Hands On Time to Event Tutorial

A hands-on workshop developed by Nick Holford (n.holford@auckland.ac.nz)

The following steps assume you have unzipped the PAWS_TTE_2021.zip file into a folder called PAWS_TTE_2021 that will then contain a tte and a BM folder. If you have unzipped the file to a different location then use that instead of PAWS_TTE_2021.

Software Requirements

1. Text editor
2. Microsoft Excel
3. Berkeley Madonna installation
4. NONMEM installation (7.3 or later)
5. Compiler installation (e.g. gfortran)
6. Wings for NONMEM installation (744 or later)

A text editor and Microsoft Excel (or compatible) are the only required tools. A functioning NONMEM environment using Wings for NONMEM allows all hands-on activities to be completed.

Graphical Exploration of Hazard, Probability Density Function and Survivor Function

Objectives

1. To simulate common baseline hazard functions (constant, Gompertz and Weibull)
2. To appreciate the shape of the hazard, survivor and probability density functions with different baseline hazards both without and with drug treatment

Hazard functions and their associated survival and probability density functions can be appreciated by plotting them in relation to time and treatment effects. Berkeley Madonna is used to implement a model and to create graphs. The baseline hazard functions (constant, Gompertz, Weibull) are determined by the basetype variable (0=constant, 1=Gompertz, 2=Weibull). A drug treatment effect on tumour growth is used to illustrate a continuous time varying effect on hazard and thus survival. The effects of treatment on hazard are determined by the timetype variable (0=no treatment effect, 1=treatment effect on survival due to tumour size, 2=treatment effect on survival due to drug concentration directly).

Steps

Hazard, Survivor and Probability Density Function

1. Open Berkeley Madonna
2. Open New model
3. Open PAGANZ_TTE_2021\ BM\const-gomp-weib_tte.txt with a text editor
4. Select all of the contents of const-gomp-weib-tte.txt then paste into a Berkeley Madonna New model window
5. Click Run and resize Equations and Graph windows so that they are both visible (e.g. Equations on left and Graphs on right).
6. Click on the Graph window then main menu Graph then Choose Variables
7. Double Click on all variables in Y axis list to remove all variables from list
8. Double Click on hazpla, survpla, pdfpla variables in Variables list, Choose Right axis for hazpla and pdfpla.
9. Click on X-axis then select weeks from the list of variables
10. Click OK
11. Click on the Equations window.
12. Check (or change) basetype is 0 (use constant baseline hazard function)
13. Check (or change) timetype is 0 (no other time varying hazard)
14. Click Run
15. Click on Graphs hazpla tab.
    Look at the graph of hazard. How would you describe the shape of the hazard graph? This is the shape of a constant hazard
16. Click on the survpla tab to see the shape of the survivor function
    The survivor function for a constant hazard is exponential. The constant hazard produces an exponential distribution.
17. Click on the pdfpla tab to see the probability density function (pdf).
    The pdf is equivalent to the likelihood of an event at the time of the pdf. It is calculated from the survivor function multiplied by the hazard. With a constant hazard the pdf is therefore exponential.
18. Click on the Equations window.
19. Change basetype to 1 (use Gompertz baseline hazard function)
20. Repeat previous steps to simulate with the Gompertz function
21. Change basetype to 2 (use Weibull baseline hazard function)
22. Repeat previous steps to simulate with this hazard function
23. Batch Run for different baseline hazards: Click on main menu Parameters, Batch Runs, Select basetype, # runs=3 , initial value=0 , final value=2
24. Click Ok on the Batch Runs window.
25. Compare the hazard function curves (hazpla).
26. Compare the survivor function curves (survpla).
27. Compare the probability density function (pdfpla) curves.

Effect of Treatment on Tumour Size and Size on Hazard, Survivor and PDF

28. Click on the Equations window.
29. Change basetype to 1 (Gompertz hazard)
30. Change timetype to 2 (tumour size and conc effect on hazard)

31. Go to Graph Choose Variables and double click tumourtrt in the Variables list to see the effect of treatment on tumour size
32. Batch Run for different treatments: Click on main menu Parameters, Batch Runs, Select dailydose, # runs=3 , initial value=0 , final value=40
33. Click OK
34. Look at the time course of different doses on tumour size (tumourtrt). When daily dose is 0 this is equivalent to placebo treatment. Describe the time profile. Why do you think it has this shape? (look at the simulation code)
35. Add variables haztrt, survtrt and pdftrt to the graph. Look at each separately to compare the effects of treatment.
36. Why does the pdf increase then fall when treatment is stopped? Look at haztrt to get a clue.
37. Statistical tests for survival are often repeated in terms of the relative risk. The relative risk is the ratio of the cumulative hazard on treatment to the cumulative hazard on placebo. Go to Graph Choose Variables and double click relrisk_trtpla in the Variables list to see the relative risk. Note that it changes with time. Traditional statistics are reported in terms of the relative risk at the end of the trial.

Hazard Model Selection Using Parameter Estimation

Objectives

1. To learn how to write time to event models for hazard model estimation and simulate time to event data.

A TTE study uses100 subjects are given either placebo or warfarin (2.5, 5, 10 mg/day) for 1 year. Each day a subject may dropout or have a major haemorrhage (the primary event of interest). The hazard of haemorrhage is modeled as a function of the warfarin daily dose. The hazard of dropout is assumed to be constant and independent of treatment. The simulation model assumes that the International Normalized Ratio determines the hazard of a major haemorrhage.

Steps

1. Change folder (WFN command window) to:
   `cd PAWS_TTE_2021\tte\warfarin_SIM`
2. Run this command to simulate data and create a Kaplan-Meier plot of the observed data and a VPC using 10 replication simulations:
   `ttevpc_SIM`
3. While this is running use a text editor to examine the code for:
   a. The simulation model (warf_INR_sim.ctl)
   b. An estimation model (warf_INR_est.ctl)
4. What is the difference between the warf_INR_est and the warf_TRT_est models in the hazard model for major haemorrhage?

Hazard Model Evaluation Using Visual Predictive Checks

Objectives

1. Create Kaplan Meier plots to compare the survivor function in an observed data set with a confidence interval for the survivor function
2. To appreciate the limitations of this kind of VPC

Each time the warf.bat file is run there are two kinds of visual predictive check performed. The first type shows a Kaplan-Meier plot of the non-parametric survivor function stratified on the treatment type (equivalent to warfarin doses of 0, 2.5, 5 and 10 mg/d). The second type shows a KM plot for all the simulated 'observed' events with a 95% confidence interval. Superimposed on the plot is a simulation of the median KM profile. If more than one replication has been performed then the 95% interval for the simulated median KM profiles will be shown.

Steps

1. Open a Wings for NONMEM command window
2. Change folder to:
   `cd PAWS_TTE_2021\tte\warfarin_OBS`
3. Run this command to create a Kaplan-Meier plot of the observed data and a VPC using 1 replication simulation:
   `ttevpc`
4. Use Windows to examine the pdf files in the warf_KM_OBS.reg and warf_KM_VPC.reg folders. You should be able to appreciate the random variation in the pattern of events that occurs in the observed data with 100 subjects. Note that the blue median line in the VPC plot named warf_INR_1_warf_INR1.pdf uses only one simulation so there is no confidence interval.
5. Running many simulations to simulate the confidence interval can take a long time.
   Run this command to create a Kaplan-Meier plot of the observed data and a VPC using 100 replication simulation:
   `ttevpc_VPC`
6. Look at the pdf files in the warf_KM_VPC.reg folder. The file named warf_INR_100_warf_INR1.pdf shows the a VPC with the simulated confidence interval.

Clinical Trial Simulation

Objectives

1. To perform a parametric bootstrap to evaluate the power of different models to detect a significant effect on the hazard of a major haemorrhage.

Clinical trial simulation is a useful tool for evaluating clinical trial designs. Stochastic simulation is especially useful for time to event based trials with competing risks for events due to the event of interest and dropout from other causes.

Steps

1. Open a Wings for NONMEM command window
2. Change folder to:
   `cd PAWS_TTE_2021\tte\warfarin_PWR`
1. Open the ttevpc_SIM.bat and confirm these settings:
   ```
   set runNONMEM=y
   set NREP=100
   set NVPC=10
   set runest=    ← no characters after "="
   ```
2. Run ttevpc_PWR.bat. This will use 100 simulated data sets to fit each of five hazard models (CONST, GOM, WBL, TRT, INR). It will take between 1 and 2 hours depending on your computer and compiler to simulate the data and finish all 500 estimation runs. The results are summarized in a .smy file in the run folders associated with each estimation model.
3. Open the Excel file warf_BS_100.xlsx in the warfarin_PWR\power folder.
4. Open the .smy file in each of the est folders in a text editor and copy the contents into the named worksheet in the Excel file.
5. Look at the Power worksheet to see the power of each model to reject the null hypothesis with alpha=0.05 and alpha=0.01. Are these results what you expect? Explain why.
6. Look at the Stats worksheet to see the average parameter estimates and their average asymptotic standard error. Is the size and sign of the hazard parameter estimate for each model what you expect? Explain why.
7. You may change the trial design by editing ttevpc_PWR.bat and modifying the NSUB variable (number of subjects) and the TLAST argument to the simdat.awk script that creates data.csv.
8. You may also change the simulation hazard model parameters for major haemorrhage and dropout in warf_INR_sim.ctl.
9. If you change the simulation design or simulation model parameters then you will need to recreate the simulated time to event data files. If you change the items saved in the warf_INR_sim.ctl NONMEM $TABLE record you will need to modify the make_t2e.awk file. This is used to extract the simulated event data from the NONMEM fit file in a format suitable for tte analysis.

Suggested Reading

Holford N. A Time to Event Tutorial for Pharmacometricians. CPT: pharmacomet syst pharmacol. 2013;2:e43 doi:10.1038/psp.2013.18. (Open Access pdf)

Holford N, Ma SC, Ploeger BA. Clinical trial simulation: a review. Clin Pharmacol Ther. 2010;88(2):166-82.