Visualization of Titrated Dose and recurrent Events Using R/ggplot2

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Medical Monitoring: active monitoring of clinical data to ensure patient safety and proper implementation of study design
Medical Monitoring of On-going Clinical Studies

- Medical Monitoring: active monitoring of clinical data to ensure patient safety and proper implementation of study design
- Visualization of overall trend and individual data is a powerful tool in Medical Monitoring
Medical Monitoring: active monitoring of clinical data to ensure patient safety and proper implementation of study design.

Visualization of overall trend and individual data is a powerful tool in Medical Monitoring.

Efficient open-source solution for internal monitoring is welcomed.
"A plotting system for R, based on the grammar of graphics, which tries to take the good parts of base and lattice graphics and none of the bad parts" http://had.co.nz/ggplot2/
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Ideal tool for quick visualization
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Ideal tool for quick visualization

Grammar of graphics helps to nail down the exact specification of plot in communication with clinical colleagues
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When Tabulating Incidence Rates is Not Enough

- Patients may experience an event repeatedly. Frequency and severity of these recurrent events need to be monitored:
  - hypoglycemia episodes in a diabetes treatment study
  - headache in a migraine trial
- Traditional tabulations only display certain aspect of the event profile
- The same metric over time need to be seen simultaneously to understand the progression of the event accumulation
- Individual contribution to the accumulating events is equally important to understand
Individual Events over Time

- Straightforward visualization of recurring events, one patient a row
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- Episodes displayed as points along the time-axis
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- Episodes displayed as points along the time-axis
- Order on y-axis can depend on various information to explore relation with covariates
Individual points may be color coded to indicate severity
Accumulated Count of Occurrence

- **Total count of accumulated events over time plotted using `geom_step`**
Accumulated Count of Occurrence

- Total count of accumulated events over time plotted using `geom_step`
- Useful for comparing different dose level but individual contributions to the total count is not reflected in the graph
Accumulated Counts, Individuals Stacked

- Different patients’ accumulated counts stacked together using `geom_area(stat="identity", position="stack")`

![Graph showing accumulated counts over relative days from randomization](image)
Accumulated Counts, Individuals Stacked

- Different patients’ accumulated counts stacked together using `geom_area(stat="identity", position="stack")`
- Each patient is color coded to enable clear distinction between individual contribution
Mean Cumulative Function Over Time + Individual Counts over Time

- Individual accumulated counts are plotted using `geom_step`
Mean Cumulative Function Over Time + Individual Counts over Time

- Individual accumulated counts are plotted using `geom_step`
- Mean cumulative function (MCF) are fitted using `geom_smooth`

![Graph of Mean Cumulative Function Over Time with Individual Counts](image)
Mean Cumulative Function Over Time + Individual Counts over Time

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- Mean cumulative function (MCF) are fitted using `geom_smooth`
- More appropriate MCF estimate accounting for censoring is available, but requires additional coding outside of ggplot2
Median Cumulative Function

Median of cumulative counts over time gives a robust estimate of a typical time-dependent path of event accumulation.
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Overall trend of titration gives clue of appropriate titration guideline.

Individual titration path relates to both efficacy and safety signals.
Dose Distribution over Time

- Distribution of dose is the first step towards the understanding of appropriate dose.

Use `geom_bar(position="fill")` to visualize the relative proportion of doses over time. Overdose can be easily identified by the graph.
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- Overdose easily identified by graph.
Heatmap-like plot uses color to code individual dose over time:
```r
gem_tile(aes(fill=factor(doserg)))
```
Color Coded Individual Dose

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Up-titration by design is visible in graph - study requires all patients to up-titrate to highest dose per day around 100 days
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- Up-titration by design is visible in graph - study requires all patients to up-titrarte to highest dose per day around 100 days
- Alternating colors indicate up or down-titration activities.
Titration Path + Average Dose over Time

Use `geom_step` to visualize individual titration path.

Mean dose over time indicates the overall titration trend.
Titration Path + Average Dose over Time

- Use `geom_step` to visualize individual titration path
- Use `alpha=0.1` to reduce overplotting
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- Mean dose over time indicates the overall titration trend
Titration at another dose level - note the different stable doses the majority of patients settled on
A question of scientific interest is how the recurring events (e.g. an adverse experience) correlate with different dose levels over time.
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Use `geom_step` to trace the individual titration path; use `geom_point` to connect the episodes over time with corresponding dose.
Distribution of recurrent Events and Corresponding Dose

A few observations
- Distribution of events at different dose level

Visualization Examples Using ggplot2
Distribution of recurrent Events and Corresponding Dose

A few observations

- Distribution of events at different dose level
- How the more frequent titration activities correlate with event occurrence
A few observations

- Distribution of events at different dose level
- How the more frequent titration activities correlate with event occurrence
- Some overdose as shown by unexpected spikes
Distribution of recurrent Events and Corresponding Dose cont.

The recurrent events and dose titration visualized at a different dose level - note the distinctive decrease in recurrence of the event after day 100.
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Rich statistical packages in R complement the graphical capability of ggplot2.
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How to differentiate up and down-titration in dose-titration graphs?
Discussion

- Further drill-down to patient level data is currently difficult as ggplot2 supports only static graphics. Is there any workaround?
- How to differentiate up and down-titration in dose-titration graphs?
- Considering time-to-next-event for a patient as multivariate survival data, what kind of visualization can help display trend and identify outliers?

- Any more ideas for clinical data visualization?
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Any more ideas for clinical data visualization?
Reference

Hadley Wickham.

Edward R. Tufte.
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