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Interactive Data Visualization and Exploration Using the Loon R Package

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ABSTRACT

Loon [1] is an open source toolkit for highly interactive data visualization with R [2]. Interactions with plots are provided with mouse and keyboard gestures as well as via command line control and with inspectors. In this paper, we illustrate how loon's interactive displays and features can be used to perform an exploratory visual analysis of adverse events data from clinical trials.

INTRODUCTION

Visualizing data is an essential part of good statistical practice. Plots are useful for revealing structure in the data, checking model assumptions, detecting outliers and finding unanticipated patterns. Compared to static visualization, interactive visualization adds natural and powerful ways to explore the data. With interactive visualization an analyst can dive into the data and quickly react to visual clues by, for example, re-focusing and creating interactive queries of the data. Further, linking visual attributes of the data points such as color and size allows the analyst to compare different visual representations of the data such as histograms and scatterplots.

Loon is a general-purpose toolkit to create interactive graphs such as scatterplots and histograms in R. The scatterplot display provides, among other features, zooming, panning, selection and moving of points, dynamic linking of plots, layering of visual information such as maps and regression lines, custom point glyphs (images, text, star glyphs), and event bindings. Event bindings provide hooks to evaluate custom code at specific plot state changes or mouse and keyboard interactions. Hence, event bindings can be used to add to or modify the default behavior of the plot widgets.

Loon is an open source R package that works on Windows, Linux and OSX. Loon's installation instructions and manual can be found on the project webpage [1]. Once the package is installed the R-code provided in this paper can be run to recreate the visualization settings we introduce. The R-code can be also found on the GitHub repository [3].

GENERATING ADVERSE EVENTS DATA

We now present R-code to generate adverse event data for 300 patients that include a subset of the variables defined in the ADaM data structure for adverse events [4]. That is, we only generate variables that are used for the visualization settings presented in this paper. We also use native R data types whenever possible (e.g. Boolean `TRUE` and `FALSE` instead of character `'Y'` and `'N'`, respectively). The variables that we generate are defined as in [4] and are listed below.

Name	Description
USUBJID	Unique Subject ID
SEX	Gender
AGE	Age
ARM	Study Arm
DISCDEAT	Discontinued Study due to Death
TRTSDT	Treatment Start
TRTEDT	Treatment End
AESEQ	Sequence Number
AETERM	Reported Term for the Adverse Event
AESEVN	Analysis Severity/Intensity (N)
ASTDT	Analysis Start Date
AENDT	Analysis End Date
ADURN	Duration of Adverse Event

The list of adverse event terms and severity numbers are taken from Table 5.3.1 in [4]. We generate the adverse events data such that patients in arm A are expected to have more adverse events and are more likely to die during the study. The number of patients is balanced between the two study arms (i.e. 150 patients in arm A and 150 in arm B). For simplicity purposes, we do not include missing data values. The following code block generates the adverse events data later used for our visual exploration. Explaining this code is out of the scope of this paper as the reader does not need to understand it in detail to be able to follow the discussion.

```r
set.seed(1)

aeterms <- c(
  'HEADACHE', 'CHRONIC BACK PAIN', 'NOSE BLEEDING RIGHT NOSTRIL',
  'PROBLEMS OF HYPOTENSION', 'LOOSE STOOL', 'ABDOMINAL DISCOMFORT',
  'DIARRHEA', 'ABDOMINAL FULLNESS DUE TO GAS', 'NAUSEA (INTERMITTENT)',
  'WEAKNESS', 'HYPOTENSIVE'
)
aesevns <- c(1, 2, 1, 1, 3, 2, 2, 1, 1, 1, 3)

normalize <- function(x)x/sum(x)
weightsA <- normalize(dlnorm(seq(0, 5, length.out = 25), meanlog = 3))
weightsB <- normalize(dlnorm(seq(0, 5, length.out = 25)))

l.aae <- Map(function(id, ARM) {

  TRTSDT <- as.Date("2016-01-01", "%Y-%m-%d") + sample(0:365, 1, replace = TRUE)
  TRTEDT <- TRTSDT + 200 + rbinom(1, 60, 0.5)
  DISCDEAT <- sample(c(TRUE, FALSE), 1, prob=if(ARM=="ARM A") c(.3,.7) else c(.15,.85))

  n_ae <- sample(1:25, 1, prob=if(ARM == "ARM A") weightsA else weightsB)
  i <- sample(1:length(aeterms), size=n_ae, replace=TRUE, prob=c(6,rep(1,10))/16)
  ASTDT <- sample(seq(TRTSDT, TRTEDT-1, by=1), n_ae, replace = TRUE)
  ADURN <- sample(1:18, size=n_ae, replace=TRUE)
  AENDT <- ASTDT + ADURN
  ii <- order(ASTDT)
  if(DISCDEAT & any(AENDT>TRTEDT)) {
    AENDT[AENDT>TRTEDT] <- TRTEDT
    ADURN <- as.numeric(AENDT - ASTDT)
  }

  list(
    USUBJID = id,
    SEX = sample(c('F', 'M'), 1),
    AGE = 20 + rbinom(1, size=40, prob=0.7),
    ARM = ARM, DISCDEAT = DISCDEAT,
    TRTSDT = TRTSDT, TRTEDT = TRTEDT,
    aes = list(
      AESEQ = 1:n_ae, AETERM = aeterms[i],
      AESEVN = aesevns[i], ASTDT = ASTDT[ii],
      AENDT = AENDT[ii], ADURN = ADURN[ii]
    )
  )
}, seq(1, 300, by=1), sample(rep(c('ARM A', 'ARM B'), 150), replace = FALSE))
```

Notice that we specify the random number generation seed at the very beginning (line 1) so that the data can be re-created exactly the same. The resulting list `l.aae` contains 300 lists, each of them containing the generated adverse events data corresponding to one patient. The non-rectangular data structure of `l.aae` is not in the AdAM format described in [4]. The steps necessary to transform `l.aae` into the AdAM format are as follows:

```r
aae <- Reduce(rbind, Map(as.data.frame, l.aae))
names(aae) <- gsub("aes.", "", names(aae), fixed = TRUE)
```

To print the first 3 rows of the rectangular data frame `aae` we can use the `head` function as follows.

```
head(aae, 3)
```

```
##   USUBJID SEX AGE   ARM DISCDEAT     TRTSDT     TRTEDT AESEQ
## 1       1   F  45 ARM B    FALSE 2016-09-03 2017-04-19     1
## 2       1   F  45 ARM B    FALSE 2016-09-03 2017-04-19     2
## 3       2   M  43 ARM B    FALSE 2016-09-20 2017-05-09     1
##               AETERM AESEVN      ASTDT      AENDT ADURN
## 1 CHRONIC BACK PAIN       2 2016-09-18 2016-09-21     3
## 2          HEADACHE       1 2017-03-07 2017-03-15     8
## 3 CHRONIC BACK PAIN       2 2016-12-01 2016-12-19    18
```

However, for the the visual analysis with loon, we use the `l.aae` data structure to query and transform the data as needed to create and modify the plots.

A VISUAL EXPLORATION OF THE ADVERSE EVENTS DATA

To start a loon session, we first have to load the loon R-package into the active R session:

```
library(loon)
```

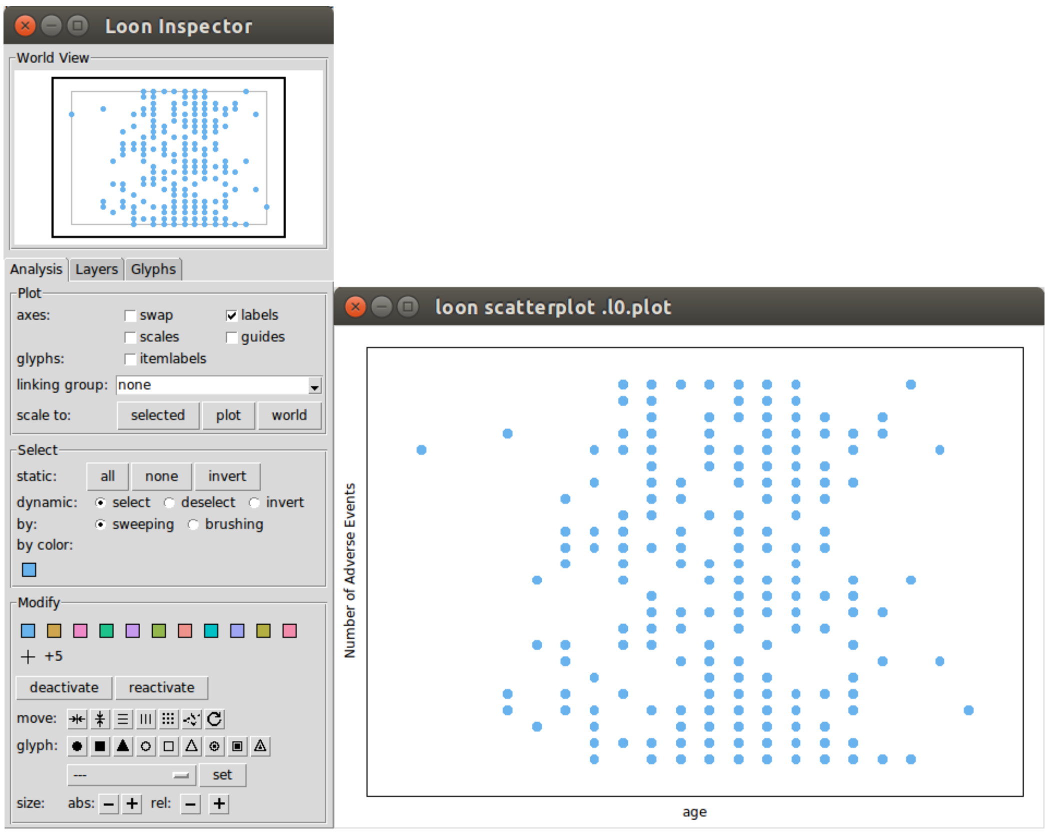
We start our exploratory analysis by looking at the relationship between age and the number of adverse events. The following code retrieves the age and number of adverse events for each patient:

```
age <- sapply(l.aae, function(x)x$AGE)
naes <- sapply(l.aae, function(x)length(x$aes$AESEQ))
```

Next, we create a loon scatterplot that displays age on the x-axis and the number of adverse events on the y-axis:

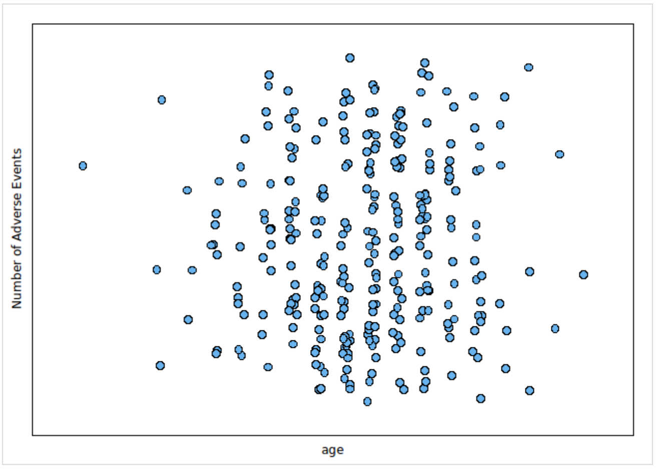
```
p <- l_plot(x=age, y=naes, ylabel="Number of Adverse Events")
```

This `l_plot` call creates two windows, the scatterplot as seen on the right side in the figure below and the loon inspector as seen on the left side.



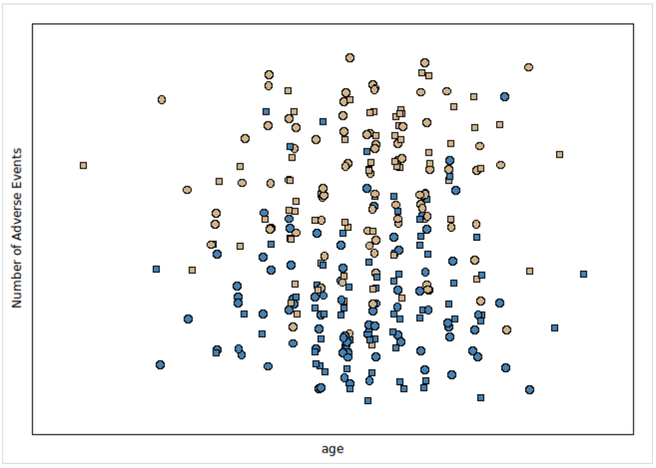
The loon inspector provides a graphical user interface for modifying and overseeing the scatterplot. For example, to display the x and y scales on the scatterplot display one can check the “scales” check-box in the loon inspector. The scatterplot display supports a number of direct interactions such as mouse-scrolling for zooming, right-click dragging for panning and left-click dragging for selecting points. Selected points can be modified with the tools provided in the “Modify” section of the loon inspector (e.g. point color, point size and point glyph). The return value of `l_plot`, here assigned to `p`, is a plot handle to access and modify the scatterplot via the command line. For example, `p['color']` returns a vector with the hexadecimal encoded color representation of each of the 300 points, and `p['size'] <- 5` sets the size of every point to 5.

One issue with the above scatterplot is the over-plotting of the point glyphs, that is, it is not possible to distinguish all 300 points. One way to deal with over-plotting is to jitter the points, that is, to add a small amount of noise to the point locations. In loon, this can be done by first selecting all the points and then by pressing the button on the inspector. Jittering might move the points outside the current plotting area of the scatterplot. In order to adjust the plotting area to include all points, one option is to press the *scale to world* button on the inspector. In addition to jittering the points, one can also choose a point glyph with an outline so that the individual points are better distinguished from each other. One way to do that is to press the button on the inspector while the points are still selected. After deselecting the points by pressing *select none* on the inspector, the scatterplot will then look similar to the following plot. Note that the seed in R does not influence the random jittering noise for loon as loon is implemented in Tcl and Tk. Therefore, the plots with jittering are not perfectly reproducible here and that is the case with the third next scatterplot.



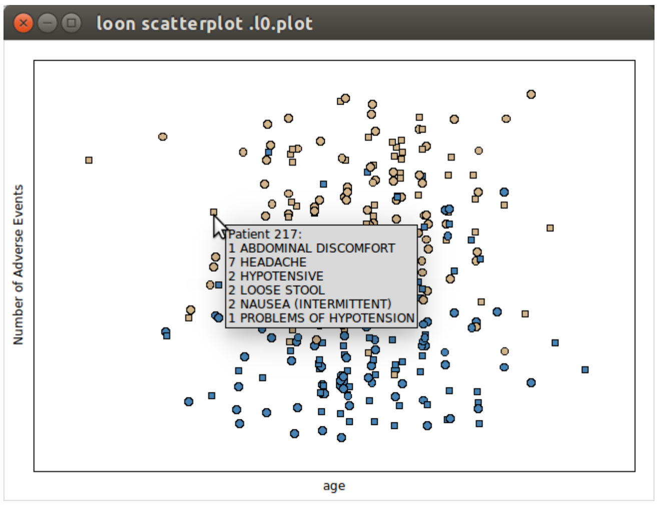
From the above jittered scatterplot we note that, for example, more patients were sampled from the center of the age range. Next, we encode gender and study arm as visual attributes onto the scatterplot. Our goal here is to check whether there is an obvious relation between age, study arm, gender and the number of adverse events. To do so, we encode gender with different point glyphs and the study arm as glyph colors in the scatterplot of the number of adverse events vs. age from above.

```r
p['glyph'] <- ifelse(sapply(l.aae, function(x)x$SEX)=='F', 'ccircle', 'csquare')
p['color'] <- ifelse(sapply(l.aae, function(x)x$ARM)=='ARM A', 'tan', 'steelblue')
```



We can now see that patients from arm A (tan colored) tend to have more adverse events than the ones from arm B (steelblue colored), which is not surprising given the way we generated the number of adverse events for each arm. Also, gender seems to be evenly distributed among the two study arms, age and the number of adverse events. Note that, instead of modifying one plot state at a time as done in the above code chunk, we can also use the `l_configure` function to modify multiple scatterplot states in one function call. It is also possible to attach a label to each scatterplot point that can be queried with the mouse pointer resulting in a "tool-tip" with the *itemlabel*. For example, the *itemlabel* could be the patient `USUBJID` with a table of the adverse events, as seen below.

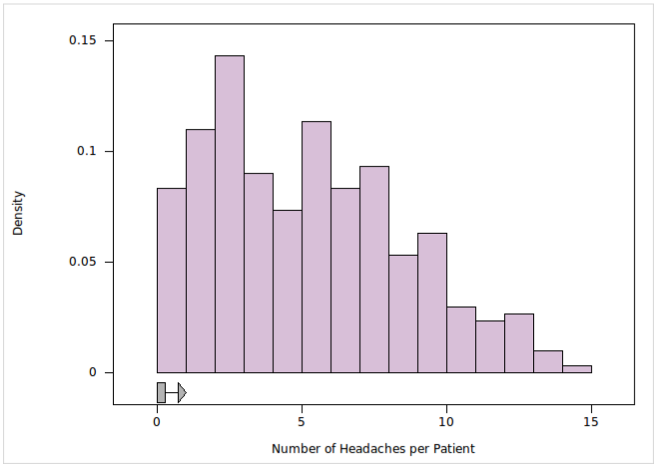
```r
t.label <- unlist(Map(function(x) {
  t.x <- table(x$aes$AETERM)
  paste(c(
    paste0('Patient ', x$USUBJID,':'),
    apply(cbind(t.x, names(t.x)), 1, function(x)paste(x, collapse = ' '))
  ), collapse = '\n')
}, l.aae))

l_configure(p, itemlabel=t.label, showItemlabels=TRUE)
```



```
Patient 217:
1 ABDOMINAL DISCOMFORT
7 HEADACHE
2 HYPOTENSIVE
2 LOOSE STOOL
2 NAUSEA (INTERMITTENT)
1 PROBLEMS OF HYPOTENSION
```

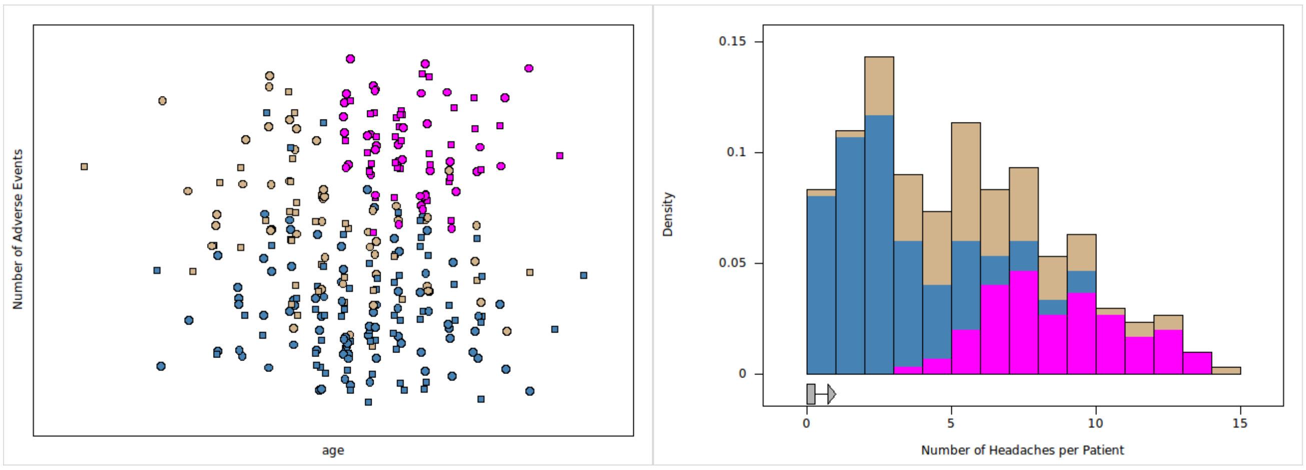
Next, we plot a histogram with the number of headaches per patient.

```r
h <- l_hist(
  x = sapply(l.aae, function(x)sum(x$aes$AETERM == 'HEADACHE')),
  xlabel = 'Number of Headaches per Patient',
  yshows = 'density',
  showScales = TRUE,
  binwidth = 1
)
```



For `l_hist`, the `yshows` argument specifies that the histogram displays the density rather than the frequency and the `binwidth` argument specifies a particular bin width for the binning algorithm. The ⊩ element in the histogram display can be used to adjust the binning origin and the bin width on the histogram interactively. This histogram of headaches count per person becomes particularly interesting when linking it with the information shown on the scatterplot above. That is, loon synchronizes certain states automatically for linked displays. For example, for a linked scatterplot and histogram, some of the linked states include `color`, `selected` and `size`. In the following code, we link the scatterplot of the number of adverse events vs. age with the histogram of number of headaches per patient. Next, we select all the patients in the scatterplot that have more than 15 adverse events and are older than 46. This selection will propagate to the histogram display as it is now linked with the scatterplot. By default, selected points are highlighted in magenta in loon's displays.

```
p['linkingGroup'] <- "aes"
l_configure(h, linkingGroup="aes", sync="pull", showStackedColors=TRUE)
p['selected'] <- naes > 15 & age > 46
```



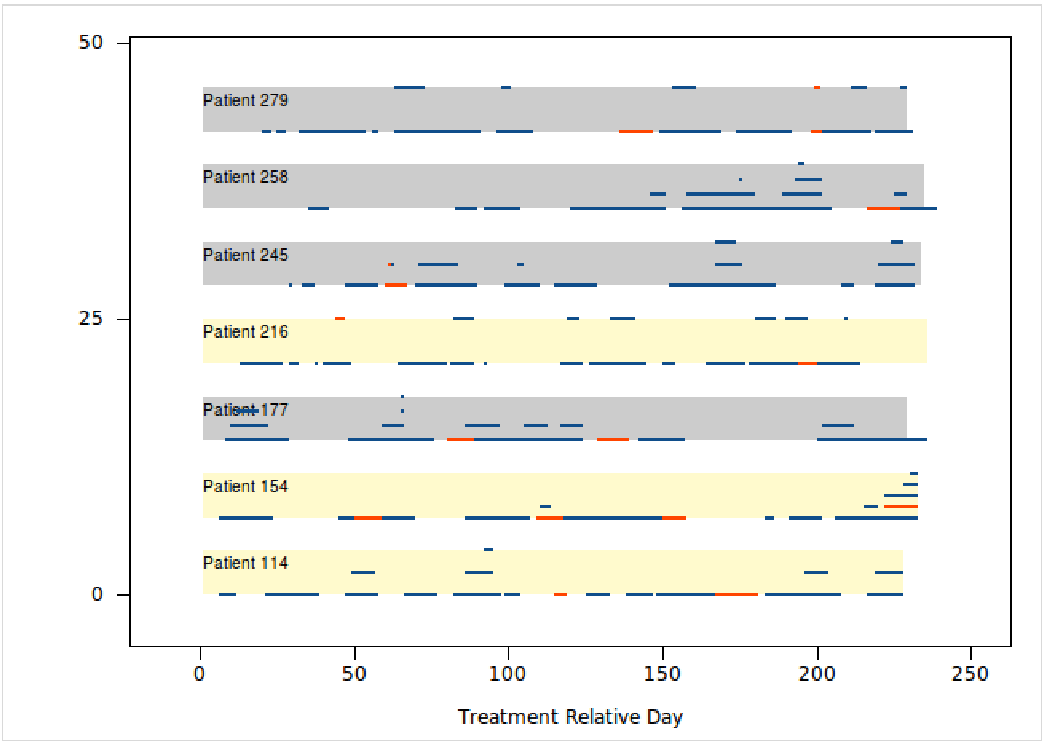
In the above code we have to specify the `sync` argument so that loon knows how to initially align the linked states between the linked displays. We also set the `showStackedColors` to `TRUE` so that the `color` state of the histogram gets visually encoded.

We end this short introduction of loon with a plot that shows the individual adverse events on a time line for each patient that is selected in the scatterplot or histogram displays. The adverse events are colored *orangered* if they are of severity 3 and *dodgerblue* otherwise. We also encode the treatment period with a rectangle that is colored *lemonchiffon1* if the patient discontinued the study due to death and *gray* otherwise. This plot can be useful in investigating whether there are any patterns within the adverse events data such as an increase in frequency and severity of adverse event preceding a patient's death. This visualization uses some advanced loon features such as event bindings and layers. More information about these features can be found in the loon manual [1].

```
createAEplot <- function() {
  pae <- l_plot(showItemlabels=TRUE, xlabel="Treatment Relative Day", showScales=TRUE)

  rectHeight <- 4
  y <- 0

  scale01 <- function(x) {
    dx <- diff(range(x))
    if (dx == 0) rep(0, length(x)) else (x-min(x))/dx
  }

  draw_patient <- function(x) {
    patient_label <- paste("Patient", x$USUBJID)
    g <- l_layer_group(pae, label=patient_label)
    l_layer_rectangle(
      pae, parent=g,
      x = c(1, x$TRTEDT - x$TRTSDT + 1), y = c(y, y+rectHeight),
      color = if(x$DISCDEAT) "lemonchiffon1" else "gray80",
      linecolor = "",
      itemlabel = paste("Treatment Period for Patient", x$USUBJID)
    )
    l_layer_text(pae, parent=g, text=patient_label, x=1, y=y+rectHeight,
                 justify='left', anchor='nw', color="black")

    if (length(x$aes$AESEQ)>0) {
      xcoords <- Map(function(t0, t1) as.numeric(c(t0, t1)-x$TRTSDT+1),
                     x$aes$ASTDT, x$aes$AENDT)
      tE <- list()
      ycoords <- Map(function(j)c(j, j), scale01(unlist(Map(function(xc) {
        k <- vapply(tE, function(tEi) xc[2]>tEi, logical(1))
        i <- if (any(k)) which(k)[1] else length(tE) + 1
        tE[[i]] <<- xc[2]
        i
      }, xcoords))) * rectHeight + y)
      col <- ifelse(x$aes$AESEVN == 3, "orangered", "dodgerblue4")
      if (length(xcoords) == 1)
        l_layer_line(pae, parent=g, x=xcoords[[1]], y=ycoords[[1]],
                     itemlabel=x$aes$AETERM, linewidth=2, color=col)
      else
        l_layer_lines(pae, parent=g, x=xcoords, y=ycoords,
                      itemlabel=x$aes$AETERM, linewidth=2, color=col)
    }
    y <<- y + rectHeight + 3
    l_scaleto_world(pae)
  }
  list(
    updateWith = function(selected) {
      y <<- 0
      for (layer in l_layer_getChildren(pae, "root"))
        if (layer != "model") l_layer_expunge(pae, layer)
      if (sum(selected)>0)
        Map(function(x)draw_patient(x), l.aae[selected])
    },
    widget = pae
  )
}
```

The `createAEplot` function creates a plot and returns a list with the plot widget handle and a closure for updating the adverse events plot with the subset of selected patients. The `createAEplot` function can be executed multiple times to create multiple adverse events plots that do not interfere with each other. Next, we create such an adverse events plot and then add a `selected` state change binding to the scatterplot widget which updates the plot every time different points are selected on the scatterplot or the linked histogram.

```
showAEs <- createAEplot()

l_bind_state(p, "selected", function() {
  showAEs$updateWith(p['selected'])
})

p['selected'] <- naes > 23 & sapply(l.aae, function(x)x$ARM) == 'ARM A' &
  sapply(l.aae, function(x)x$SEX) == 'M'
```



This adverse events plot supports *itemlabels* for the individual adverse events. Notice that the adverse events lines are stacked in a space-efficient manner.

CONCLUSION

In this paper, we illustrate some of loon's displays and features in the context of adverse events data. We generate the data to closely match the AdAM data structure specifications for adverse events [4]. Therefore, it should be possible to use the code provided in this paper to analyze adverse events data from actual clinical trials without too much additional work. The tools and techniques used for our visualization settings include jittering, encoding information with glyph color and shape, interactive querying using tool-tips, linking, layering, and bindings. We encourage the reader to run this visual analysis on a local installation of R and loon and further explore loon's features. Loon is a powerful interactive visualization toolkit that has many more features and capabilities to visually explore high-dimensional data.

REFERENCES

[1] Loon's website with installation instructions and user manual: http://waddella.github.io/loon/
[2] R Core Team (2016). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria.
[3] GitHub repository with R-code for PhUSE 2016 adverse events paper by Adrian Waddell: http://github.com/waddella/phuse2016_adverse_events
[4] Analysis Data Model (ADaM) Data Structure for Adverse Event Analysis: http://www.cdisc.org/system/files/all/standard_category/application/pdf/adam_ae_final_v1.pdf

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