Global Biometrics and Data Sciences

Modulation of Dynamic Borrowing from Historical Control by Fine-Tuning the Parameters of Prior Distribution for Inter-Trial Variance

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Introduction

In order to save sample size and increase statistical power, the current control is augmented by borrowing historical control data in a Bayesian framework (BAC: Bayesian Augmented Control Design):

- Augment the current control data by fixed informative prior
  (caveat: discordance b/w current control and historical data lowers the power or inflates the type I error)

- Bayesian hierarchical model that borrows historical information dynamically based on the concordance b/w the current and historical control
  (Strength: more alike, more borrowing
  caveat: difficulty to properly estimate inter-trial variance when the # of historical trials are small)

Bayesian Hierarchical Model in Survival Analysis:

- Assuming an exponential likelihood model:

$$\lambda_{Ti} = \lambda_C \, e^{\sum_{j=0}^{n} \theta_j I_{ij}}$$

  where:
  - λ_{Ti} is hazard rate of the treatment arm for i^{th} patient;
  - λ_C is hazard rate of the control arm with minimally informative prior distribution;
  - Θ is the log hazard ratio (HR) between the current treatment arm and the historical or current control;
  - I is indicator variable for the historical trials or the current trial
  - j is the index number of the current and historical trials. j=0 for the current trial
- The prior distribution for the current and historical log HR:

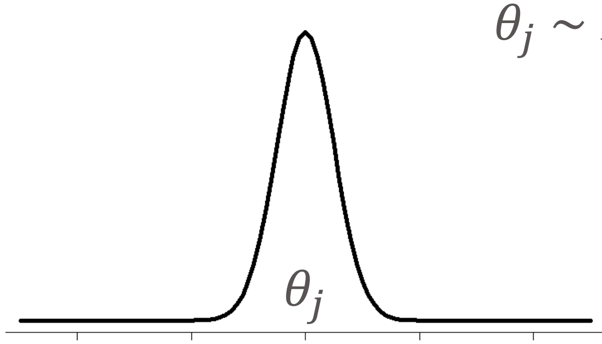
$$\theta_j \sim N\,(\mu_\gamma, \tau^2)$$

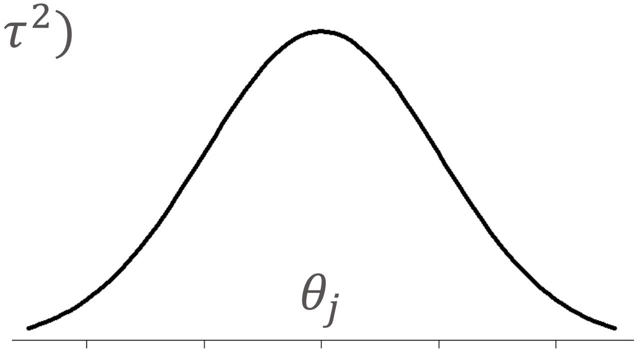
- The mean and variance for log HR form hyperparameters

$$\mu_\gamma \sim N\,(0,1);\ \tau^2 \sim IG(\alpha, \beta)$$

The Amount Dynamic Borrowing is Controlled by the Variance of log HR of Historical Trials

$$\theta_j \sim N\,(\mu_\gamma, \tau^2)$$





Small inter-trial variance τ^2 indicates consistency among historical trials thus favor strong borrowing/pooling

Large inter-trial τ^2 variance indicates discordance among historical trials thus prefer less borrowing/separate analysis

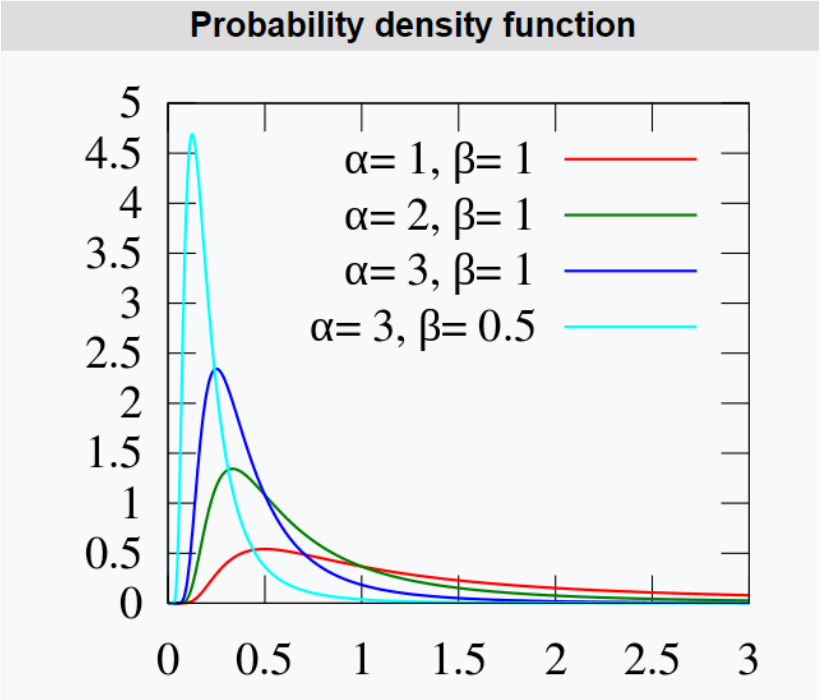
Parameterization of Inverse Gamma Distribution for the hyperparameter τ^2 as the Prior Distribution

$$f(x|\alpha,\beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}(\alpha-1)!}$$

In Bayesian software such as FACTs alpha and beta are re-parameterized to:

Central value (approximate): $\mu = \sqrt{\beta/\alpha}$
(mean doesn't exist if alpha < 1)

Weight: $n = 2\alpha$



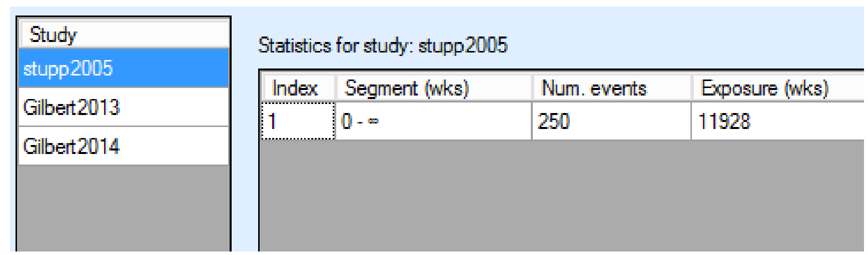
In general, large central value and small weight favor non-borrowing

Historical Control Data (Glioblastoma Multiforme Study)

	N	mPFS (months)
Stupp 2005		
All comers	287	6.9
Gilbert 2013		
All comers	411	7.5
Gilbert 2014		
All comers	317	7.3

weighted mean mPFS ≈ event rate = 0.023/week

Sufficient Statistics used in hierarchical Modeling: # of Events and Exposure time



Simulation of the current control (as demo)

N = 80, 2:1 randomization ratio favoring treatment, median PFS ranging from 6 -12m, HR = 1 or 0.6, 10 pts/month accrual, follow-up time = 6 m, 1000 – 5000 simulated trials

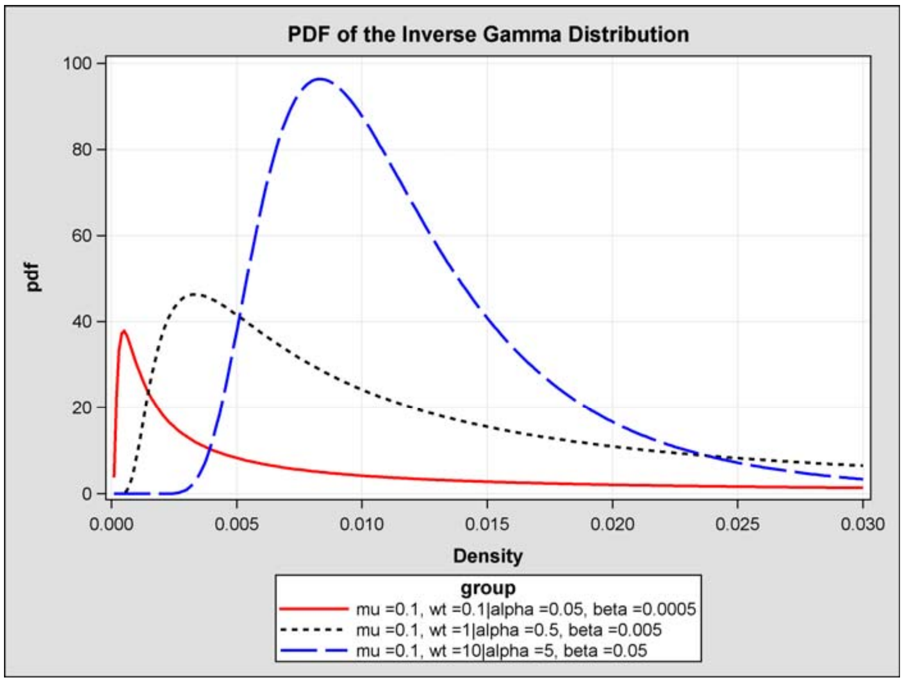
Achieving Desired Dynamic Borrowing by Specifying the Prior Distribution of Hyperparameter τ^2

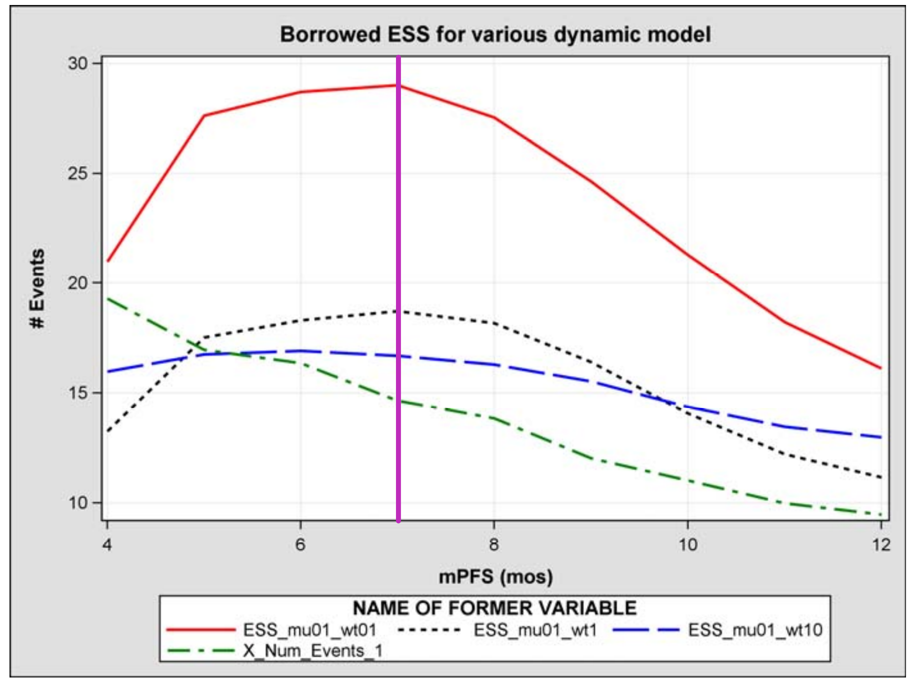
- Quantification of Amount of Borrowing:

$$E_{borrowed} = E_C\left(\frac{\sigma^2(log\lambda_c| - \ borrowing)}{\sigma^2(log\lambda_c| + borrowing)} - 1\right)$$

- Use the weakly informative prior with large central value (10) and small weight (0.1) to generate minimal model lacking borrowing as baseline;
- For each simulated trial, log HR can be estimated from posterior distributions based on models with and without borrowing using the formular above;
- The variance of log HR is calculated from 1000 simulated trial datasets;
- The estimated # of borrowed events is plotted against the difference between the hazard rates of the current and historical trials.

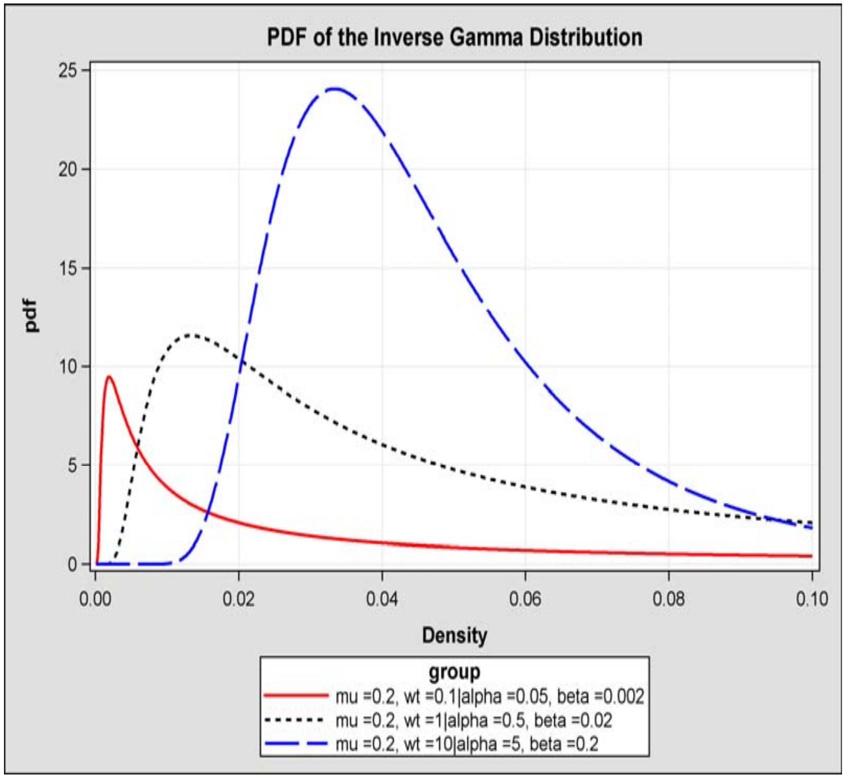
With small central value (0.1) , lowering the weight (10 -> 1 -> 0.1) for the prior render the model more responsive to the discordance b/w current and historical data

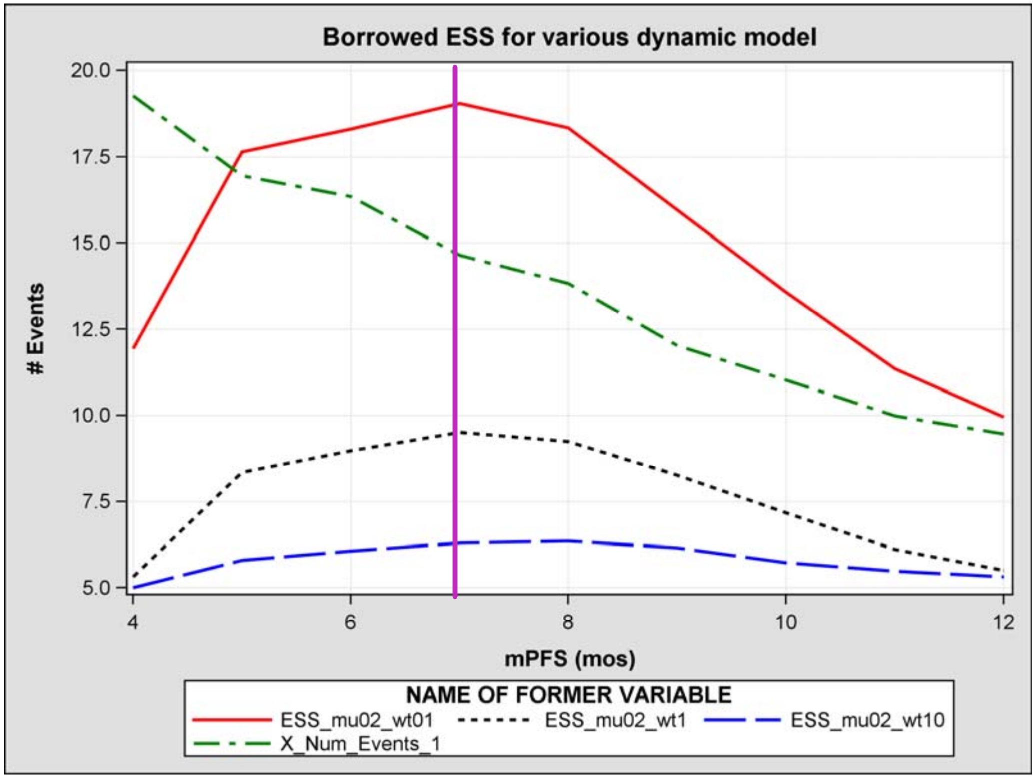




# of Events from current control — Historical control

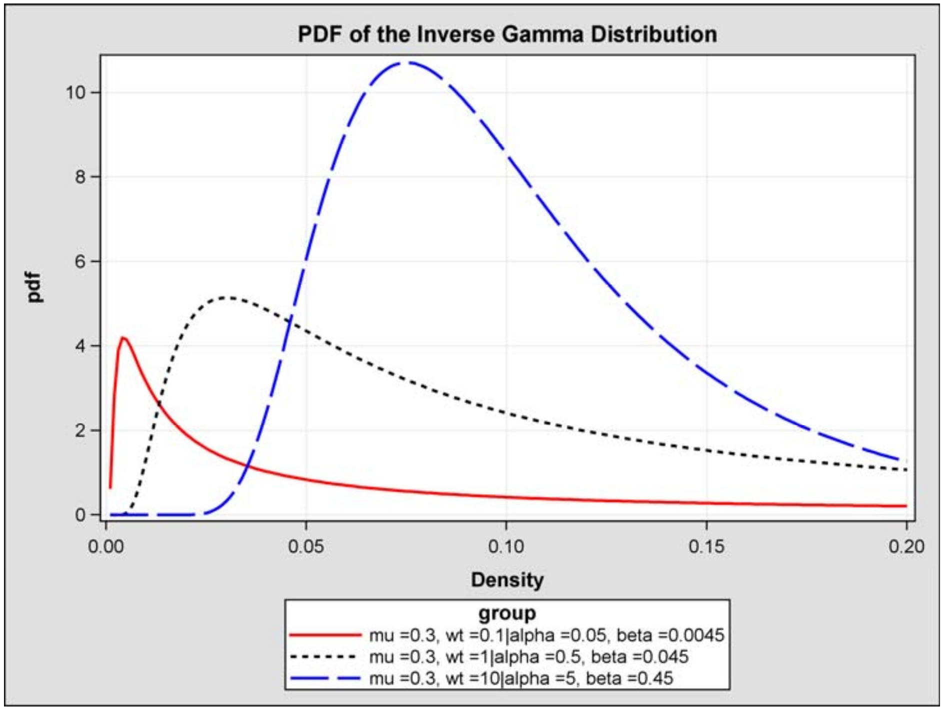
Central value = 0.2, weight = 10 -> 1 -> 0.1

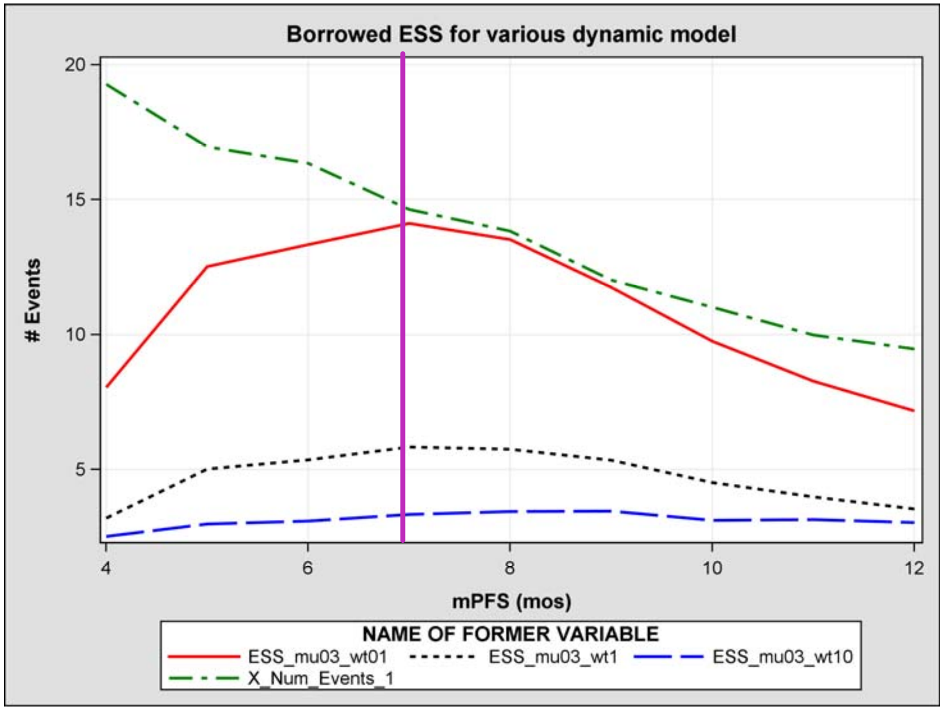




# of Events from current control
Historical control

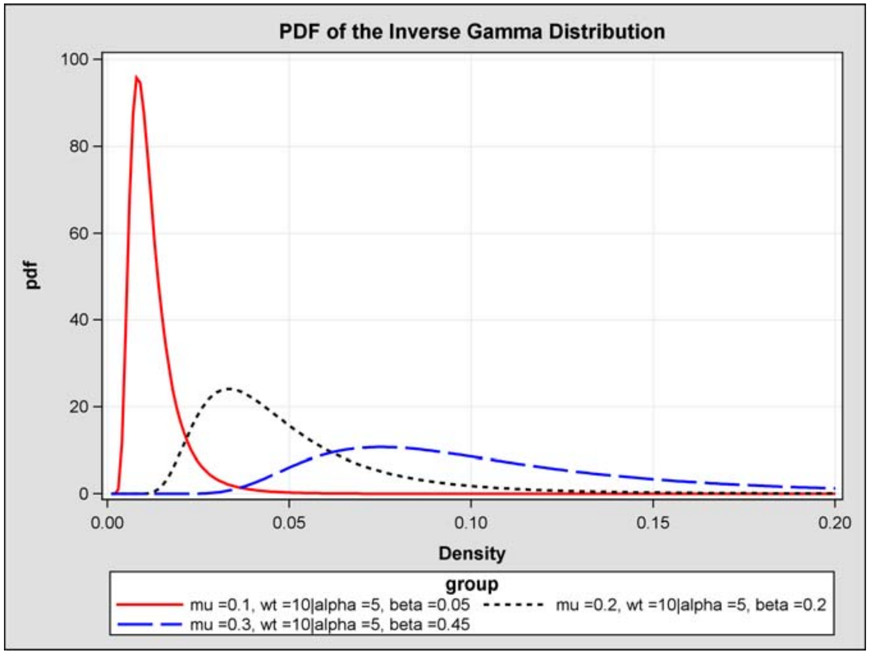
Central value = 0.3, weight = 0.1 -> 1 -> 10

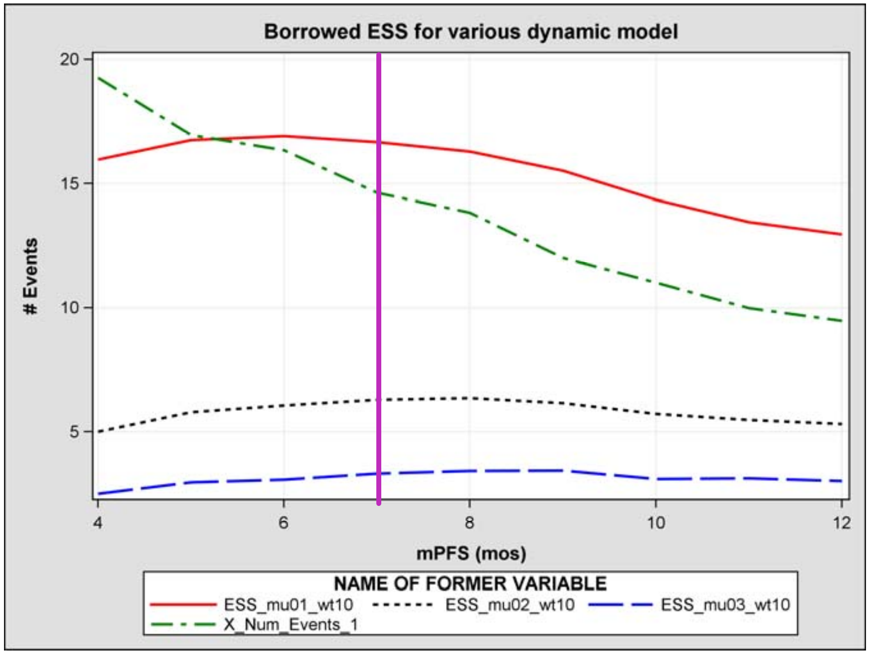




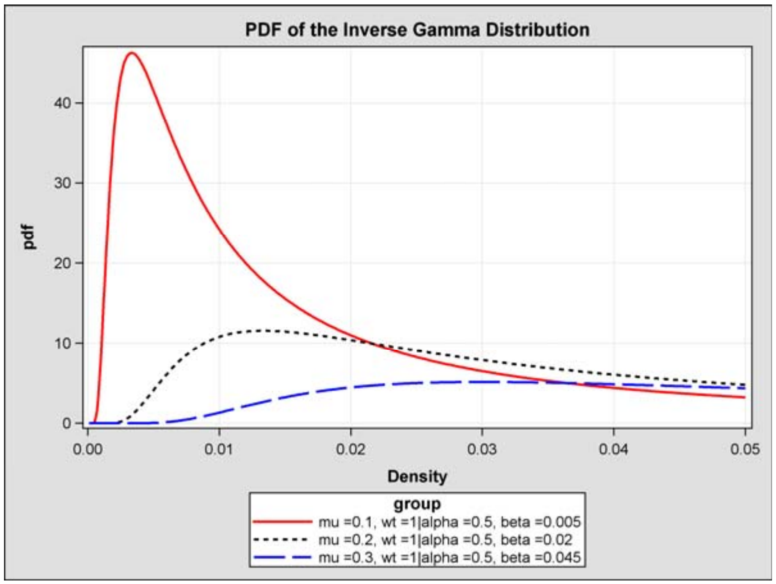
# of Events from current control — Historical control

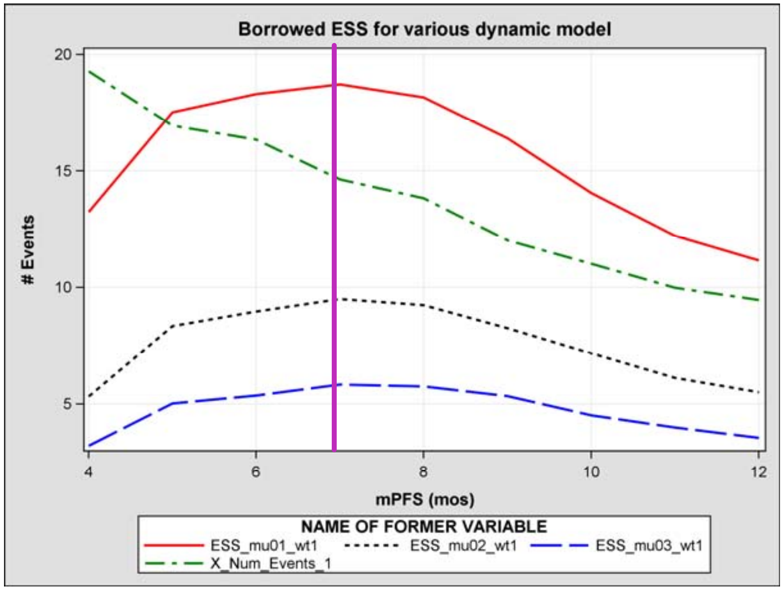
From another angel: lowering the central value increases the absolute amount of borrowing after large weight flattens the curve





# of Events from current control — Historical control





# of Events from current control

Historical control

Conclusion

For the inverse Gamma distribution as hyperparameter prior in BAC:

- With the same weight, smaller central value leads to more aggressive borrowing
- With the same central values, more dispersed distribution (large weight) render the model less sensitive to the discordance b/w the current and historical data

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Reference:

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