Pooled Analysis

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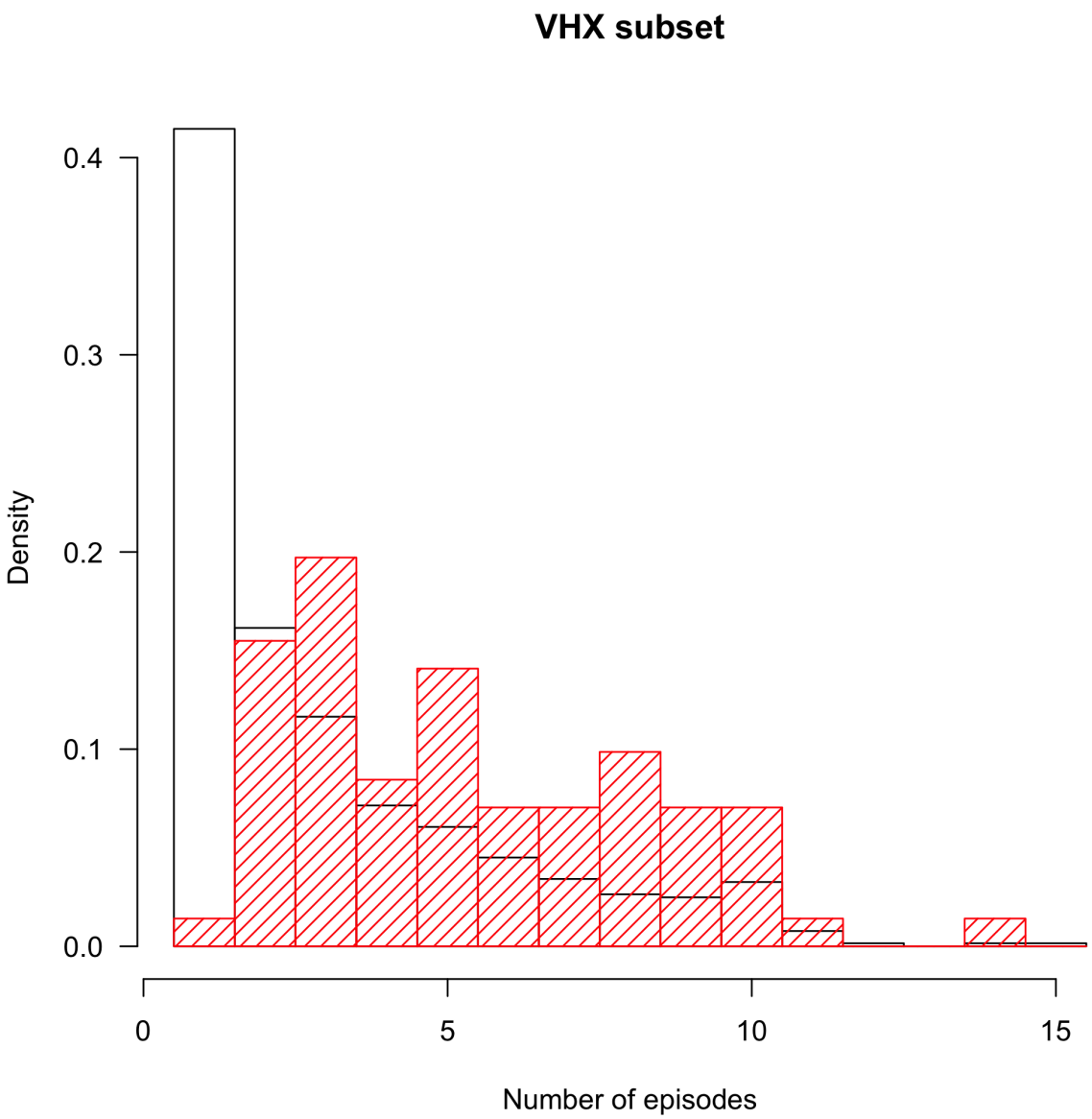
Preamble

Load R packages, functions and data.

Summary of the data and the whole of the VHX data versus the subset typed (in terms of number of episodes):

```
## Number of individuals with at least one episode typed: 164
## Number of episodes typed: 599
## Number of recurrences typed: 435
## Number of individuals with at least two episodes typed: 159
## Number of recurrences typed: 435
```



Define the sets of microsatellite markers for the various datasets.

```
MSs_VHX = c("PV.3.502","PV.3.27","PV.ms8","PV.1.501","PV.ms1","PV.ms5","PV.ms6")
MSs_all = c("PV.3.502","PV.3.27","PV.ms8","PV.1.501","PV.ms1","PV.ms5","PV.ms6",
            "PV.ms7","PV.ms16")
MSs_BPD = MSs_all
MSs_Main = c('PV.3.27', 'PV.3.502', 'PV.ms8') # These are typed for all episodes (the core group)
```

The approach is fully Bayesian and consists of the following:

- A prior probability vector for the recurrence state
- A likelihood based on the genetic data of being a *relapse*, a *recrudescence*, or a *reinfection* given the observed microsatellite data.

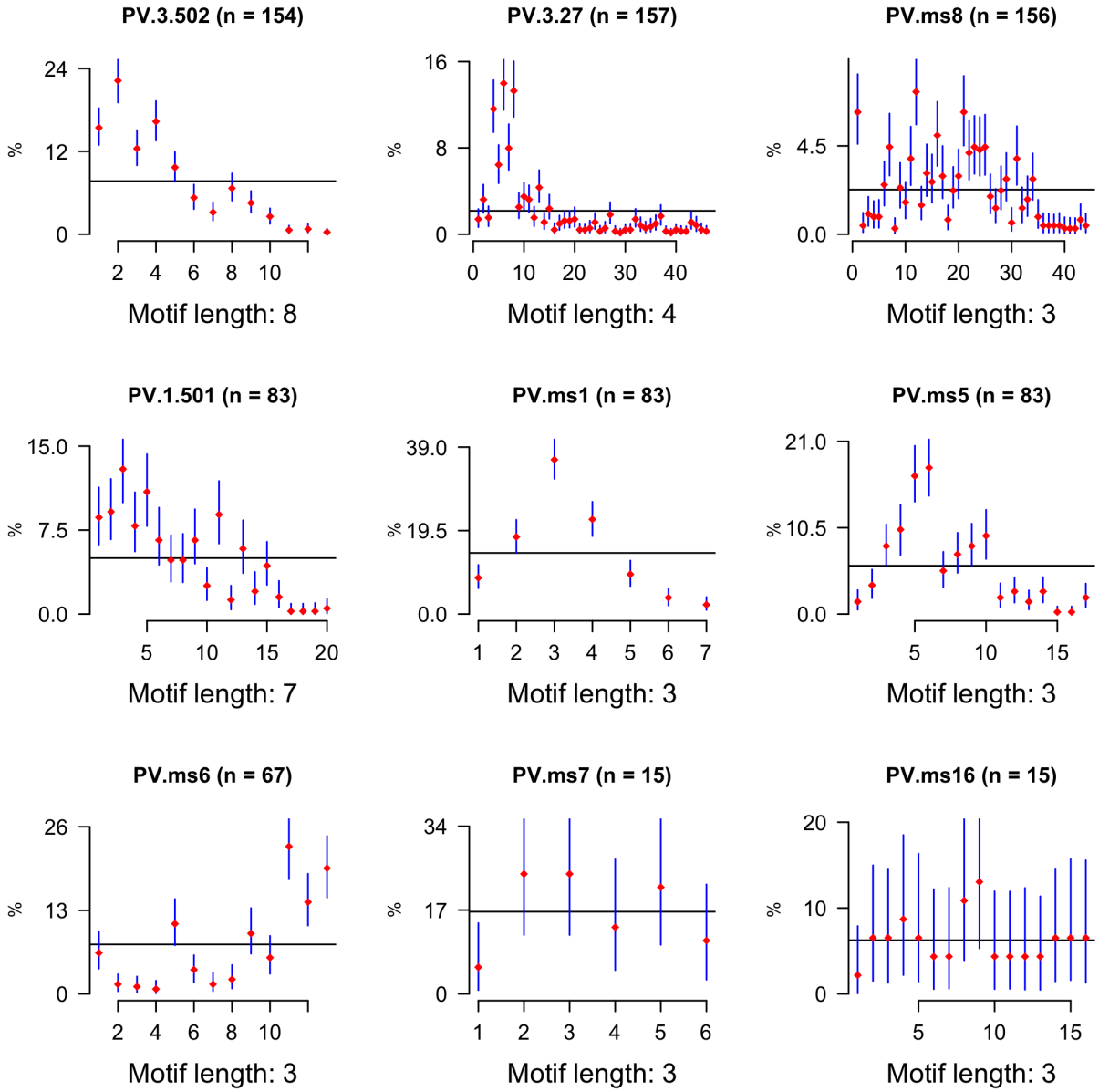
Allele frequencies

We use a multinomial-dirichlet model with subjective weight. Setting the weight to 0 recovers unweighted empirical allele frequencies.

```
## Number of episodes used to compute frequencies: 159
```

Plotting allele frequencies

These are the observed allele frequencies in the pooled data. We show 80% credible intervals (lo) (Aimee: seems to be 95%)



Computing the probability of relatedness across infections

The following iterates through each individual and computes the probability of relatedness states.

Load the time-to-event priors

```
inds = grepl('mean_theta', colnames(Mod3_ThetaEstimates)) # Extract mean
Episode_Identifier = Mod3_ThetaEstimates$Episode_Identifier
p = data.frame(Episode_Identifier = Episode_Identifier, Mod3_ThetaEstimates[,inds],
               stringsAsFactors = F) # Reformat
colnames(p) = c('Episode_Identifier', 'C', 'L', 'I')

genetic_AND_time_data_eps = intersect(p$Episode_Identifier, MS_pooled$Episode_Identifier)
p = p[p$Episode_Identifier %in% genetic_AND_time_data_eps,]
Post_samples_matrix = Post_samples_matrix[Post_samples_matrix$Episode_Identifier %in% genetic_AND_time_
```

Computation using full dataset

We use all 9MS markers (when available).

Full posterior computation

Plot results

These dataframes are sorted by episode number so the columns correspond between them. We make some data.frames that store the results for ease of plotting.

```
mycols = brewer.pal(n=3, name = 'Set1')
thetas_9MS = arrange(thetas_9MS, Episode_Identifier)
thetas_9MS_Tagnostic = arrange(thetas_9MS_Tagnostic, Episode_Identifier)

Time_Estimates_1 = filter(Mod3_ThetaEstimates,
                          Episode_Identifier %in% thetas_9MS$Episode_Identifier)
Time_Estimates_1 = arrange(Time_Estimates_1, Episode_Identifier)

thetas_9MS$drug = Time_Estimates_1$arm_num
thetas_9MS_Tagnostic$drug = Time_Estimates_1$arm_num

# for plotting
thetas_9MS$drug_col = mapvalues(x = thetas_9MS$drug,
                                c('AS','CHQ','CHQ/PMQ'), mycols)
```

```
## The following `from` values were not present in `x`: AS
```

```
thetas_9MS_Tagnostic$drug_col = mapvalues(x = thetas_9MS_Tagnostic$drug,
                                          c('AS','CHQ','CHQ/PMQ'), mycols)
```

```
## The following `from` values were not present in `x`: AS
```

```
BPD_data = Thetas_full_post[grep('BPD',rownames(Thetas_full_post)),]
Thetas_BPD = thetas_9MS[grep('BPD', thetas_9MS$Episode_Identifier),]
```

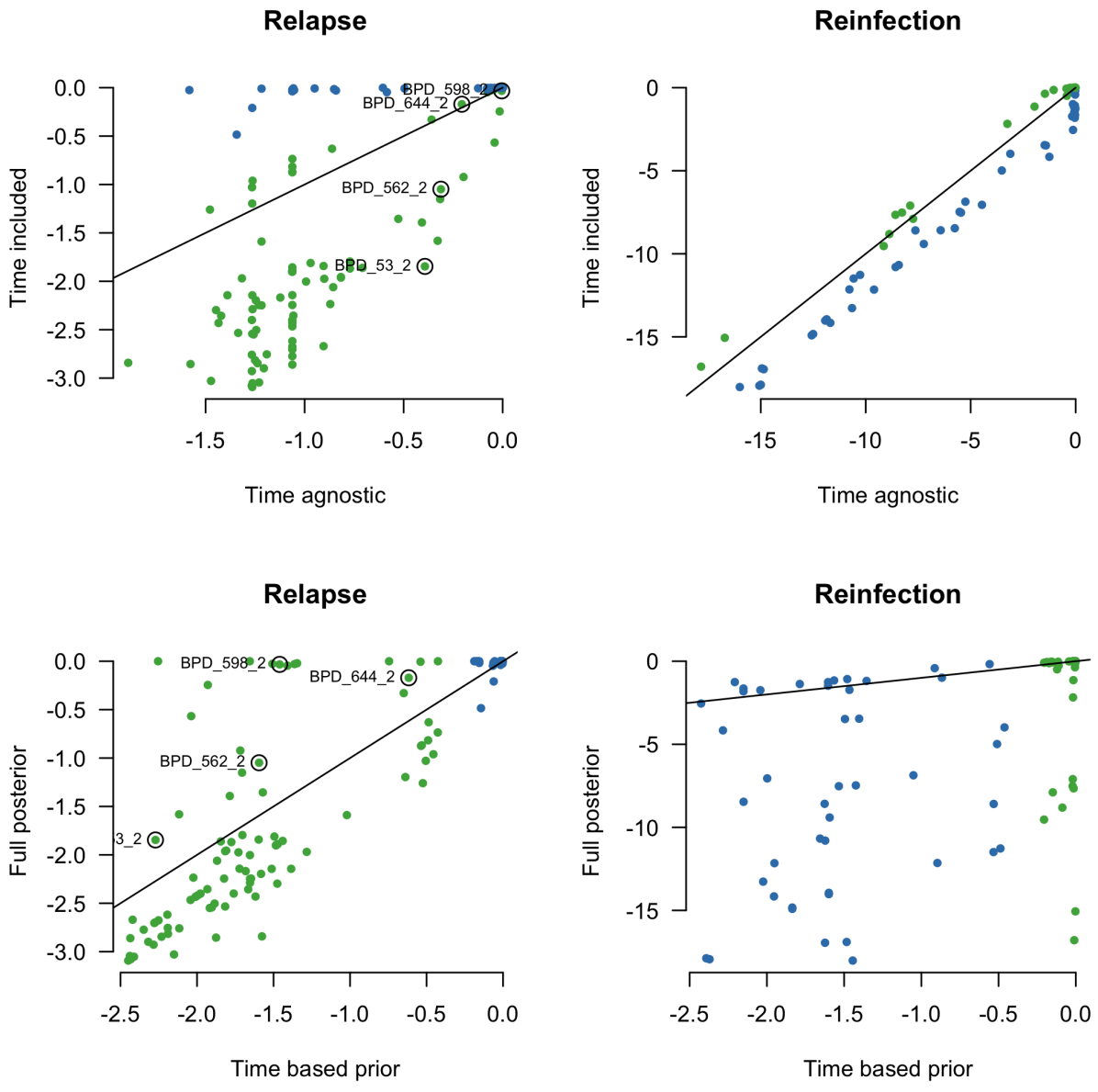
```
# Added by Aimee: some examples
# Colour some specific examples
example_inds = grepl('_644_', Thetas_BPD$Episode_Identifier) |
  grepl('BPD_598_', Thetas_BPD$Episode_Identifier) |
  grepl('BPD_562_', Thetas_BPD$Episode_Identifier) |
  grepl('BPD_53_', Thetas_BPD$Episode_Identifier)
example_ids = Thetas_BPD$Episode_Identifier[example_inds]
example_inds_times = MS_pooled$timeSinceLastEpisode[MS_pooled$Episode_Identifier %in% example_ids]
Tagnostic_example_inds = thetas_9MS_Tagnostic$Episode_Identifier %in% example_ids
thetas9MS_example_inds = thetas_9MS$Episode_Identifier %in% example_ids
Time1_example_inds = Time_Estimates_1$Episode_Identifier %in% example_ids
```

Going from time-to-event prior to posterior

Have broken it down by radical cure and no radical cure, as that is the most informative distinction here.

```
if(CREATE_PLOTS){
  par(mfrow=c(2,2),las=1, bty='n')
  # Time agnostic versus full posterior
  plot(log10(thetas_9MS_Tagnostic$L), log10(thetas_9MS$L),
       col = thetas_9MS$drug_col, main = 'Relapse',pch=20,
       xlab = 'Time agnostic', ylab = 'Time included')
  lines(-10:0,-10:0)

  # Annotate by examples
  points(x = log10(thetas_9MS_Tagnostic$L[Tagnostic_example_inds]),
         y = log10(thetas_9MS$L[thetas9MS_example_inds]),
         pch=1, cex = 1.5, col='black')
  text(x = log10(thetas_9MS_Tagnostic$L[Tagnostic_example_inds]),
       y = log10(thetas_9MS$L[thetas9MS_example_inds]),
       labels = example_ids, pos = 2, cex = 0.7)

  plot(log10(thetas_9MS_Tagnostic$I), log10(thetas_9MS$I),
       col=thetas_9MS$drug_col, main = 'Reinfection',pch=20,
       xlab = 'Time agnostic', ylab = 'Time included')
  lines(-20:0,-20:0)


  ##### Prior versus full posterior
  plot(log10(Time_Estimates_1$Relapse_mean_theta),
       log10(thetas_9MS$L),main = 'Relapse',
       col=thetas_9MS$drug_col,pch=20,
       xlab = 'Time based prior', ylab = 'Full posterior')
  lines(-10:10,-10:10)

  # Annotate by examples
  points(x = log10(Time_Estimates_1$Relapse_mean_theta[Time1_example_inds]),
         y = log10(thetas_9MS$L[thetas9MS_example_inds]),
         pch=1, cex = 1.5, col='black')
  text(x = log10(Time_Estimates_1$Relapse_mean_theta[Time1_example_inds]),
       y = log10(thetas_9MS$L[thetas9MS_example_inds]),
```

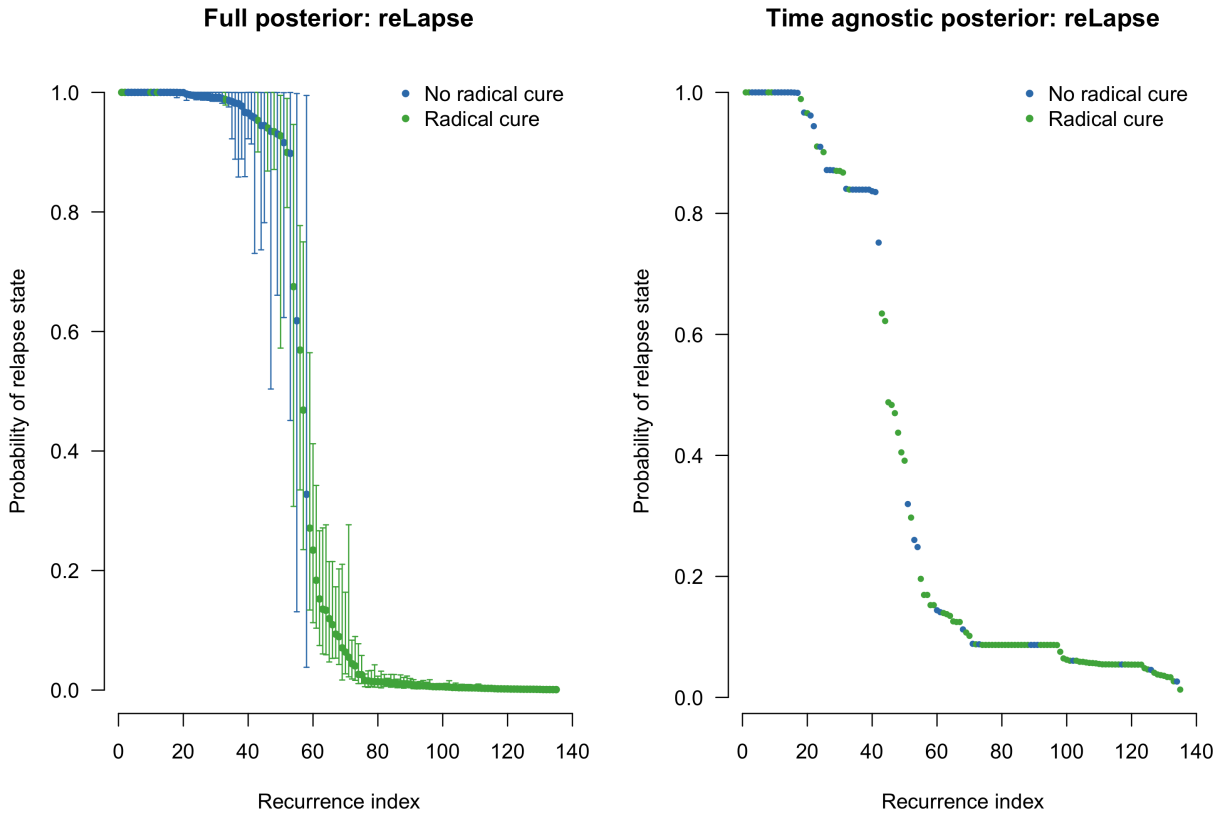
```
      labels = example_ids, pos = 2, cex = 0.7)

  plot(log10(Time_Estimates_1$ReInfection_mean_theta),
      log10(thetas_9MS$I),main = 'Reinfection',
      col=thetas_9MS$drug_col,pch=20,
      xlab = 'Time based prior', ylab = 'Full posterior')
  lines(-10:10,-10:10)

}
```



Probability of relapse, ordered from most to least likely:

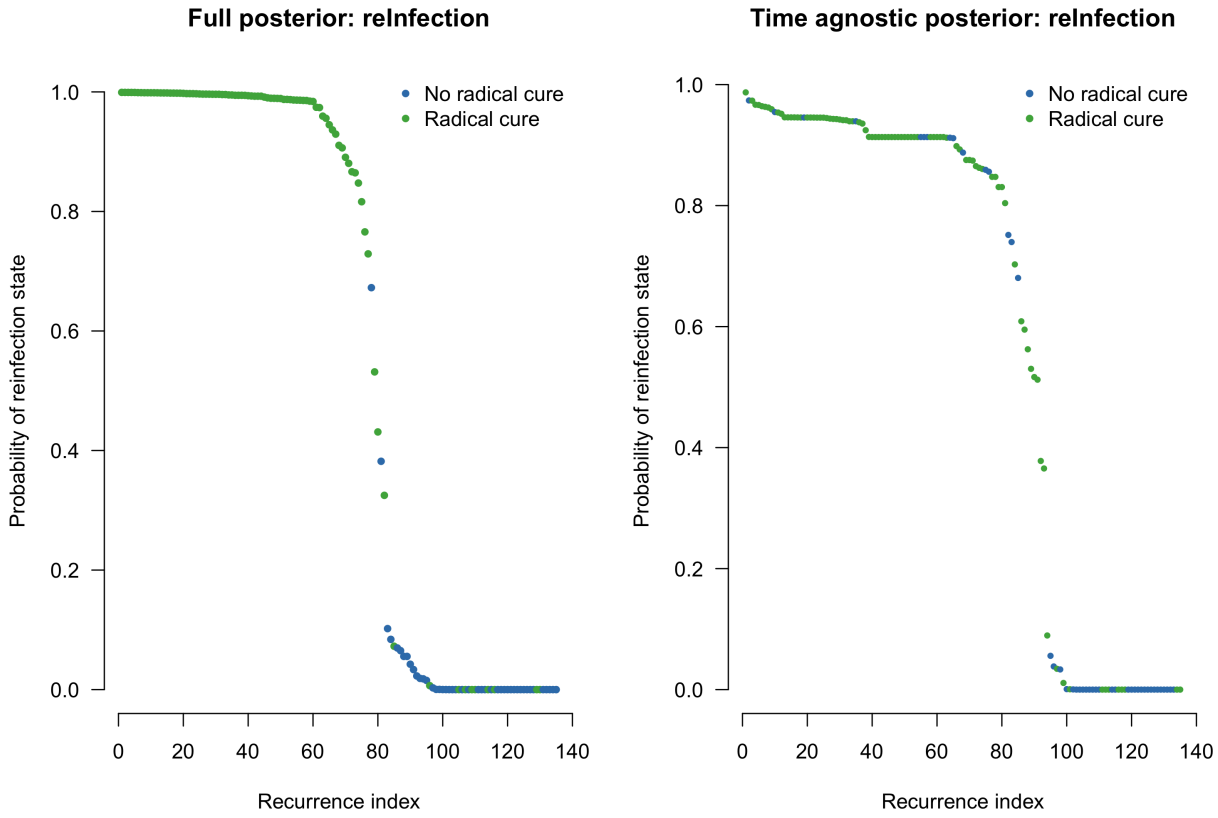
```
if(CREATE_PLOTS){
```

```
  par(mfrow=c(1,2),las=1, bty='n')

  reLapse_ordered = sort.int(thetas_9MS$L, decreasing = TRUE, index.return = TRUE)
  plot(reLapse_ordered$x, pch=20, col = thetas_9MS$drug_col[reLapse_ordered$ix],
       xlab = 'Recurrence index', ylab = 'Probability of relapse state',
       main = 'Full posterior: reLapse')
  CI = cbind(apply(
    Thetas_full_post[reLapse_ordered$i,grep('L',colnames(Thetas_full_post)),],
    1, quantile, probs = 0.025),
    apply(Thetas_full_post[reLapse_ordered$i,grep('L',colnames(Thetas_full_post)),],
          1, quantile, probs = 0.975))
  for(i in 1:length(reLapse_ordered$x)){
    if(diff(CI[i,]) > 0.005) arrows(i,CI[i,1],i,CI[i,2],
                                    length = 0.02,angle = 90,
                                    code = 3,
                                    col=thetas_9MS$drug_col[reLapse_ordered$ix[i]])
  }

  legend('topright',col = mycols[2:3], bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)

  reLapse_ordered_Tagn = sort.int(thetas_9MS_Tagnostic$L,
                                  decreasing = TRUE, index.return = TRUE)
  plot(reLapse_ordered_Tagn$x, pch=20, cex=.8,
       col = thetas_9MS_Tagnostic$drug_col[reLapse_ordered_Tagn$ix],
       xlab = 'Recurrence index', ylab = 'Probability of relapse state',
       main = 'Time agnostic posterior: reLapse')
  legend('topright',col = mycols[2:3], bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)
}
```



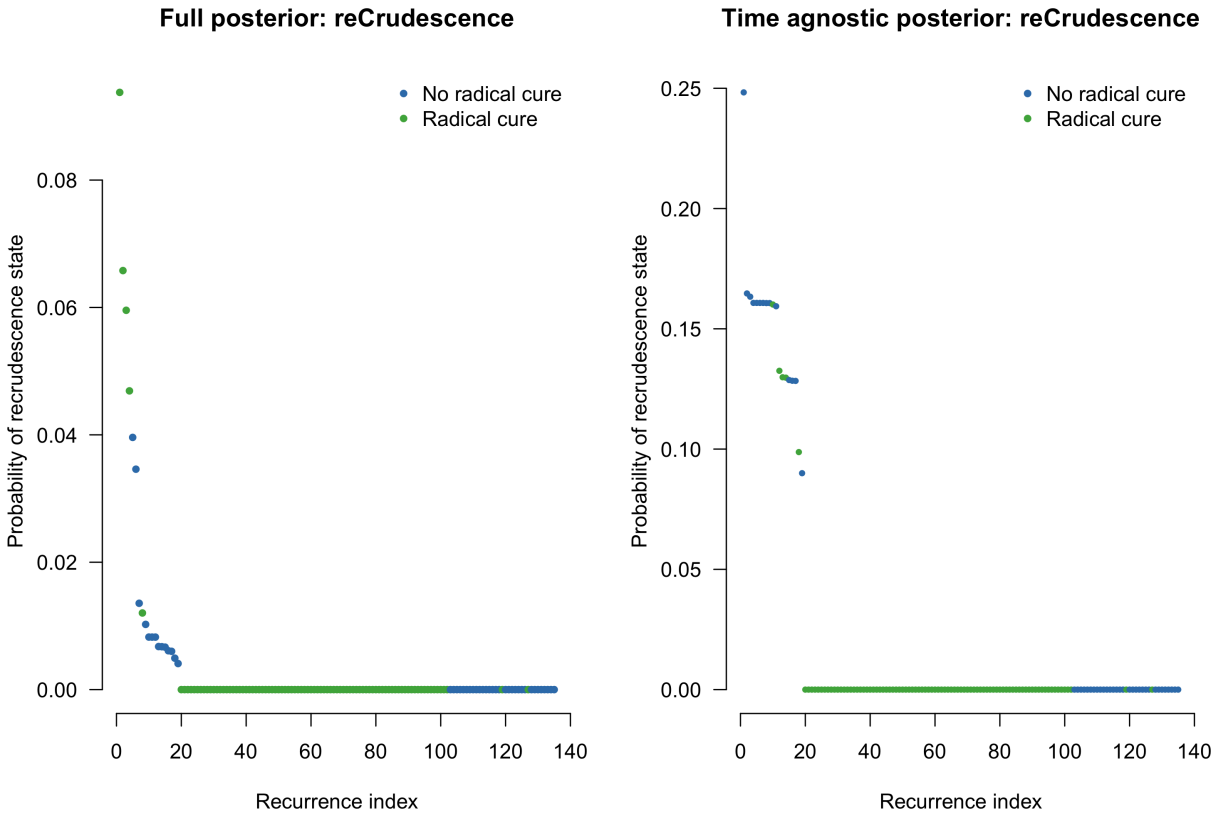
Probability of reinfection, ordered from most to least likely:

```
if(CREATE_PLOTS){

  par(mfrow=c(1,2),las=1, bty='n')
  reinfection_ordered = sort.int(thetas_9MS$I, decreasing = TRUE, index.return = TRUE)
  plot(reinfection_ordered$x, pch=20, col = thetas_9MS$drug_col[reinfection_ordered$ix],
       xlab = 'Recurrence index', ylab = 'Probability of reinfection state',
       main = 'Full posterior: reInfection')
  legend('topright',col = mycols[2:3],bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)

  reinfection_ordered_Tagn = sort.int(thetas_9MS_Tagnostic$I, decreasing = TRUE, index.return = TRUE)
  plot(reinfection_ordered_Tagn$x, pch=20, cex=.8,
       col = thetas_9MS_Tagnostic$drug_col[reinfection_ordered_Tagn$ix],
       xlab = 'Recurrence index', ylab = 'Probability of reinfection state',
       main = 'Time agnostic posterior: reInfection')
  legend('topright',col = mycols[2:3],bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)
}
```



Probability of recrudescence, ordered from most to least likely:

```
if(CREATE_PLOTS){
  par(mfrow=c(1,2),las=1, bty='n')
  recrud_ordered = sort.int(thetas_9MS$C, decreasing = TRUE, index.return = TRUE)
  plot(recrud_ordered$x, pch=20, col = thetas_9MS$drug_col[recrud_ordered$ix],
       xlab = 'Recurrence index', ylab = 'Probability of recrudescence state',
       main = 'Full posterior: reCrudescence')
  legend('topright',col = mycols[2:3],bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)

  recrud_ordered_Tagn = sort.int(thetas_9MS_Tagnostic$C, decreasing = TRUE, index.return = TRUE)
  plot(recrud_ordered_Tagn$x, pch=20, cex=.8,
       col = thetas_9MS_Tagnostic$drug_col[recrud_ordered_Tagn$ix],
       xlab = 'Recurrence index', ylab = 'Probability of recrudescence state',
       main = 'Time agnostic posterior: reCrudescence')
  legend('topright',col = mycols[2:3],bty = 'n',
         legend = c('No radical cure','Radical cure'),pch=20)
}
```

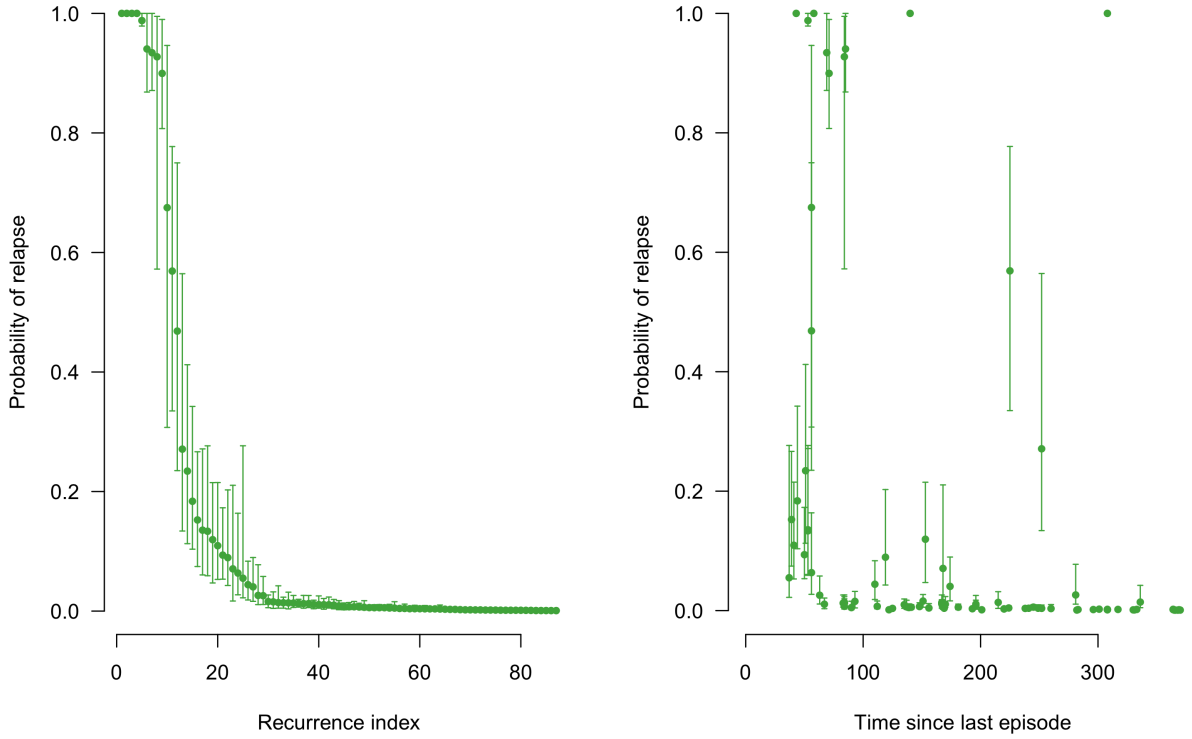


BPD Final Plot

```
if(CREATE_PLOTS){

  # Get rid of duplicated episode IDs (MOI > 1)
  MS_pooled_summary = MS_pooled[!duplicated(MS_pooled$Episode_Identifier),]
  par(mfrow=c(1,2),las=1, bty='n')
  reLapse_ordered = sort.int(Thetas_BPD$L, decreasing = TRUE, index.return = TRUE)
  plot(reLapse_ordered$x, pch=20, col = Thetas_BPD$drug_col[reLapse_ordered$ix],
       xlab = 'Recurrence index', ylab = 'Probability of relapse',
       main = '')
  CI = cbind(apply(
    BPD_data[reLapse_ordered$ix,grep('L',colnames(BPD_data)),],
    1, quantile, probs = 0.025),
    apply(BPD_data[reLapse_ordered$ix,grep('L',colnames(BPD_data)),],
          1, quantile, probs = 0.975))
  for(i in 1:length(reLapse_ordered$x)){
    if(diff(CI[i,]) > 0.005) arrows(i,CI[i,1],i,CI[i,2],
                                    length = 0.02,angle = 90,
                                    code = 3,
                                    col=Thetas_BPD$drug_col[reLapse_ordered$ix[i]])
  }
```

```
  writeLines(sprintf('The mean percentage of recurrences which are estimated to be relapses is %s%%',
                     round(100*sum(Thetas_BPD$L + Thetas_BPD$C)/nrow(Thetas_BPD))))


  plot(NA,NA,xlim=c(0,max(MS_pooled_summary$timeSinceLastEpisode,na.rm=T)), ylim=c(0,1),
       ylab = 'Probability of relapse', xlab = 'Time since last episode')
  for(i in 1:length(reLapse_ordered$x)){
    kk = reLapse_ordered$ix[i]
    x_time = MS_pooled_summary$timeSinceLastEpisode[Thetas_BPD$Episode_Identifier[kk]==
                                                      MS_pooled_summary$Episode_Identifier]
    points(x_time,
           Thetas_BPD$L[kk], pch=20, col=mycols[3])
    if(diff(CI[i,]) > 0.005) arrows(x_time,CI[i,1],x_time,CI[i,2],
                                    length = 0.02,angle = 90,
                                    code = 3,
                                    col=Thetas_BPD$drug_col[reLapse_ordered$ix[i]])
  }

  # Annotate by examples
  # points(example_inds_times,Thetas_BPD$L[example_inds], pch=1, cex = 1.5, col='black')
  # text(x = example_inds_times, y = Thetas_BPD$L[example_inds],
  #      labels = example_ids, pos =3)
}
```

```
## The mean percentage of recurrences which are estimated to be relapses is 15%
```



Extra computations for VHX: too complex episodes

We remove the IDs that can be straightforwardly calculated:

```
ind_calculated = which(MS_pooled_summary$Episode_Identifier %in% thetas_9MS$Episode_Identifier)
IDs_calculated = unique(MS_pooled_summary$ID[ind_calculated])
IDs_remaining = unique(MS_pooled_summary$ID[! MS_pooled_summary$ID %in% IDs_calculated])
```

We blow up the pooled analysis into all pairs within individuals:

Construct adjacency graphs and compute probabilities of relapse and reinfection.

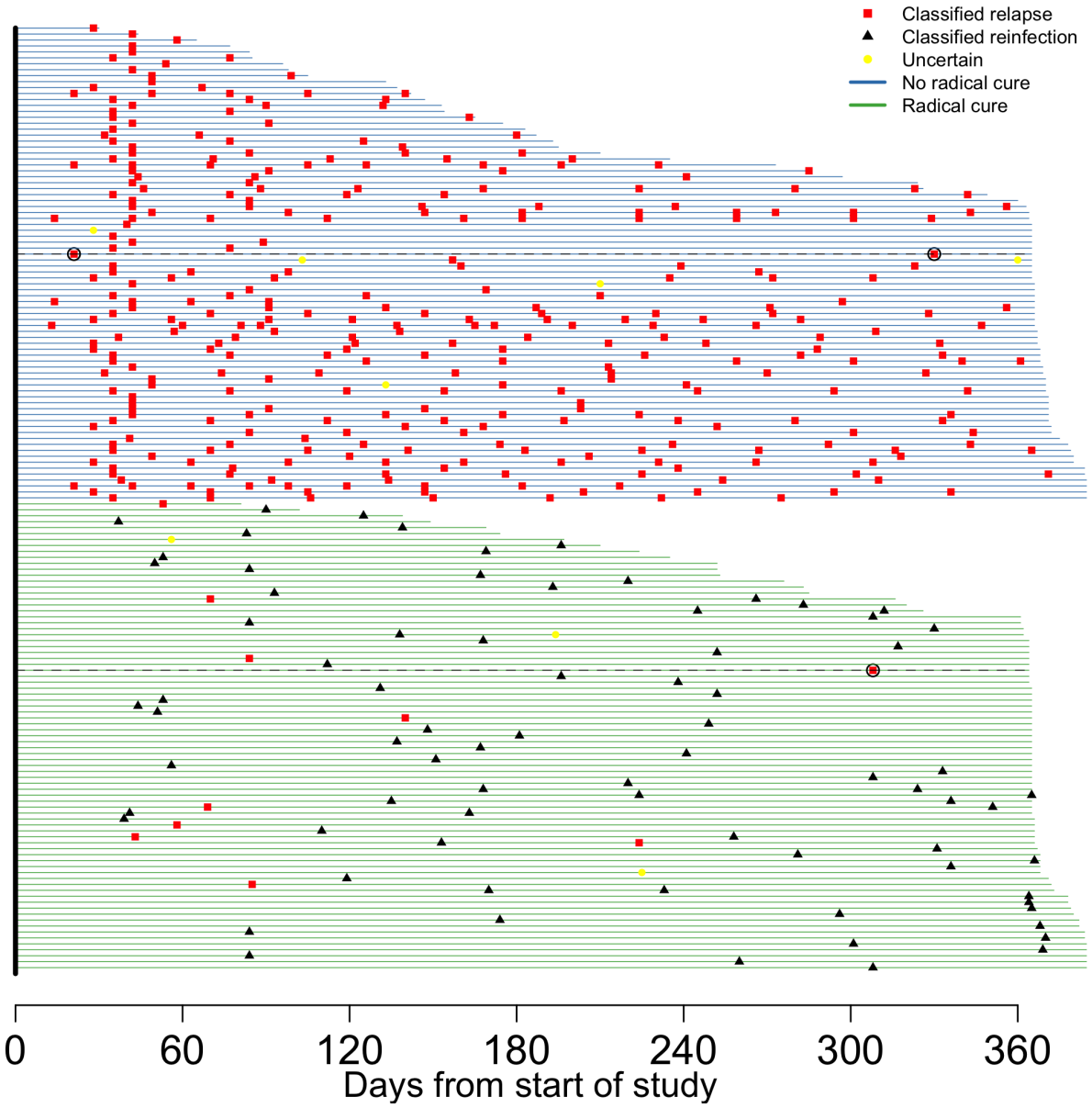
```
MS_pooled_summary$L_or_C_state = MS_pooled_summary$TotalEpisodes = NA
MS_pooled_summary$L_lower = MS_pooled_summary$L_upper = MS_pooled_summary$L_mean = NA
MS_pooled_summary$C_lower = MS_pooled_summary$C_upper = MS_pooled_summary$C_mean = NA
MS_pooled_summary$I_lower = MS_pooled_summary$I_upper = MS_pooled_summary$I_mean = NA
# Arrange by complexity
# Get single rows per episode (throw away the extra MOI information)
MS_inflated = MS_inflated[!duplicated(MS_inflated$Episode_Identifier) & MS_inflated$Episode>1,]
Res$ID_True = MS_inflated$ID_True
Res$First_EpNumber = MS_inflated$First_EpNumber
Res$Second_EpNumber = MS_inflated$Second_EpNumber


## Threshold value for classification
```

```
Epsilon = 0.5

# Iterate through the ones we can calculate in one go
episodes_full_model = unique(Thetas_full_post$Episode_Identifier)
cols_remove = grep('Episode_Identifier', colnames(Thetas_full_post))
Thetas_full_post = Thetas_full_post[, -cols_remove]
for(ep in episodes_full_model){
  ind1 = (MS_pooled_summary$Episode_Identifier==ep)
  ind2 = rownames(Thetas_full_post)==ep

  ## Summaries for relapse
  MS_pooled_summary$L_upper[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('L',colnames(Thetas_full
                                             probs=0.9)
  MS_pooled_summary$L_lower[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('L',colnames(Thetas_full
                                             probs=0.1)
  MS_pooled_summary$L_mean[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('L',colnames(Thetas_full_
                                            probs=0.5)

  ## Summaries for recrudescence
  MS_pooled_summary$C_upper[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('C',colnames(Thetas_full
                                             probs=0.9)
  MS_pooled_summary$C_lower[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('C',colnames(Thetas_full
                                             probs=0.1)
  MS_pooled_summary$C_mean[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('C',colnames(Thetas_full_
                                            probs=0.5)

  ## Summaries for reinfection
  MS_pooled_summary$I_upper[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('I',colnames(Thetas_full
                                             probs=0.9)
  MS_pooled_summary$I_lower[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('I',colnames(Thetas_full
                                             probs=0.1)
  MS_pooled_summary$I_mean[ind1] = quantile(unlist(Thetas_full_post[ind2, grep('I',colnames(Thetas_full_
                                            probs=0.5)

  # Just going to classify on relapse versus reinfection
  if(MS_pooled_summary$L_upper[ind1] < Epsilon){
    MS_pooled_summary$L_or_C_state[ind1] = 'I'
  } else if(MS_pooled_summary$L_lower[ind1] > Epsilon){
    MS_pooled_summary$L_or_C_state[ind1] = 'L'
  } else if(MS_pooled_summary$L_upper[ind1] > Epsilon & MS_pooled_summary$L_lower[ind1] < Epsilon){
    MS_pooled_summary$L_or_C_state[ind1] = 'Uncertain'
  }
}

for(i in 1:length(IDs_remaining)){
  id = IDs_remaining[i]
  Doubles_Thetas = filter(Res, ID_True==id)

  for(ep in unique(Doubles_Thetas$Second_EpNumber)){
    ind1 = which(MS_pooled_summary$ID==id & MS_pooled_summary$Episode==ep)
    ind2 = which(Doubles_Thetas$Second_EpNumber == ep)

    MS_pooled_summary$L_lower[ind1] = mean(Doubles_Thetas$L_min[ind2])
```

```
    MS_pooled_summary$L_upper[ind1] = mean(Doubles_Thetas$L_max[ind2])
    MS_pooled_summary$L_mean[ind1] = mean(Doubles_Thetas$L_mean[ind2])

    MS_pooled_summary$C_lower[ind1] = mean(Doubles_Thetas$C_min[ind2])
    MS_pooled_summary$C_upper[ind1] = mean(Doubles_Thetas$C_max[ind2])
    MS_pooled_summary$C_mean[ind1] = mean(Doubles_Thetas$C_mean[ind2])

    MS_pooled_summary$I_lower[ind1] = mean(Doubles_Thetas$I_min[ind2])
    MS_pooled_summary$I_upper[ind1] = mean(Doubles_Thetas$I_max[ind2])
    MS_pooled_summary$I_mean[ind1] = mean(Doubles_Thetas$I_mean[ind2])

    if(!is.na(MS_pooled_summary$L_upper[ind1])){
      if(MS_pooled_summary$L_upper[ind1] < MS_pooled_summary$L_lower[ind1]){
        print(id)
      }
      if(MS_pooled_summary$L_upper[ind1] < Epsilon){
        MS_pooled_summary$L_or_C_state[ind1] = 'I'
      }
      if(MS_pooled_summary$L_lower[ind1] > Epsilon){
        MS_pooled_summary$L_or_C_state[ind1] = 'L'
      }
      if(MS_pooled_summary$L_upper[ind1] > Epsilon &
         MS_pooled_summary$L_lower[ind1] < Epsilon){
        MS_pooled_summary$L_or_C_state[ind1] = 'Uncertain'
      }
    }
  }

}

MS_pooled_summary$Drug = MS_pooled_summary$FU = NA
for(id in MS_pooled_summary$ID){
  ind = MS_pooled_summary$ID==id
  MS_pooled_summary$TotalEpisodes[ind] = max(MS_pooled_summary$Episode[ind])
  MS_pooled_summary$Drug[ind] = as.numeric(
    Combined_Time_Data$arm_num[Combined_Time_Data$patientid==id][1] == 'CHQ/PMQ') + 2
  MS_pooled_summary$FU[ind] = Combined_Time_Data$FU_time[Combined_Time_Data$patientid==id][1]
}

MS_pooled_summary$Plotting_pch_Values =
  as.numeric(mapvalues(MS_pooled_summary$L_or_C_state,
                       from = c('L','Uncertain','I'), to = 15:17))
MS_pooled_summary$Plotting_col_Values =
  as.numeric(mapvalues(MS_pooled_summary$L_or_C_state,
                       from = c('L','Uncertain','I'), to = 1:3))
```

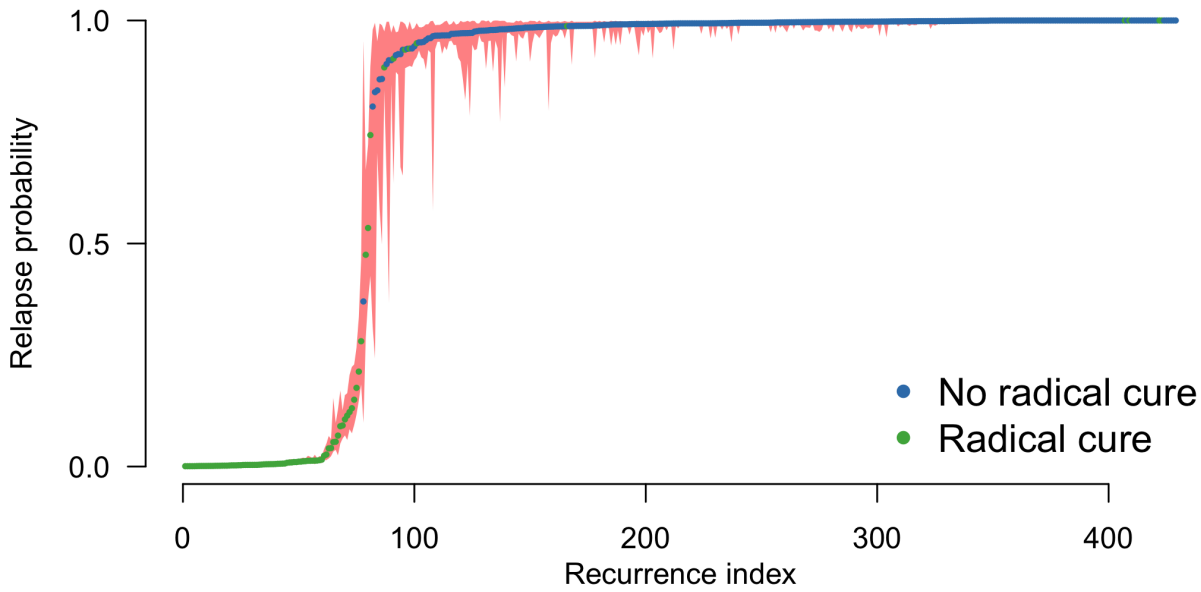
```
if(CREATE_PLOTS){
  ## Time series data colored by genetic STATE: classification
  mycols_states = c('red','yellow','black') # colors for states - need uncertain ones as well
  mycols_drugs = brewer.pal(n=3, name = 'Set1')

  # Only the recurrences for which we can compute estimates of recurrence state
  MS_final = filter(MS_pooled_summary, !is.na(L_mean))
  MS_final = arrange(MS_final, desc(Drug), desc(FU), desc(TotalEpisodes))
```

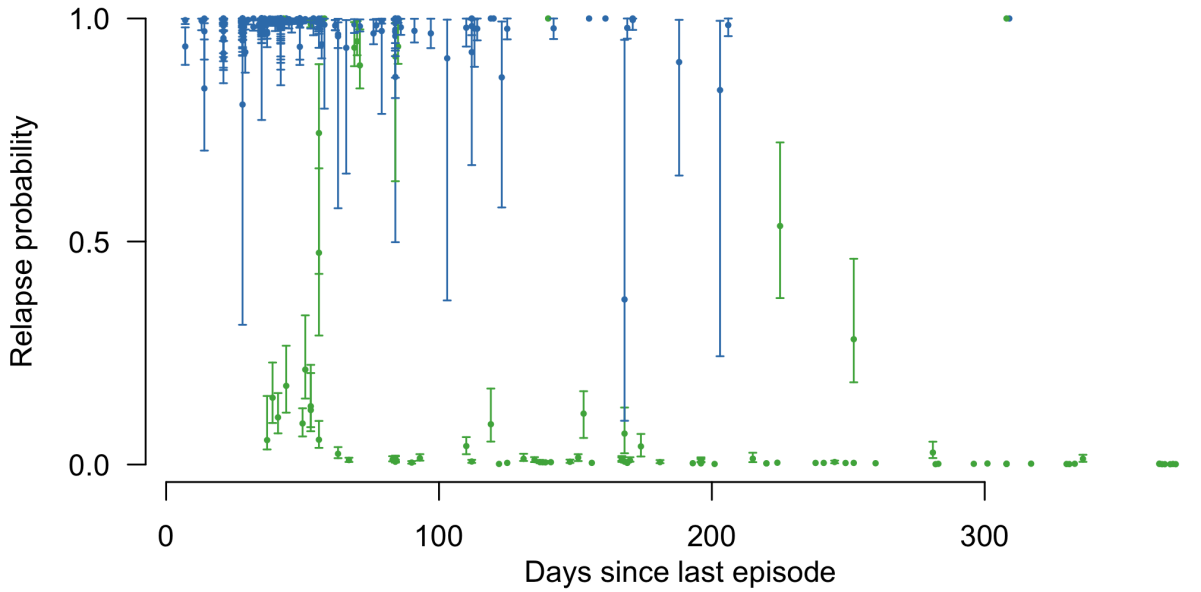
```
  ids = unique(MS_final$ID)

  par(las=1, bty='n', cex.axis=.3, mar=c(3,0,1,1))
  plot(NA, NA, xlim = c(0,370), ylim = c(1,length(ids)),
       xaxt='n', yaxt='n')
  mtext(text = 'Days from start of study', side = 1, line=2, cex=1.3)
  axis(1, at = seq(0,370, by=60), cex.axis=1.5)

  for(i in 1:length(ids)){

    id = ids[i]
    ind = which(MS_final$ID==id)

    # Add the follow up time line
    lines(c(0,MS_final$FU[ind[1]]),
          c(i,i), lty=1,
          lwd=.5, col= mycols_drugs[MS_final$Drug[ind[1]]])

    cols = mycols_states[MS_final$Plotting_col_Values[ind]]
    points(MS_final$timeSinceEnrolment[ind], rep(i,length(ind)),
           pch=MS_final$Plotting_pch_Values[ind],
           col=cols,cex=.6)

    # For highlighting long-latency
    # Add the follow up time line
    if(id == 'VHX_235' | id == 'BPD_27'){
      lines(c(0,MS_final$FU[ind[1]]),
            c(i,i), lty = 'dashed',
            lwd=.5, col= 'black')

      cols = mycols_states[MS_final$Plotting_col_Values[ind]]
      points(MS_final$timeSinceEnrolment[ind], rep(i,length(ind)),
             pch=1,
             col='black',cex=1)}

  }
  lines(x = c(0,0), y = c(0,length(ids)),lwd=3)
  # Hacky colour legend
  legend('topright', col = c('red', 'black', 'yellow',mycols_drugs[2:3]),
         pch = c(15,17,16, NA,NA), cex = 0.7, bty = 'n',
         lty = c(NA,NA,NA,1,1), lwd = c(NA,NA,NA,2,2),
         legend = c('Classified relapse', 'Classified reinfection', 'Uncertain',
                    'No radical cure', 'Radical cure'))
}
```




```
if(CREATE_PLOTS){
  par(las=1, mfcol = c(2,1), mar=c(3,4,1,1), bty='n')
  MS_final = arrange(MS_final, L_mean)
  plot(1:nrow(MS_final), MS_final$L_mean,
       col = mycols_drugs[MS_final$Drug],
       pch=20, cex=.3, yaxt='n', ylab='')
  axis(2, at = c(0,.5,1))
  polygon(c(1:nrow(MS_final), rev(1:nrow(MS_final))),
          y = c(MS_final$L_lower,
                rev(MS_final$L_upper)),
          border = NA, col = rgb(1, 0, 0,0.5))
  points(1:nrow(MS_final), MS_final$L_mean,
         col = mycols_drugs[MS_final$Drug],
         pch=20, cex=.5)
```

```
  mtext(side = 1, text = 'Recurrence index', line = 2)
  mtext(side = 2, text = 'Relapse probability', line = 3,las=3)
  legend('bottomright', col = mycols_drugs[2:3],
         pch = 20, cex = 1.3, bty = 'n',
         legend = c('No radical cure','Radical cure'))

  plot(MS_final$timeSinceLastEpisode, MS_final$L_mean,
       col = mycols_drugs[MS_final$Drug],
       pch=20, cex=.51, xlab = '',yaxt='n',
       ylab = '')
  axis(2, at = c(0,.5,1))
  for(i in 1:nrow(MS_final)){

    if(abs(MS_final$L_upper[i] - MS_final$L_lower[i]) > 0.005){
      arrows(x0 = MS_final$timeSinceLastEpisode[i],
             y0 = MS_final$L_lower[i],
             x1=MS_final$timeSinceLastEpisode[i],
             y1 = MS_final$L_upper[i],
             length = 0.02,angle = 90,
             code = 3,
             col=mycols_drugs[MS_final$Drug[i]])
    }
    i=i+1
  }
  mtext(side = 1, text = 'Days since last episode', line = 2)
  mtext(side = 2, text = 'Relapse probability', line = 3,las=3)
}
```





Individuals who appear to relapse very late (more than 300 days after last episode):

```
MS_pooled = reformat_MSdata(MS_pooled)
IDs_late_relapse = MS_final[which(MS_final$timeSinceLastEpisode>300 & MS_final$L_lower>.9),'ID']

writeLines(sprintf('The episode ids of interest are: %s',
                   MS_final[which(MS_final$timeSinceLastEpisode>300 & MS_final$L_lower>.9),
                            'Episode_Identifier']))
```

```
## The episode ids of interest are: VHX_235_3
## The episode ids of interest are: BPD_27_2
```

```
library(knitr)
#ColorPlot_MSdata(MS_data = MS_pooled[MS_pooled$ID%in%IDs_late_relapse,])

print( MS_pooled[MS_pooled$ID%in%IDs_late_relapse,])
```

```
##          ID       Date MOI_id PV.1.501 PV.3.27 PV.3.502 PV.ms1 PV.ms16
## 60   BPD_27 2012-03-28      1        3      23        7      4       9
## 61   BPD_27 2013-01-30      1        3      23        7      4       9
## 62   BPD_27 2013-01-30      2        3      24        7      4       9
## 313 VHX_235 2010-07-20      1        1       6        1      3      NA
## 314 VHX_235 2010-07-20      2        1       6        1      3      NA
## 315 VHX_235 2010-08-10      1        1       6        2      4      NA
## 316 VHX_235 2011-06-15      1        1       6        2      4      NA
##     PV.ms5 PV.ms6 PV.ms7 PV.ms8 timeSinceEnrolment timeSinceLastEpisode
## 60      11      5      2     13                  0                   NA
## 61      11      5      2     13                308                  308
## 62      11      5      2     13                308                  308
## 313      7      9     NA     12                  0                   NA
## 314      7     12     NA     32                  0                   NA
## 315      7      9     NA     12                 21                   21
## 316      6     12     NA     12                330                  309
##     Episode Episode_Identifier
## 60        1           BPD_27_1
## 61        2           BPD_27_2
## 62        2           BPD_27_2
## 313       1          VHX_235_1
## 314       1          VHX_235_1
## 315       2          VHX_235_2
## 316       3          VHX_235_3
```

The summaries of the final dataset:

```
table(MS_final$Drug[!duplicated(MS_final$ID)]) # James, this sums to 159 - surely should sum to 164? Ha
```

```
##
##  2  3
## 80 79
```

```
# Yes: gotten rid of the 5 people who don't have recurrent episodes

ind_CQ = MS_final$Drug==2
writeLines(sprintf('In chloroquine monotherapy individuals, the weighted average of relapses is %s (%s-%
                   round(100*sum(MS_final$L_mean[ind_CQ])/sum(ind_CQ),1),
                   round(100*sum(MS_final$L_lower[ind_CQ])/sum(ind_CQ),1),
                   round(100*sum(MS_final$L_upper[ind_CQ])/sum(ind_CQ),1)))
```

```
## In chloroquine monotherapy individuals, the weighted average of relapses is 98.6 (96-99.8)
```

```
writeLines(sprintf('In chloroquine monotherapy individuals, the weighted average of recrudescences is %s
                   round(100*sum(MS_final$C_mean[ind_CQ],na.rm=T)/sum(ind_CQ),1),
                   round(100*sum(MS_final$C_lower[ind_CQ],na.rm=T)/sum(ind_CQ),1),
                   round(100*sum(MS_final$C_upper[ind_CQ],na.rm=T)/sum(ind_CQ),1)))
```

```
## In chloroquine monotherapy individuals, the weighted average of recrudescences is 0.7 (0.2-1.1)
```

```
writeLines(sprintf('In chloroquine monotherapy individuals, the weighted average of reinfections is %s
                   round(100*sum(MS_final$I_mean[ind_CQ],na.rm=T)/sum(ind_CQ),1),
                   round(100*sum(MS_final$I_lower[ind_CQ],na.rm=T)/sum(ind_CQ),1),
                   round(100*sum(MS_final$I_upper[ind_CQ],na.rm=T)/sum(ind_CQ),1)))
```

```
## In chloroquine monotherapy individuals, the weighted average of reinfections is 0.7 (0-2.9)
```

```
ind_PMQ = MS_final$Drug==3
writeLines(sprintf('In chloroquine+primaquine individuals, the weighted average of relapses is %s (%s-%s
                   round(100*sum(MS_final$L_mean[ind_PMQ])/sum(ind_PMQ),1),
                   round(100*sum(MS_final$L_lower[ind_PMQ])/sum(ind_PMQ),1),
                   round(100*sum(MS_final$L_upper[ind_PMQ])/sum(ind_PMQ),1)))
```

```
## In chloroquine+primaquine individuals, the weighted average of relapses is 15 (12.8-17.4)
```

```
writeLines(sprintf('In chloroquine+primaquine individuals, the weighted average of recrudescences is %s
                   round(100*sum(MS_final$C_mean[ind_PMQ],na.rm=T)/sum(ind_PMQ),1),
                   round(100*sum(MS_final$C_lower[ind_PMQ],na.rm=T)/sum(ind_PMQ),1),
                   round(100*sum(MS_final$C_upper[ind_PMQ],na.rm=T)/sum(ind_PMQ),1)))
```

```
## In chloroquine+primaquine individuals, the weighted average of recrudescences is 0.3 (0-0.5)
```

```
writeLines(sprintf('In chloroquine+primaquine individuals, the weighted average of reinfections is %s (
                   round(100*sum(MS_final$I_mean[ind_PMQ],na.rm=T)/sum(ind_PMQ),1),
                   round(100*sum(MS_final$I_lower[ind_PMQ],na.rm=T)/sum(ind_PMQ),1),
                   round(100*sum(MS_final$I_upper[ind_PMQ],na.rm=T)/sum(ind_PMQ),1)))
```

```
## In chloroquine+primaquine individuals, the weighted average of reinfections is 84.7 (82.5-86.7)
```

False positive rate of relapse

We want to know how often our model estimates evidence of relapse across pairs of episodes when the episodes are in different people (e.g.)

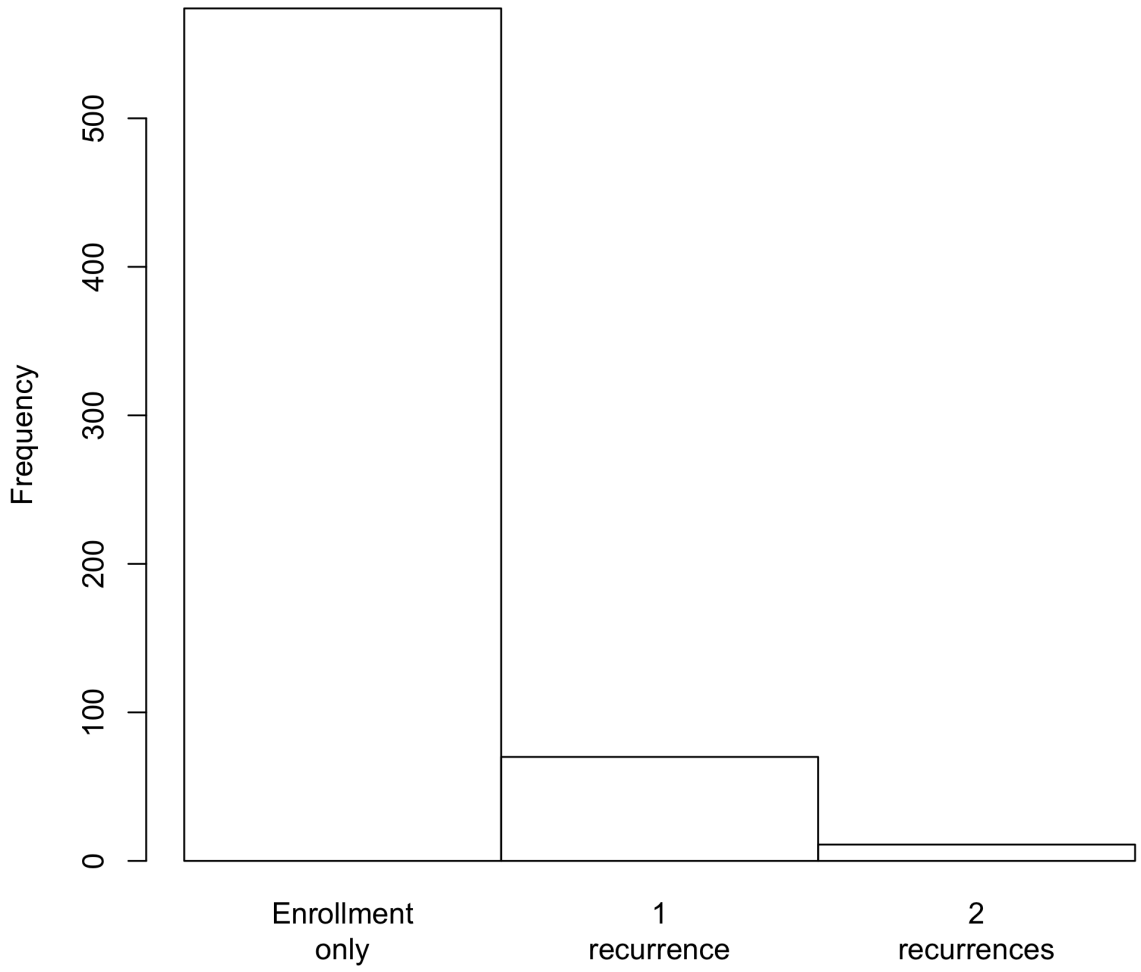
```
if(RUN_MODELS_CLUSTER_INFLATED){
  # The pooled MS data from BPD and VHX
  load('../RData/GeneticModel/MS_data_PooledAnalysis.RData')
  tic()
  APC_MS_data = Make_All_Pairwise_Comparisons(MS_data = MS_pooled, ncores=42)
  save(APC_MS_data, file = 'APC_MS_data.bigRData')
  toc()
  Inflated_Results = post_prob_CLI(MS_data = APC_MS_data,
                                   Fs = Fs_Combined,
                                   UpperComplexity = 10^6,
                                   verbose = F,
                                   cores = 42)
  save(Inflated_Results, file = 'Inflated_Results.bigRData')

} else {
  # load('Inflated_Results.bigRData')
  # load('APC_MS_data.bigRData')
}
```

```
## NULL
```

Analysis of radical cure efficacy in BPD

Almost all episodes in BPD were typed. Therefore we can estimate the true efficacy comparing with historical controls (VHX).

```
BPD_data = Combined_Time_Data[grep('BPD', Combined_Time_Data$patientid),]
hist(table(BPD_data$patientid),breaks = seq(0.5,3.5,by=1),main='',
     xlab = '', xaxt='n')
axis(1, at = 1:3, labels = c('Enrollment\nonly','1\nrecurrence','2\nrecurrences'),
     tick = FALSE)
```




```
BPD_data$Episode_Identifier = apply(BPD_data,1,
                                    function(x){
  paste(x['patientid'],x['episode'],sep='_')} )

# iterate over recurrences and use either the joint posterior or if missing the time probability
BPD_data$Reinfection_Probability=
  BPD_data$Reinfection_Probability_LL=
  BPD_data$Reinfection_Probability_UL = NA
```

```
ind_recurrences = which(BPD_data$episode>1)
sss=0
for(i in ind_recurrences){
  ep_id = BPD_data$Episode_Identifier[i]
  if(ep_id %in% MS_final$Episode_Identifier){
    BPD_data$Reinfection_Probability[i] =
      MS_final$I_mean[MS_final$Episode_Identifier==ep_id]
    BPD_data$Reinfection_Probability_UL[i] =
      MS_final$I_upper[MS_final$Episode_Identifier==ep_id]
    BPD_data$Reinfection_Probability_LL[i] =
      MS_final$I_lower[MS_final$Episode_Identifier==ep_id]
  } else {
    BPD_data$Reinfection_Probability[i] =
      Mod3_ThetaEstimates$ReInfection_mean_theta[Mod3_ThetaEstimates$Episode_Identifier==ep_id]
    BPD_data$Reinfection_Probability_UL[i] =
      Mod3_ThetaEstimates$ReInfection_975_theta[Mod3_ThetaEstimates$Episode_Identifier==ep_id]
    BPD_data$Reinfection_Probability_LL[i] =
      Mod3_ThetaEstimates$ReInfection_025_theta[Mod3_ThetaEstimates$Episode_Identifier==ep_id]
    sss=sss+1
  }
}
```

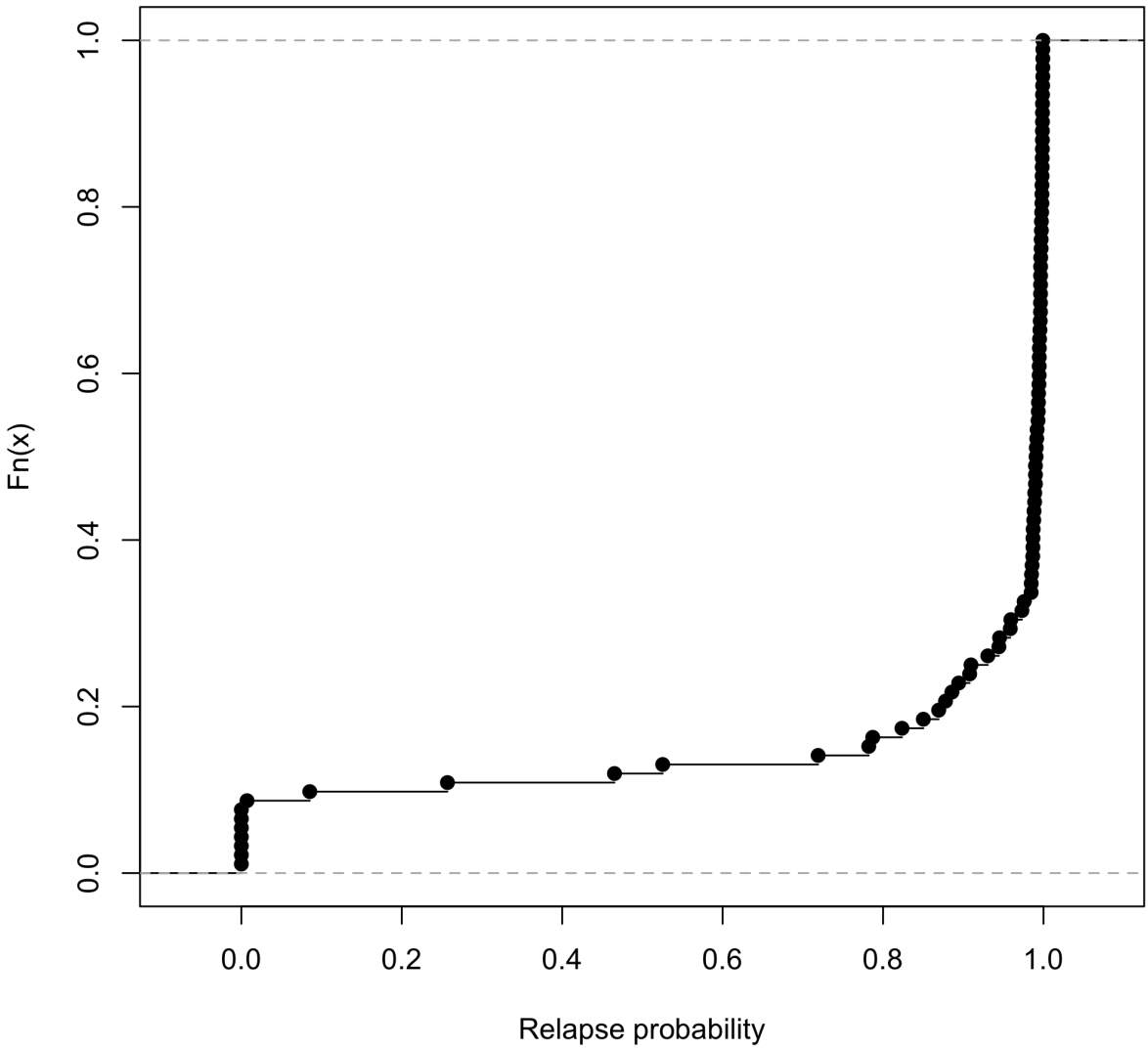
```
writeLines(sprintf('%s recurrences did not have MS data to inform posterior probability',sss))
```

```
## 5 recurrences did not have MS data to inform posterior probability
```

```
writeLines(sprintf('Number of recurrences without posterior probability assigned: %s',
                   sum(is.na(BPD_data$Reinfection_Probability[ind_recurrences]))))
```

```
## Number of recurrences without posterior probability assigned: 0
```

```
plot(ecdf(BPD_data$Reinfection_Probability), main='', xlab='Relapse probability')
```




```
# now we calculate the primaquine failure rate
# For individuals with multiple episodes this is P(Rec 1 not L)*P(Rec 2 not L)
N = length(unique(BPD_data$patientid))
N_recurring = 0
P_Not_Failure = P_Not_Failure_LL = P_Not_Failure_UL = 0
for(id in unique(BPD_data$patientid)){
  ind = which(BPD_data$patientid==id)
  if(length(ind)>1){
    N_recurring = N_recurring + 1
    P_Not_Failure = P_Not_Failure + prod(BPD_data$Reinfection_Probability[ind[-1]])
    P_Not_Failure_LL = P_Not_Failure_LL +
      prod(BPD_data$Reinfection_Probability_LL[ind[-1]])
    P_Not_Failure_UL = P_Not_Failure_UL +
      prod(BPD_data$Reinfection_Probability_UL[ind[-1]])
```

```
  }
}
P_Failure = (N_recurring-P_Not_Failure)/N
# invert the intervals here - optimistic for not failure = pessimistic for failure
P_Failure_UL = (N_recurring-P_Not_Failure_LL)/N
P_Failure_LL = (N_recurring-P_Not_Failure_UL)/N

writeLines(sprintf('The primaquine failure rate in the %s individuals is %s%% (%s-%s) over the course o
                   N, round(100*P_Failure,2),
                   round(100*P_Failure_LL,2),
                   round(100*P_Failure_UL,2), round(sum(BPD_data$FU_time[!duplicated(BPD_data$patientid)]
```

```
## The primaquine failure rate in the 655 individuals is 1.97% (1.69-2.28) over the course of 522 years
```

Now we look at whether the PK (carboxy-primaquine) can predict failure:

```
BPD_data = arrange(BPD_data, patientid, episode)
load('../RData/PK_data/BPD_pk.RData')
BPD_pk = filter(BPD_pk, !is.na(Episode))
BPD_data$log10_carboxyPMQ = NA
BPD_data$log10_PMQ = NA
BPD_data$Failure = NA
for(i in 1:nrow(BPD_data)){
  id = BPD_data$patientid[i]
  ep_i = BPD_data$episode[i]
  all_id_eps = BPD_data$episode[BPD_data$patientid==id]
  pk_ind = BPD_pk$ID == id & BPD_pk$Episode==ep_i
  if(sum(pk_ind)>0){
    BPD_data$log10_carboxyPMQ[i] = mean(BPD_pk$log10_carboxyPQ_PK[pk_ind])
    BPD_data$log10_PMQ[i] = mean(BPD_pk$log10_PQ_PK[pk_ind])
  }
  if(ep_i < max(all_id_eps)) { # observed recurrence
    BPD_data$Failure[i] = 1-BPD_data$Reinfection_Probability[BPD_data$patientid==id & BPD_data$episode==
  } else {
    # Going to put the estimates of failure from time to event model
    # this will take into account censoring
    #ind = which(Mod3_ThetaEstimates$patientid==id & Mod3_ThetaEstimates$episode==ep_i)
    BPD_data$Failure[i] = 0#1 - Mod3_ThetaEstimates$ReInfection_mean_theta[ind]
  }
}
```

```
require(lme4)
```

```
## Loading required package: lme4
```

```
## Warning: package 'lme4' was built under R version 3.4.4
```

```
# add a random effect term for patient ID
mod = lmer(Failure ~ log10_carboxyPMQ + log10_PMQ + (1 | patientid), data = BPD_data)
summary(mod)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: Failure ~ log10_carboxyPMQ + log10_PMQ + (1 | patientid)
##    Data: BPD_data
##
## REML criterion at convergence: -1038.8
##
```

```
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -1.3384 -0.2130 -0.1237 -0.0450  8.8369
##
## Random effects:
##  Groups    Name        Variance  Std.Dev.
##  patientid (Intercept) 8.802e-19 9.382e-10
##  Residual              1.348e-02 1.161e-01
## Number of obs: 721, groups:  patientid, 639
##
## Fixed effects:
##                  Estimate Std. Error t value
## (Intercept)       0.21771    0.04490   4.849
## log10_carboxyPMQ -0.08410    0.01904  -4.418
## log10_PMQ         0.04494    0.01396   3.219
##
## Correlation of Fixed Effects:
##             (Intr) lg10_cPMQ
## lg10_crbPMQ -0.986
## log10_PMQ    0.729 -0.820
```

So there is a predictive effect of carboxy primaquine on drug failure. This also suggests that higher concentrations of primaquine are associated with more chance of failure. This also came up in the time to event analysis in the BPD paper but wasn't significant.

This could actually make sense: higher concentrations of primaquine could mean that it's hasn't been effectively metabolised. Higher concentrations of carboxy indicating it has been effectively metabolised (active pathway is unknown).

```
BPD_data = filter(BPD_data, episode==1)
BPD_data$Failure_YN = as.numeric(BPD_data$Failure > 0.5)
mod1 = glm(Failure_YN ~ log10_carboxyPMQ, data = BPD_data, family='binomial')
summary(mod1)
```

```
##
## Call:
## glm(formula = Failure_YN ~ log10_carboxyPMQ, family = "binomial",
##     data = BPD_data)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -0.4363  -0.1924  -0.1622  -0.1341   3.2343
##
## Coefficients:
##                  Estimate Std. Error z value Pr(>|z|)
## (Intercept)       -0.2348     1.8708  -0.125   0.9001
## log10_carboxyPMQ  -1.4376     0.7099  -2.025   0.0429 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 102.926  on 636  degrees of freedom
## Residual deviance:  99.309  on 635  degrees of freedom
##   (18 observations deleted due to missingness)
## AIC: 103.31
```

```
##
## Number of Fisher Scoring iterations: 7
```

```
plot(BPD_data$log10_carboxyPMQ, BPD_data$Failure_YN,
     xlab = 'Carboxy PMQ', ylab = 'PMQ', pch=20)
xs=seq(0,4,by=.01)
lines(xs, predict(mod1, newdata = data.frame(log10_carboxyPMQ=xs),
                  type = 'response'), col='red', lwd=3)
```