulations. We added a sentence indicating that *hillsfile* and *acealanme* are identical.

We made a correction to the script generating a video sequence (*tfes* was accidentally replaced by *acealanme*).

We changed the command to generate Figure 2 as suggested by you.

The code listed in the paper should be cleaned up: it should not use deprecated constructs like T/F variables where TRUE/FALSE values were meant. The formatting should be consistent: spaces around assignment operators and remove superfluous book-keeping lines (such as opening or closing of devices).

We fixed all T/F. We fixed formatting.

Regarding opening and closing of devices, in the manuscript we use it just once in the script generating a video sequence. We would prefer to keep it there because, as already mentioned, our motivation is to attract the metadynamics and molecular simulation community to use R. Opening and closing devices and use of % operator in file name is familiar to experienced R users. For inexperienced ones this example may be useful and inspiring.

The reweighting code should be re-written in proper R using sapply() instead of vector concatenation and the second loop is unnecessary as ix, iy can be computed directly on the whole dataset. Ideally, the use of the file COLVAR should be avoided if it can be made part of the package since the dataset is internal to the package and thus it's unclear why another special file is needed and would require additional explanation.

We rewritten the code as:

```
bf <- 15
kT <- 8.314*300/1000
npoints <- 50
maxfes <- 75
outfes <- 0*fes(hillsfile, npoints=npoints)
step <- 1:50*length(hillsfile$time)/50
s1 <- sapply(step, FUN=function(x) {
          sum(exp(-fes(hillsfile, imax=x)$fes/kT))
})
s2 <- sapply(step, FUN=function(x) {
          sum(exp(-fes(hillsfile, imax=x)$fes/kT/bf))
})
ebetac <- s1/s2
cvs <- read.table("COLVAR")
nsamples <- nrow(cvs)
xlim <- c(-pi,pi)
ylim <- c(-pi,pi)
step <- (1:nsamples-1)*50/nsamples+1
ix <- npoints*(cvs[,2]-xlim[1])/(xlim[2]-xlim[1])+1
iy <- npoints*(cvs[,3]-ylim[1])/(ylim[2]-ylim[1])+1
for(i in 1:nsamples) {
  outfes$fes[ix[i],iy[i]] <- outfes$fes[ix[i],iy[i]] + exp(cvs[i,4]/kT)/ebetac[step[i]]
}
outfes$fes <- -kT*log(outfes$fes)
outfes <- outfes - min(outfes)
outfes$fes[outfes$fes>maxfes] <- maxfes
plot(outfes, xlab="phi", ylab="psi")
```

We replaced the first loop by a simple vector operation and a pair of *sapply* functions. We replaced three of four lines in the second loop by vector operations. Unfortunately we were not able to entirely remove the loop and we kept it with one line. This step is reasonably fast and all alternatives were more complicated and counterintuitive, with similar speed. As already mentioned above, we prefer to present the opening of data files, so we kept the *COLVAR* file in supporting material. Another reason was to keep the package small. Addition of *COLVAR* would double the size of the package. To better introduce *COLVAR* we added a sentence:

A file containing values of collective variables and the bias potential at different snapshots of

the simulation (default filename COLVAR) is required.

Beside these changes we made minor changes in the manuscript mostly in connection to the revisions. We also added a new grant ID for a funding grant (ELIXIR project), because the project acknowledged in the original manuscript has finished. Since the mission of ELIXIR is to prolong the life of data and code, rather than produce them, we believe this change in funding statement is adequate.

The manuscript was generated and checked by rjtools. We ignored the error of using lower-case letters in package names in the title (same issue as https://github.com/rjournal/rjtools/issues/37) and we copied the generated metadynminer.pdf file to RJwrapper.pdf (same issue as https://github.com/rjournal/rjtools/issues/36).

Many thanks again for your editorial work and help with the manuscript.

Yours sincerely,

Vojtěch Spiwok
University of Chemistry and Technology, Prague
spiwokv@vscht.cz