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A Future “View” of Digital Data from Wearable Devices

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ABSTRACT

Pharmaceutical companies are increasingly using New Digital Technologies in clinical studies. These comprise of a broad range of solutions including protocol crowd-sourcing, patient recruitment through social networks as well as the use of devices equipped with sensors that collect data almost on real-time. In this paper, a member of GSK's Advanced Analytics for Digital Data workstream will present and discuss an overview of the current use of some of these new digital technologies in our clinical studies and the benefits and the associated challenges with respect to data analysis and visualization. These will be illustrated with real examples.

INTRODUCTION

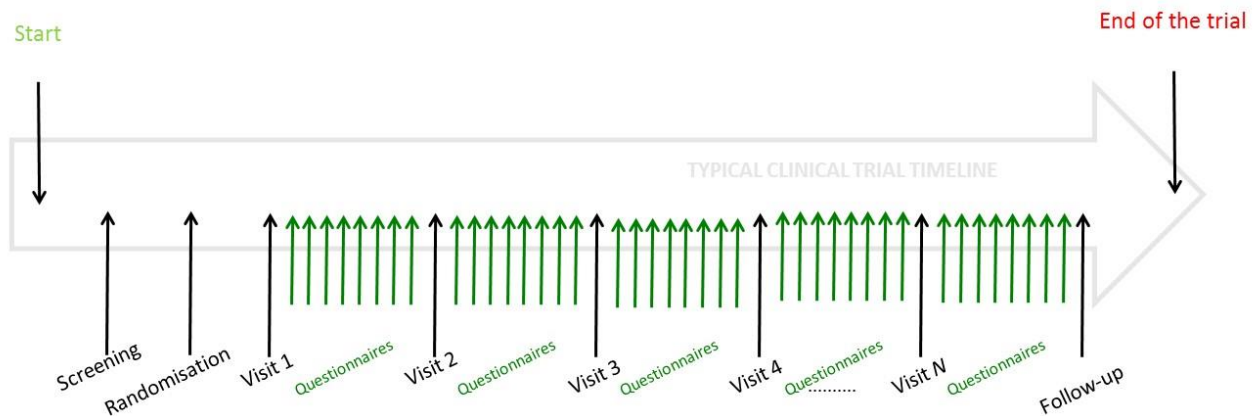
In our culture today, wearable devices that collect actigraphy data (e.g., pedometers and smart watches) are commonplace and fitness-focused people can spend hours reviewing continuous and summarized activity data on various mobile applications. Friends and family are joining step count competitions on a weekly basis. Can the popularity and omnipresence of wearable devices be incorporated and implemented into the clinical trial arena? By building on this cultural momentum, adoption of continuous activity sensors in clinical trials has the potential to provide many benefits and improve study conduct logistics while also presenting novel challenges that need to be addressed. As technology advances, the future of clinical trials may rely heavily on these types of actigraphy data. Even more so than other kinds of clinical data, actigraphy data need visualization techniques in order to make sense of the large volume of collected data.

In this paper, actigraphy data from digital wearable devices will be introduced and described. The advantages of incorporating actigraphy data into clinical trials will be discussed as well as the unique challenges with this type of data will be explored. The emphasis on visualization of actigraphy data including the types of individual and summary plots that best represent the data will be presented.

BACKGROUND

What is actigraphy? Actigraphy is a non-invasive method of monitoring human rest and activity cycles. Being non-invasive, actigraphy data comes from devices worn by the participant that can sense when a person is active (moving) or at rest. Wearable devices can be adorned for long periods of time and is only limited to the device power charging needs. The ability of the device to collect data continuously for long time periods (e.g., one week) can be implemented into a clinical trial which traditionally only collects endpoint data at discrete visits or time-points (i.e., not continuous). Figure 1 illustrates the traditional discrete visit design that most trials employ.

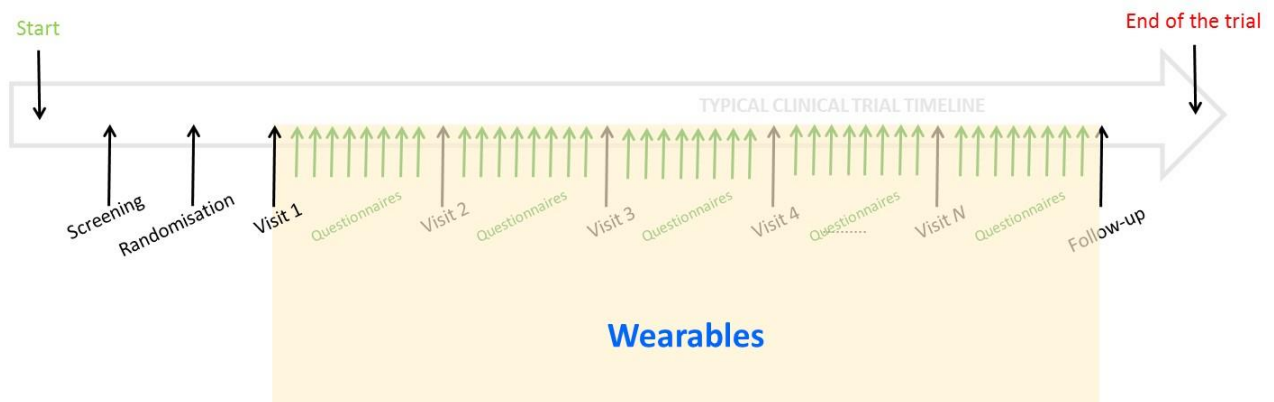
Figure 1 Traditional Study Design with Discrete Visits and Planned Times



For the participant, the trial begins with screening visits and, once successfully passing, will be randomized or enrolled into the study. Next, there will be baseline visits and the initiation of a study intervention. After the initiation of the study intervention, the participant will be followed for a period as specified in the protocol for safety, efficacy and other endpoints of interest. This follow-up period for a participant is at discrete visits and timepoints and may include physical trips to a clinic for evaluations or blood draws or filling out various validated questionnaires.

Wearable devices and the associated data collection, on the other hand, can encompass and cover continuously all timepoints of interest as shown in Figure 2.

Figure 2 Wearable devices with continuous collection provide complete participant monitoring and provide additional monitoring than traditional discrete clinical encounters.



Collecting data in this way provides a more complete picture as the continuous collection will include the entire follow-up period of interest and not only while the participant is at the clinic. The actigraphy data itself is objective and does not require human subjectivity or interpretation on the part of clinical site staff and investigators. To take it further, wearable devices allow for the potential for *real-time* capture of data for greater sensitivity and response to serious safety issues. It is also more patient focused because actigraphy endpoints matter more to the participant and are more relevant than traditional efficacy endpoints (e.g., walking test or questionnaire endpoints) and can contribute more “real-world” evidence that goes beyond simple efficacy.

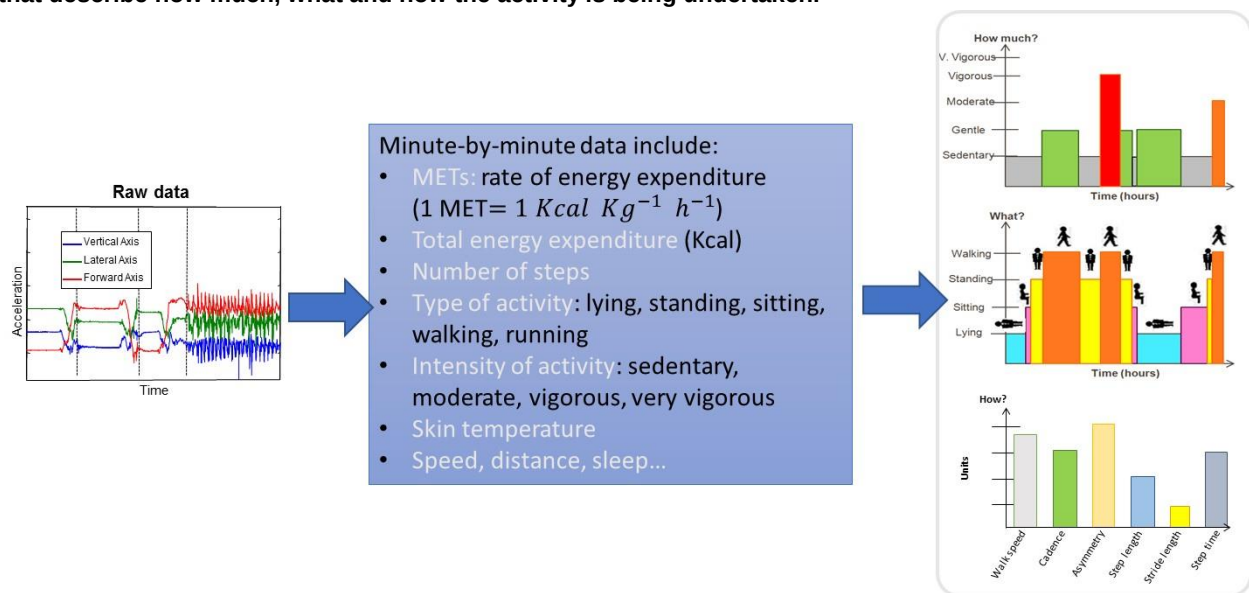
However, there are also many challenges with actigraphy data that will need to be resolved before wearable devices and actigraphy data become standalone collection tools and endpoints in clinical trials. Regulatory agencies will need to agree on the objective and novel endpoints which will need to face and pass the burden of validation. The agencies will also need to agree on which devices to use and locations to be worn which could potentially be different across the world. Clinicians will need to adopt the new technology and buy-in to the advantages in order for actigraphy data to be incorporated into the trials of the future. Participants should be willing to wear and comply with the protocols by wearing the devices over extended periods of time. Actigraphy data yield very large datasets and there needs to be cost-effective, efficient and safe ways to transmit and transfer data for analysis and retention. Suitable statistical analytical techniques need to be developed and validated against traditional clinical endpoints

before actigraphy endpoints can be considered as the primary analyses. Until many of these issues are resolved, actigraphy data will be limited to exploratory “add-ons” to trials with traditional trial endpoints. Trying to do both traditional and actigraphy endpoints can lead to very costly and complex clinical trials.

As already mentioned, actigraphy data is very complex (see raw data traces later) and voluminous. A sample actigraphy sensor equipped with an accelerometer can measure and record 300 data points per second. A trial design that collects data continuously for one week will yield $300 \text{ data points} \times 3600 \text{ seconds per hour} \times 24 \text{ hours per day} \times 7 \text{ days per week} = \mathbf{181.44 \text{ million}}$ data points for a single collection for one participant! Multiply that number by 3 as there are usually sensors in three axes. Therefore, algorithms must be in place to provide meaningful summaries from the raw data. In the data described later in this paper, the sensor raw data is converted into minute-by-minute averages. However, it is still debatable whether minute-by-minute means are the best compromise between reducing noise but still being sensitive enough to detect meaningful activity parameters. Can second-by-second, hourly or even daily summaries be even better times to use for analysis? Since the default summary values are minute-by-minute from the sensor (Figure 3), the examples used in this paper are derived from that.

Minute-by-minute values from one type of sensor can include METs (metabolic equivalents which are a rate of energy expenditure of the participant), total energy expenditure in Kcal, number of steps, type of activity (lying, standing, sitting, walking and running), intensity of activity (sedentary, moderate, vigorous and very vigorous), speed, distance, sleep and many more. The data can be represented graphically to understand how much (intensity of activity), what (type of activity) and how (e.g., speed, distance, sleep time, etc.) the activity was undertaken.

Figure 3 Raw actigraphy tracings have algorithms applied to calculate minute-by-minute activity parameters that describe how much, what and how the activity is being undertaken.



DATA VISUALIZATIONS

What kind of visualizations can be employed to provide greater insight into the complex and large data set that comes from actigraphy sensors? Visualization of activity data can be used to understand individual participant level details and also for summarization over days, visits and across study interventions. Let's first discuss how plotting a participant's individual data can help provide insight into the quality of the data collection itself.

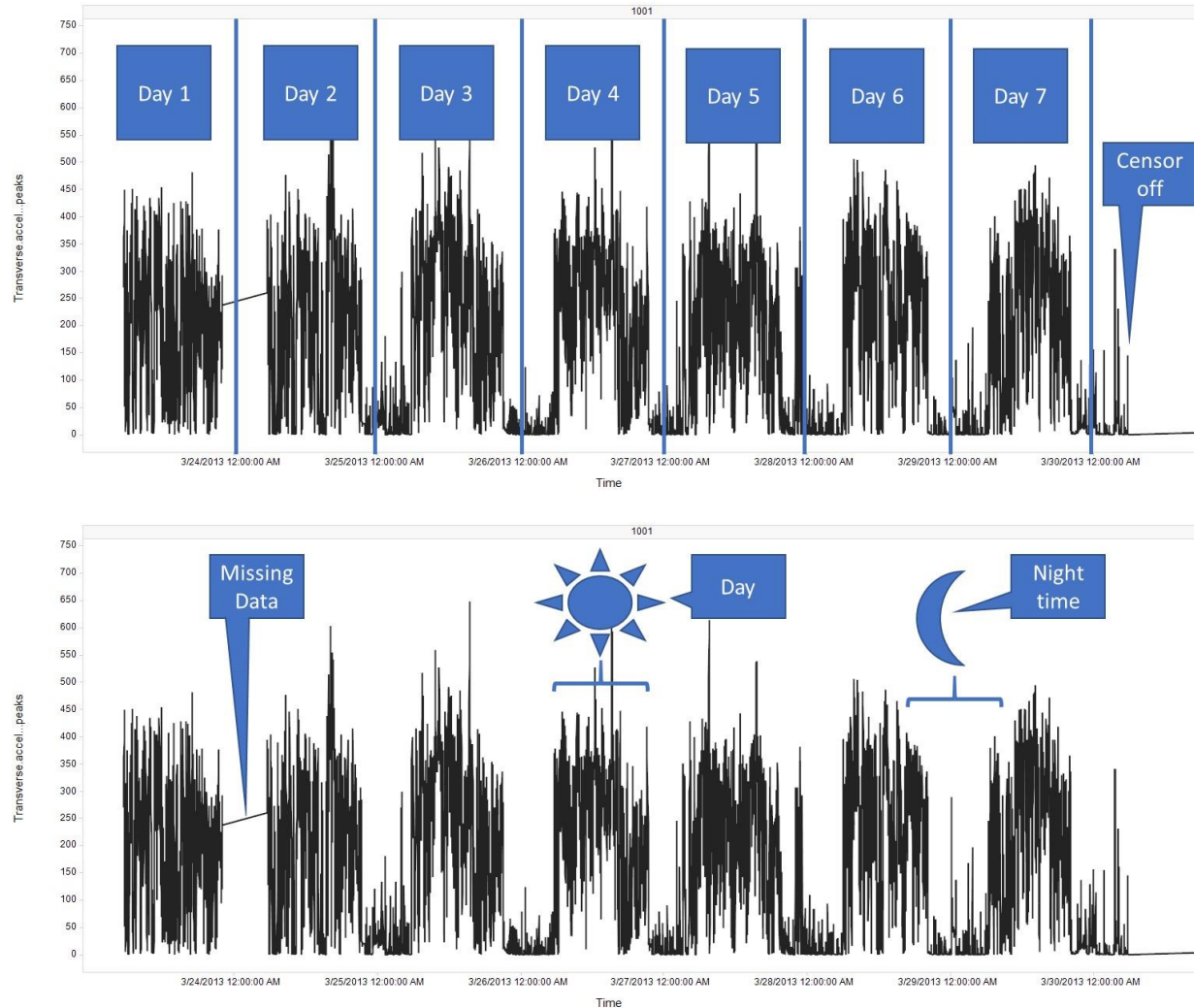
Time series Plots

Plotting the minute-by-minute data over the full time of collection gives a complete picture for each participant at each visit. By quickly reviewing the trace, it can be easy to identify how much missing data there is or how noisy the data may be. In addition, the reviewer will be able to see the diurnal patterns and other periods of interest (e.g., weekday/weekend). Interactive tools (e.g., Tibco Spotfire®) are very useful to zoom in on areas of interest using zoom sliders and drill down to further details.

As can be seen in Figure 4, a participant has minute-by-minute data from a sensor that was worn for over 7 days for one of the three accelerometer parameters (transverse acceleration). It is immediately apparent the cyclical nature of the data that can easily be separated into days. When initially examining and reviewing the data for the first time,

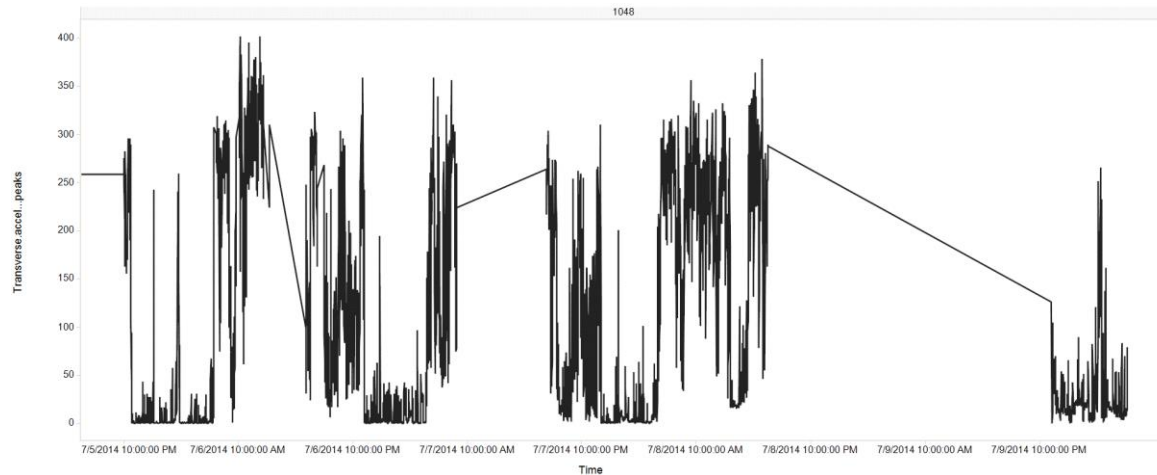
the figure can provide useful information on how noisy the data is, how many days of data were collected, how much missing data there are, if the participant was active during the night, if the participant was inactive during the day, etc.

Figure 4 Time series plot of the minute-by-minute trace from one accelerometer axis



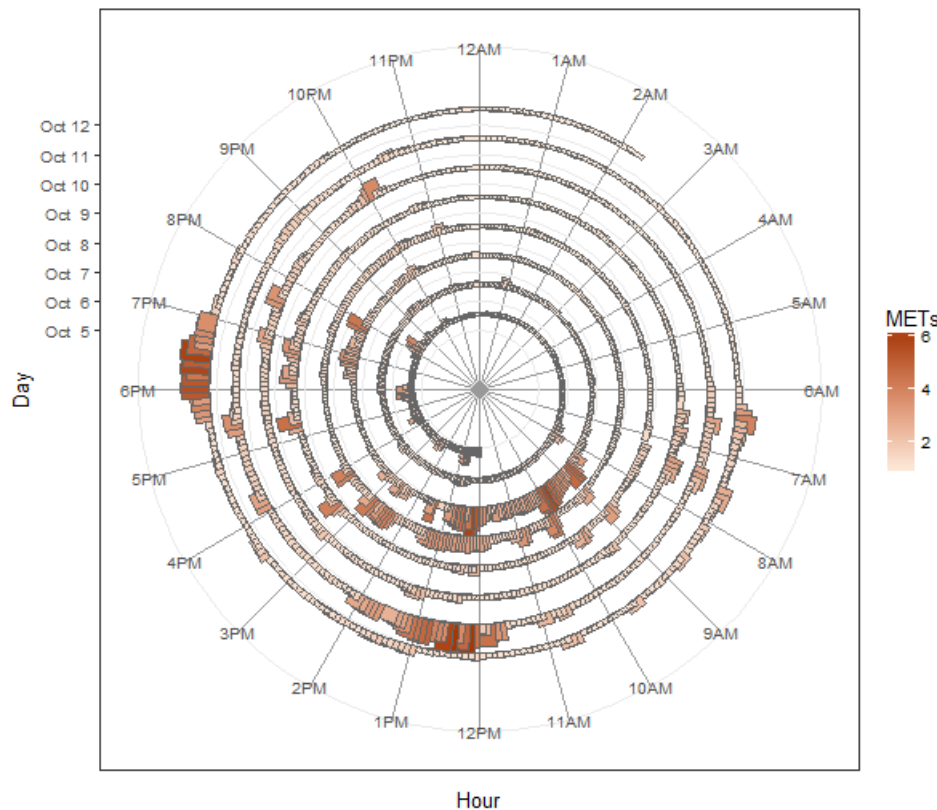
Plotting individual time course data also alerts one quickly to compliance issues (participant did not wear the censor for the minimum stipulated time) and participants that may be ineligible due to noise or missing data. Compare the first participant from Figure 4 which has a mostly complete dataset with the participant from Figure 5. The participant from Figure 5 has missing data throughout the collection period and only has partial data for four days (out of seven planned days). Thus, plotting individual line plots over time like this can provide the analyst with quick information into data quality, compliance and missing data then would otherwise be available in tabular format.

Figure 5 Minute-by-minute trace showing periods of missing data and incomplete collection



Plotting the individual time courses horizontally over time can make it hard to compare similar time periods. For example, what time does the participant usually go to sleep? What time does the participant usually wake up? Is the participant more active in the morning or the afternoon, on weekends or weekdays? By creating a spiral plot, we are able to group similar time periods closer together for observation. In order to do this, we lose a little of the granularity by binning the time data into quarter hours. What we lose in detail, we more than make up for in the ability to compare similar times. As can be inferred from Figure 6, the participant tends to go to sleep around 11 PM every night (activity levels drop for several hours) and wakes up after 6 AM (consistent burst of activity at roughly the same time each day). There are bouts of activity in the morning, in the middle of the day and during the evening. Perhaps this can suggest activity around eating breakfast, lunch and dinner. This plot is not useful for distinguishing weekday periods versus weekend periods or if the participant has a very irregular activity schedule. Spiral plots in this setting are useful for a single visit or collection period. It is difficult to plot multiple visits next to each other for comparison purposes (e.g., baseline and post-baseline visits).

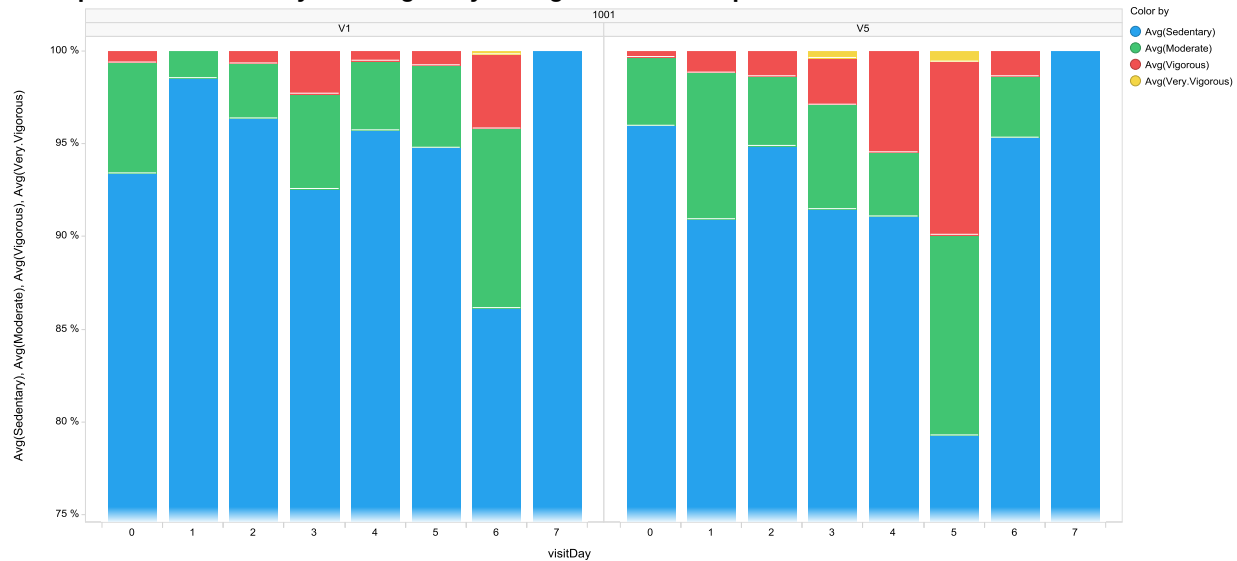
Figure 6 Spiral plot of a METs data over several days; Acknowledgment: V Ashwin, GSK



BAR CHARTS

Individual participant data can further be categorized into the proportion of time a participant fits into each activity category. Activity can be separated into different levels such as sedentary, moderate, active and very active. The analyst can plot these categories as a 100% stacked bar charts for each participant trellised by visit and with one column for each day as can be seen in Figure 7:

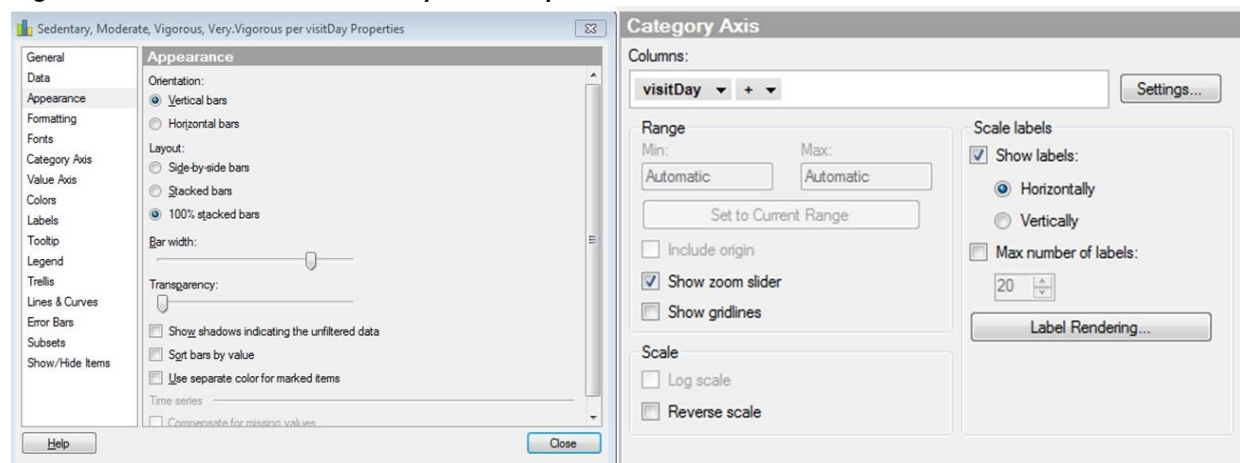
Figure 7 100% Stacked Bar Chart for a single participant colored by activity level and trellised by visit. Each bar represents the activity of a single day during the collection period.



These participants tended to spend most of the day in a sedentary activity state. For this participant, approximately 80-90% of each day is sedentary. To help visualize the other activity states the analyst can use the Spotfire Y-axis zoom slider to highlight the 75 to 100% region. This makes the other states easier to distinguish as the time spent in the moderate, vigorous and very vigorous are easier to see. There is an apparent trend that the participant is slightly more active at the second visit (right panel, V5) than the first visit (left panel V1). This is a potential way of determining if any intervention or therapy is having an effect on activity. If a participant has much more activity at the second visit, then this kind of visual is useful for showing it. If many participants follow this pattern then the analyst can feel more comfortable in the study intervention having an effect. However, this is not a definitive summary and how this visual correlates to clinical outcomes and endpoints needs to be further studied and refined.

To plot this in Spotfire, create a bar chart and select the following properties:

Figure 8 100% Stacked Bar Charts Spotfire Properties



Value Axis

Columns:

4 columns

Settings...

☒ One axis with a single scale
 ☐ Multiple scales

Range

Min: Automatic
Max: Automatic

Set to Current Range

☐ Include origin
☒ Show zoom slider
☐ Show gridlines

Scale labels
☒ Show labels

☒ Horizontally
☐ Vertically

☐ Max number of labels: 20

Scale
☐ Reverse scale

Trellis

☒ Rows and columns

Rows: (None)

Settings...

Columns: visit

Settings...

Pages: subjid

Settings...

☐ Panels

Split by: (Column Names)

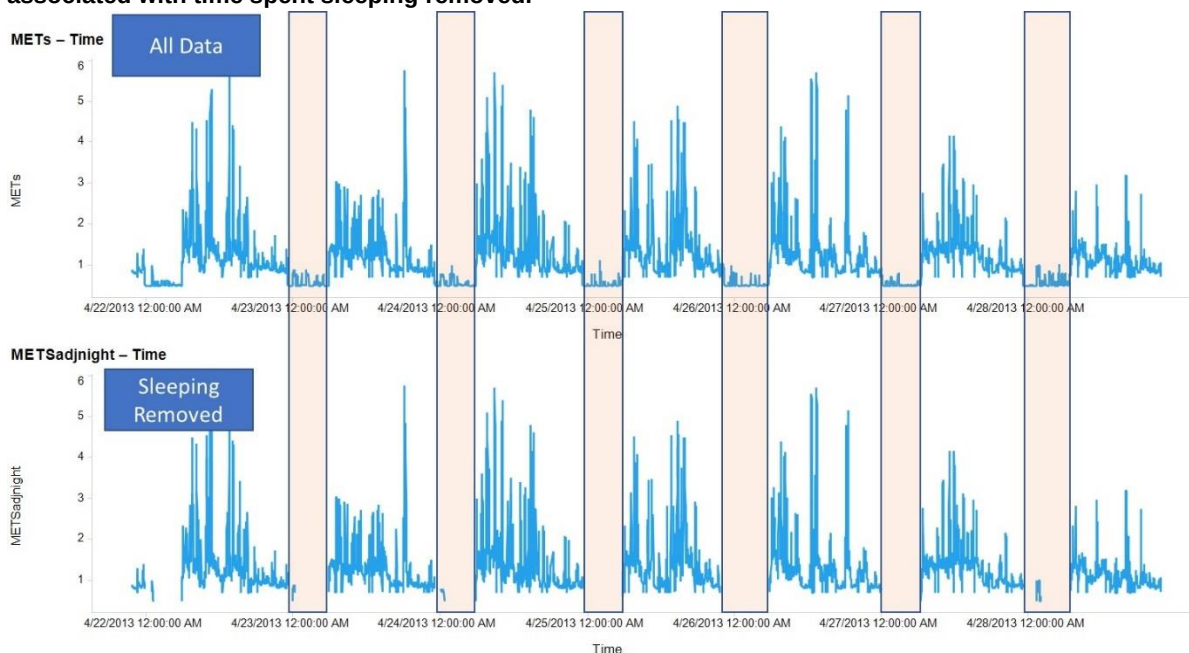
Settings...

☐ Manual layout

Max number of rows: 2
Max number of columns: 2

Because most of the activity is in the sedentary position and the censor is being worn constantly, one may question if the time spent sleeping is skewing or making the data hard to interpret. Is there a way to algorithmically identify sleep periods? Using the collected data, our colleagues have identified the times where a participant was identified as lying down and sleeping and flagging it in the datasets. By filtering or removing the time spent sleeping, we may be able to enhance or improve the precision of the plots in identifying changes in activity levels. As can be seen in Figure 9, the algorithm does a very good job of identifying programmatically the times when the participant is most likely asleep. The light red box indicates the time lying down and sleeping. Note, it is not removing all the data during the night. There are a few activity blips of data that remain, and these could be due to movement while awake at night.

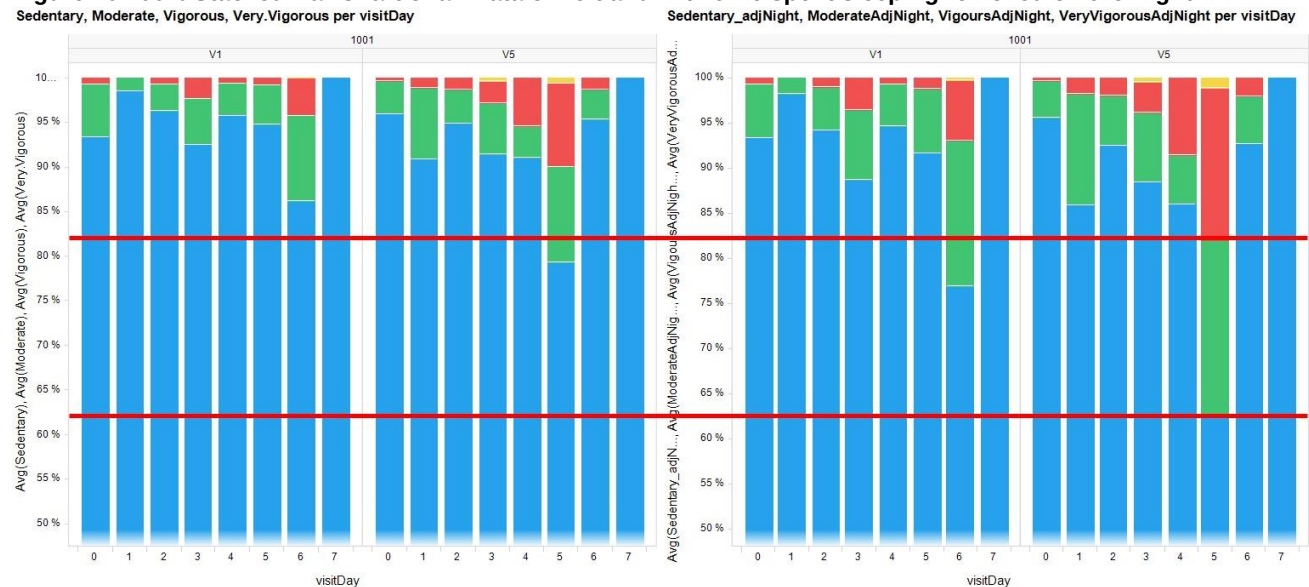
Figure 9 Time series plot of METs over time. Plot on top shows all the data. Bottom plot shows the data associated with time spent sleeping removed.



Let's see how the removal of sleeping time data changes the 100% stacked bar chart that was shown earlier. As can be seen in Figure 10, when both plots are shown with the same y-axis, removing the data while sleeping increases the percentage of time for the moderate, vigorous and very vigorous activity classifications. This is what would be expected and desired because we want to enhance our ability to detect changes in activity level while participants are awake. The red horizontal lines indicate a greater percentage of time spent in the moderate and vigorous stage in second plot compared to the first plot on the left. The overall pattern and trend of the plot is

generally the same between the all data version and the version where sleeping time is removed. However, the non-sedentary activity categories are more enhanced and pronounced allowing for easier trend identification.

Figure 10 100% Stacked Bar Chart of all Data on left and with time spent sleeping removed on the Right.



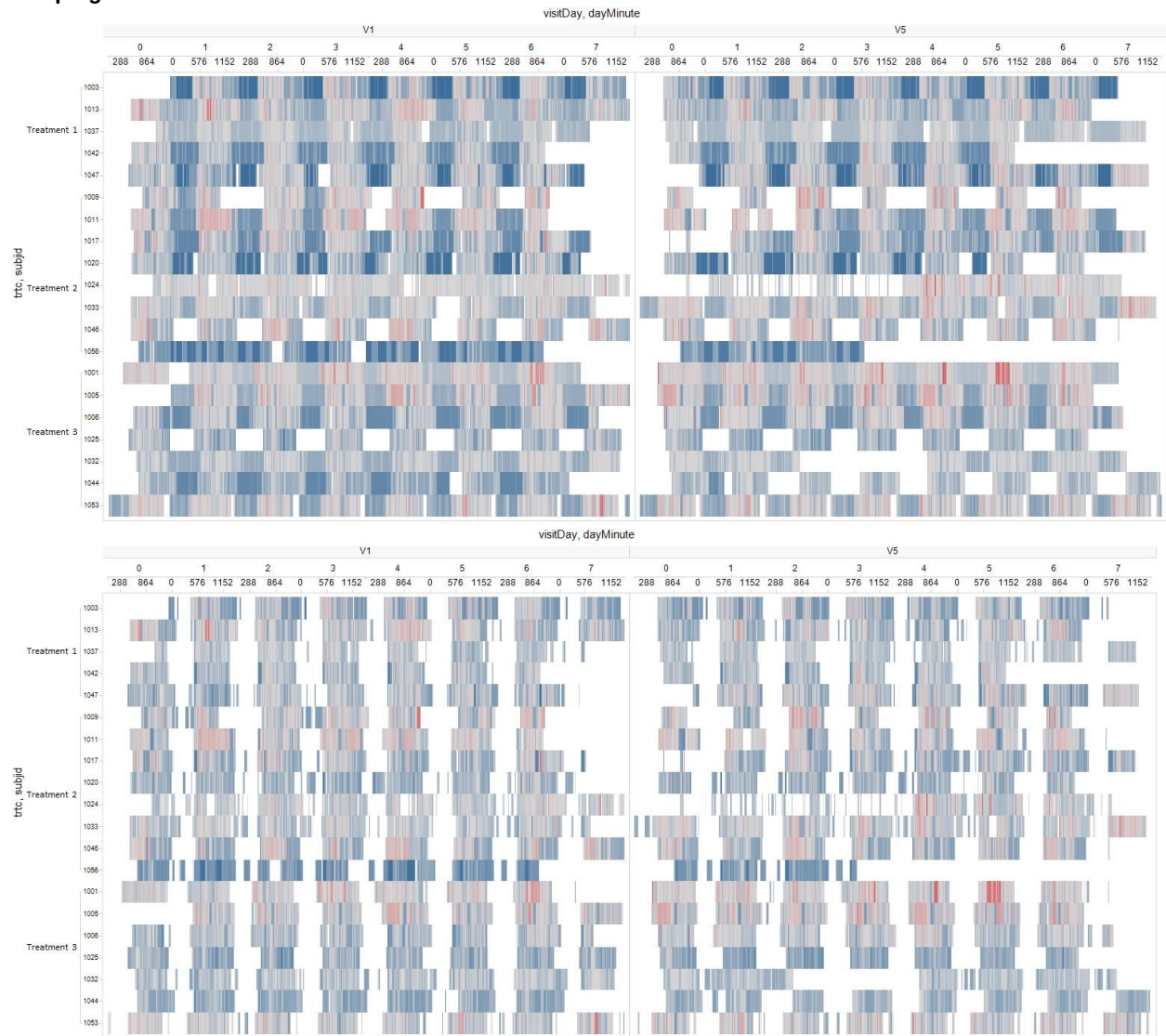
SUMMARY GRAPHS

Once all the individual data and figures are reviewed, it will be useful to produce summary figures to understand if there are any trends across days, visits and study interventions. Are there any types of visualizations then can summarize the data in a way that can illustrate differences in days, visits and study interventions?

HEAT MAPS

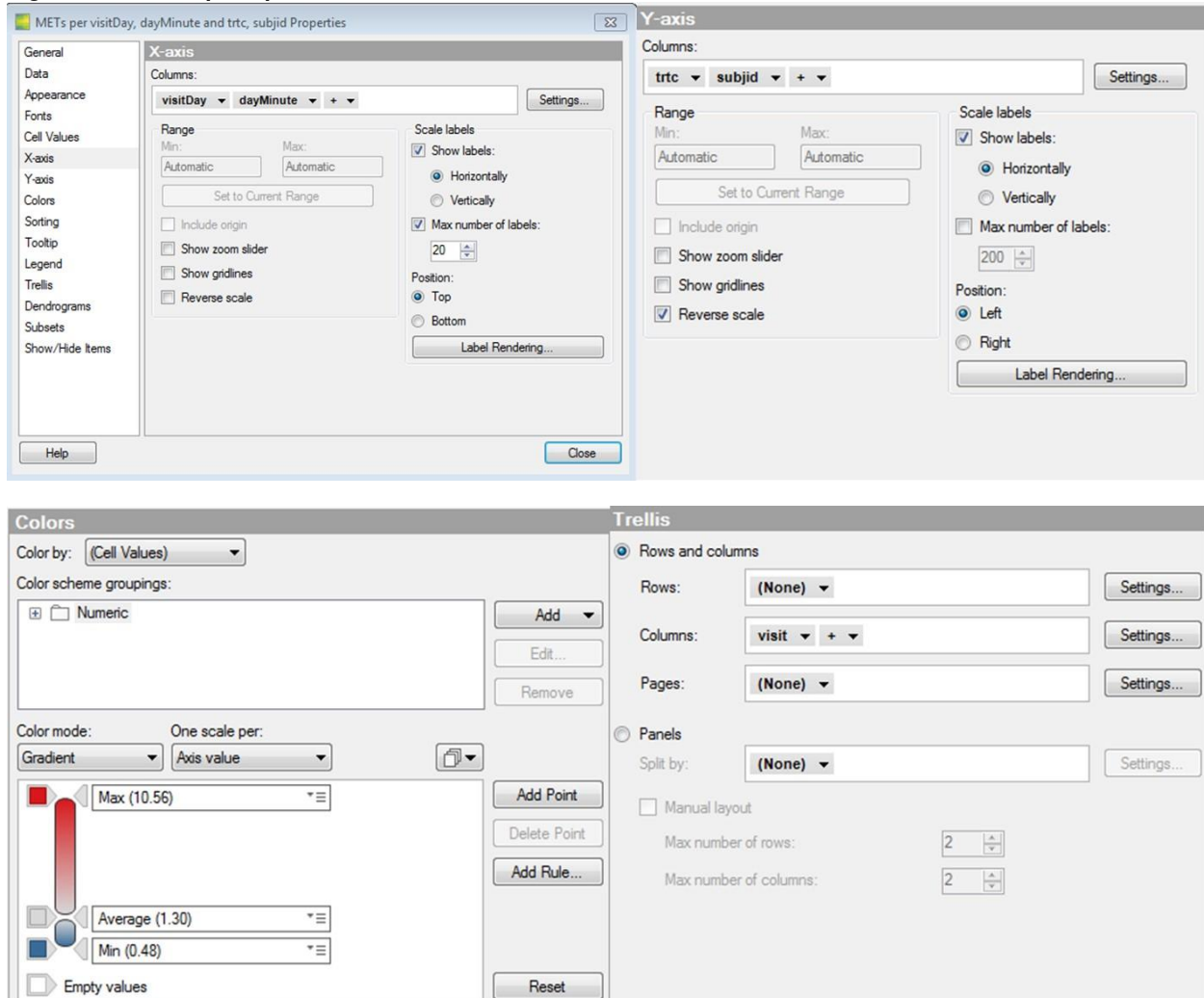
Heat maps are one type of visualization that is very useful in identifying trends across days, visits and study interventions. These plot types take advantage of our ability to recognize changes or patterns with colors that would otherwise be hard to see with other plots or with summary tables. In addition, the minute-by-minute detail can be used to maintain granularity and sensitivity. Figure 11 shows a heat map for all participants and is organized and grouped into three hypothetical study interventions on the y-axis. Each 'swim-lane' or row is a participant's data showing the minute-by-minute METs (vertical bar) across both the baseline visit (V1) and the post-baseline visit (V5). The color gradient denotes blue for lower activity, grey for neutral level of activity and red for the highest level of activity. The individual days are also marked along the x-axis. The white space indicates missing data; however, it is not included in the color gradient. If there appears to be a pattern of more red in the post-baseline visit this is an indication of more activity, and the opposite for blue. The first plot (top) displays all the data and the second plot (bottom) shows the data with the time spent sleeping removed. Removing the time spent sleeping adds to the missing data but does not generally change the pattern or trend of the activity to any significant degree. More work will need to be done to confirm the usefulness of removing time spent sleeping from these visuals.

Figure 11 Heat Map of minute-by-minute METs data. Rows indicate individual participants grouped into three hypothetical interventions. The columns represent minutes and are further marked by day. The visits are also trellised as columns. The top figure represents all data. The bottom figure contains time spent sleeping removed.



To create this display in Spotfire utilize the following settings:

Figure 12 Heat Map Properties

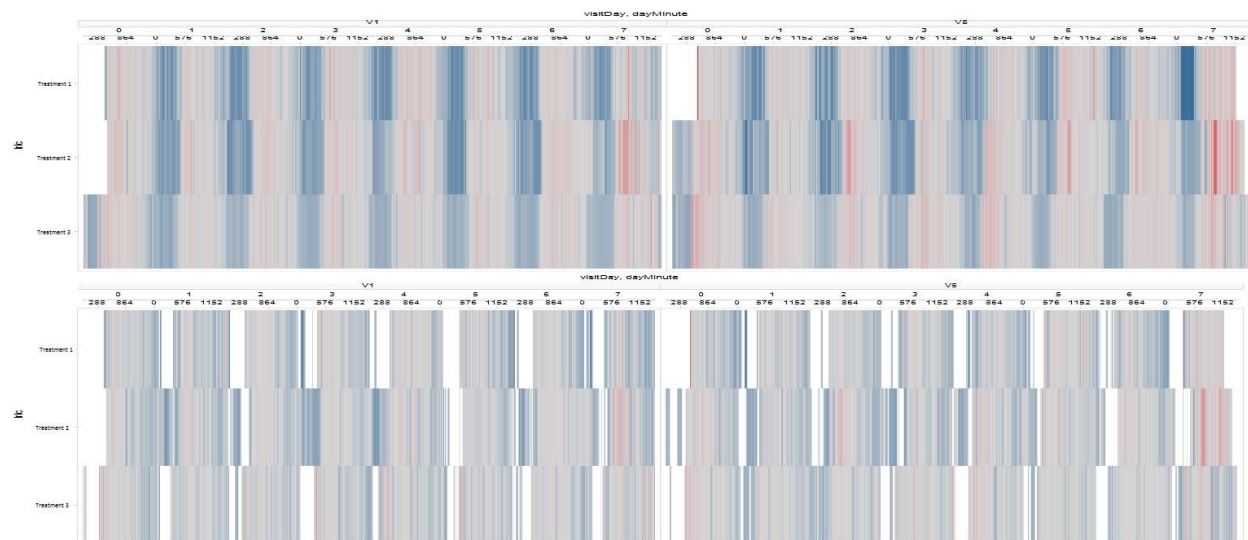


The image displays four configuration panels for a Spotfire visualization:

- X-axis:** Columns are 'visitDay' and 'dayMinute'. Range is set to 'Automatic'. Scale labels are 'Horizontally' and 'Show labels' is checked. Max number of labels is 20. Position is 'Top'.
- Y-axis:** Columns are 'trtc' and 'subjid'. Range is set to 'Automatic'. Scale labels are 'Horizontally' and 'Show labels' is checked. Max number of labels is 200. Position is 'Left'.
- Colors:** Color by is '(Cell Values)'. Color scheme groupings include 'Numeric'. Color mode is 'Gradient' and One scale per is 'Axis value'. The color bar shows a gradient from blue (Min: 0.48) to red (Max: 10.56).
- Trellis:** Rows and columns are selected. Rows are '(None)' and Columns are 'visit'. Pages are '(None)'. Panels are '(None)'. Max number of rows is 2 and Max number of columns is 2.

As can be seen in Figure 13, If we remove participant from the y-axis we are left with one summary for each of the study interventions. The analysis values are the median METs at each of the minutes of each day at each visit. The top heat map visual shows the entire dataset and the bottom visual shows with sleep time removed.

Figure 13 Summary Heat Map. Top figure contains all data. Bottom figure has time spent sleeping removed.



CONCLUSION

Digital wearable devices and the associated actigraphy data will likely become commonplace on clinical trials in the future. This kind of data are different in type and volume from any other data that we collect in our studies. Collecting participant data over a continuous period of time with objective data from sensors result in a more patient focused trial than traditional trial designs and yield more complete information on how study interventions impacts the aspects of the disease most important to patients. It should also yield better information to inform regulatory and labeling claims as well as subsequent reimbursement decisions. Because the sensors are non-invasive, participation and retention of patients in clinical trials should also increase. However, there are many challenges that will need to be resolved including buy-in from regulatory agencies and clinicians around meaningful and validated endpoints and finding ways to transform the complex data into a more simplistic and interpretable form.

Given the increased amount of information and associated complexity, novel and innovative data mining approaches are necessary to take full advantage of the richness of the data. Sophisticated statistical analysis and elegant visualizations will be required to consistently output relevant clinical information across a number of diseases and interventions. Clinical statisticians, quantitative data scientists and programmers are the key roles that will be needed in the future to maximize the value of the analysis and ultimately to benefit patients.

ACKNOWLEDGMENTS

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