Goal: To simulate survival data has

1. competing event: death and ICU discharge
2. Recurrent event: coma and delirium.
3. Followed up to 28days.

Assumption:

A patient can get discharged from the ICU to a post-acute care facility where they will take ventilated but stable patients.

Assume time to ICU discharge and time to death follows exponential distribution with rate = hazard. (cox model)

Assume Weibull hazard for coma/delirium onset, and duration of event follow negative binomial distribution (we use negative binomial instead of poisson because the duration in data is over-dispersed)

Parameter prepare:

1. Ignore death and ICU discharge, run recurrent model for coma and delirium, get parameter for ,; ,
2. Ignore recurrent event (coma & delirium), fit Weibull model for icu discharge, time to death within ICU and time to death after ICU separately, and get parameter for ,;,; ,;
3. Fit joint model between delirium and icu discharge, delirium and death, and get parameter alpha.icu, alpha.m
4. Fit Weibull model on time to coma free, and time to delirium free, and get ,; ,

We are going to simulate coma/delirium based on recursive simulation algorithm from Jahn-Eimermacher 2015 paper (page 4):

1. Generate frailty term z follow lognormal distribution/gamma distribution to account for within-patient dependency.
2. Generate time to ICU discharge as:
   1. Generate
   2. Generate
   3. Generate
   4. Generate time to ICU discharge and time to death
3. When Tdeath< = Tdischarge -> death

When Tdeath > Tdischarge -> ICU discharge, and generate time to death after icu discharge in the similar way generate time to death.

And censor at 28day

1. Generate recurrent coma and delirium:
   1. Generate
   2. Generate
   3. Generate

While coma & delirium has weibull hazard ,

Cumulative hazard

* 1. For 1st event, generate

For recursive coma/delirium:

* 1. The ith event would be coma if , and delirium if , with
  2. Generate duration of the coma and duration of delirium as time to event free (in the similar way that generate time to event onset) using parameter ,; ,
  3. If ith event is delirium,

If ith event is coma,

for generate

for generate

* 1. Repeated a-g until ti >= 28

1. Truncate simulated coma or delirium status at death or ICU discharge.

Code:

Define function:

Function\_V10.R

data\_format: create two type of frailty data:

1) when set death.after.icu=1, treat death as terminal event for patient died after icu discharge. We could use this data to run the marginal model for death.

2) when set death.after.icu=0, treat icu discharge as terminal event for patient died after icu discharge. We could use this data to run icu discharge and death among icu model.

data\_duration\_format: format data to run model on time to event free

fit.model.onset: fit reccurent model and terminal model on time to onset

fit.model.duration: fit Weibull model on time to event free

simulate10: simulate delirium and coma data with time to ICU discharge and time to death. The simulated data are in wide format (one person per record, with status of each day as covariate)

simulate\_V10.R: code to call function, simulate data and plot lasagna plot.

`