Phase-Specific Parameter Correlation in Hierarchical Changepoint Model for Prostate Specific Antigen Level

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Introduction

Prostate cancer is the most common cancer in men in the United States [1]. Serial PSA measurements from a clinical trial where patients had received anti-androgen or Liarozole treatment revealed distinct response patterns (Fig. 1). For many of them, there is a decline phase of PSA level immediately after the treatment, followed by another growth phase possibly due to recurrence. Researchers have used Piecewise Linear Model (PWL) with a random changepoint to fit the PSA level over time. However, in our data, it could be observed that not all patients have responded to the therapy. For these patients, their PSA level increases right after the therapy. In literature [2], Bayesian Mixture PWL model has been used to explicitly model PSA patterns of responders and non-responders to account for this problem.

Nevertheless, there had not been a study focusing on the dependency between parameters that characterize the PSA change rate over different phases, as well as their correlation with the latent changepoint. For instance, it is possible that a responder will generally experience a less progressive recurrence, if the treatment had successfully postponed the phase-change point. We reasoned that a fully structured covariance matrix could improve the PSA modeling under the Mixture PWL framework, and of great importance to gain insights about the disease progression mechanism.

Models and Methods

$$\Omega_{\beta} = diag(\tau_{\beta,k}),\ 1 \leq k \leq 4$$

Data Analysis

Our dataset contains records from two multicenter trials for 485 patients with advanced (metastatic) prostate cancer, having received either anti-androgen or Liarozole, an experimental drug as treatment. Serial PSA measurements were recorded monthly for 6 months, and at a

3-month interval until treatment discontinuation or death. The number of PSA measurements per subject ranges from 2 to 19. We excluded individuals that have less or equal to 3 measurements to ensure model identifiability. Records of 445 patients were included in our model fitting step, among them 232 received anti-androgen therapy and 213 received liarozole therapy.

Convergence

First, we use Gelman-Rubin diagnosis to check the convergence of our models. In all the cases, we run 5 to 10 chains, with 10,000 iterations, burned in the first 1,000 iterations, and thinned each chain 100 times. Gelman-Rubin diagnostic factors for parameters are included in table 1. For most parameters, convergence was achieved. Trace plot, auto-correlation and posterior distribution plots are shown for some randomly picked parameters (figure 2.).

Parameter Estimates

To assess how well our models describe individual trajectories, we plot the fitted PSA level from model 1 for randomly picked responders and non-responders, and compared them with the observed values (figure 3.). As we can see from the figure, for most individuals, the expected value describes the trajectories fairly well. For patients whose PSA level immediately declined after treatment, the model correctly assigned a changepoint to distinguish the responding-phase and recurrence-phase, with each piece closely modeled by two linear curves.

By comparing the posterior mean of mixture rate (p_1, p_2) for the two treatments from model 1 (table 2.), we conclude that the experimental drug, Liarozole, displayed overall better performance in this clinical trial comparing to conventional anti-androgen therapy. However, if we compare the DIC number of Model 1 and Model 2, there is no apparent improvement by assigning two mixture ratio to distinguish these two treatments.

Sensitivity Analysis and Goodness of Fit

To investigate how the prior distribution affect our parameter estimation, we performed sensitivity analysis by comparing results from model 3 and 4. The main purpose to compare these 2 models is to understand whether a specified correlation structure could impact our outcome. For example, in model 3, we use uninformative Wishart prior to catch any potential correlations between a_i, b_i, r_i, s_i; in model 4, all the parameters was assumed to be

independent. By comparing the DIC's for model 3 and model 4 (table 2.), we found that uninformative one (model 3) fitted the data much better. In addition, we also found that the response rate resulting from these two models are quite different. Since there was a mixing issue with p in model 3, we reasoned that the posterior mean may not truly reflect the rate. However, the conclusion we had for treatment performance is reversed in model 4, suggesting the mixture PWL model is sensitive to prior correlation specification.

Discussion

One of the main interests of our study is to learn about the nature of dependency between phase-specific parameters. We found that for patients with changepoints, the time lapse from the treatment to the changepoint is negatively correlated with the rate at which the PSA increases after the changepoint. This shows that the longer the treatments holds the PSA from increasing, the slower it will increase after the changepoint. The negative correlation is supported by the results from both Model 2 and Model 3. Notice that the magnitude of the correlation coefficient differs. This is due to the different paramizations in the two models.

Moreover, by allowing correlation between the regression coefficients, we make the convergence of MCMC much faster. Notice that the Gelman-Rubin diagnostic factors for μ_β in Model 3 are round 1.01, but those in Model 4 can be as large as 24. This can be due to the fact that in Model 4, the MCMC is trying to fit the data into a model that does not match its pattern well. Thus the inclusion of the correlation coefficients is important to the analysis.

References

[1] Prostate Cancer Foundation. https://www.pcf.org/c/prostate-cancer-risk-factors/

[2] Zhao, L., Feng, D., Neelon, B., & Buyse, M. (2015). Evaluation of treatment efficacy using a Bayesian mixture piecewise linear model of longitudinal biomarkers. *Statistics in medicine*, *34*(10), 1733-1746.

Acknowledgement

We would like to thank Dr. Lili Zhao for sharing the PSA dataset and providing many constructive suggestions for our project.

Appendix

Table 1.a Gelman Diagnostic for Model 1

a.0	**a.1**	**b.1**	**b.0**	**b.2**	**r**	**b.2.star.tausq**
1.000324017	1.011847273	2.153092334	1.010261195	1.002548544	1.003895557	1.221544
1.00068814	1.005711736	2.485265441	1.065085109	1.507736975	1.001576655	**deviance**
2.306557056	3.040376511	0.999439075	1.298832797	2.006440949	1.034988425	1.000692
1.000625735	3.987407596	1.000751058	1.017505863	2.328149748	1.327727382	**r.star.tausq**
0.999376855	2.418704722	0.999531012	1.046008927	1.596669761	1.037621452	1.029262
1.000920964	1.003503855	2.652629887	1.013962801	1.112272735	1.007484437	**rho**
1.000298089	2.496483059	2.658031351	1.13435747	3.045179336	1.007371277	1.137484
3.601988633	4.590681536	1.661481998	1.008638428	1.668699899	1.028986463	**tausq**
1.000689301	1.011480163	1.000014422	1.075961875	2.536790287	1.005009182	1.027772
1.00147017	0.999839921	1.000620352	1.0224147	1.011890238	1.002683422	

Table 1.b Gelman Diagnostic for Model 2

a.one	**a.two**	**ber.one**	**ber.two**	**byi.two**	**r**	**ber.two.star.tausq**
1.754870382	1.000057885	0.999997566	1.081727934	1.004562427	1.002440244	1.160533
1.000674254	1.389064885	1.714593511	1.045680208	3.391852634	1.008157484	**deviance**
1.000436387	1.000109498	2.605692477	1.10654457	1.349082788	1.006414729	0.9999349
1.870130835	0.999771751	1.000205558	1.016164039	1.995359107	1.003059442	**p_pool**[1]
1.57336919	1.001719152	1.001157797	1.058539768	1.000257602	1.011182242	1.000029
2.279886602	1.000575445	2.576660997	1.006730272	1.019381119	1.013409296	**p_pool**[2]
1.609046875	1.000287977	1.930625744	1.00317623	1.005058337	1.002566396	1.003924
2.21301201	1.201833544	3.378549669	1.055860318	1.142143832	1.006185936	**r.star.tausq**
1.000680782	2.073658044	1.000459453	1.016195933	1.94237274	1.01117393	1.006011
1.000247335	1.799769034	1.978922268	1.002212458	1.181574489	1.025873669	**rho**
						1.097704
						tausq
						1.005889

Table 1.c Gelman Diagnostic for Model 3

a	**b**	**r**	**s**	**deviance**	
1.003617	1.001963	1.131975	1.363718	1.013005	
1.015191	1.003729	1.352512	1.051070	**beta.mu_1,1**	**beta.Omega_1,1,1**
1.004655	1.004102	1.135817	1.039950	1.017167	1.001979
1.000760	1.001251	1.220538	1.029860	**beta.mu_1,2**	**beta.Omega_1,1,2**
1.000103	1.001074	1.445860	1.179687	1.015435	1.010525
1.000815	1.005542	1.471766	1.373577	**beta.mu_2,1**	**beta.Omega_2,1,1**
1.003688	1.003149	1.337637	1.156702	1.132645	1.044742
1.001107	1.021771	1.317454	1.075707	**beta.mu_2,2**	**beta.Omega_2,1,2**
1.002476	1.001141	1.226072	1.018427	1.242923	1.021865
1.003258	1.003078	1.003227	1.006765		

Table 1.d Gelman Diagnostic for Model 4

a	**b**	**r**	**s**	**deviance**
1.569906	1.746812	1.830074	1.306848	1.013005
3.278830	2.059152	3.247705	2.317583	**beta.mu_1,1**
1.125130	1.129070	1.459096	1.469888	24.945875
1.267593	1.304584	1.733108	1.310020	**beta.mu_1,2**
1.106597	1.139923	1.295059	1.402312	21.866143
1.429279	1.267082	1.515720	1.369462	**beta.mu_2,1**
2.095386	1.096359	1.102537	1.225703	1.540424
3.623610	3.470900	2.337991	2.175793	**beta.mu_2,2**
3.587641	1.101676	1.431307	4.010727	4.892831
1.388727	1.185632	1.687516	1.462470	

Table 2. Parameter Estimates from Models

Model 1		**Model 2**		**Model 3**		**Model 4**	
p1	5.468872e-01	p		p	0.018657	p1	0.6047893
p2	6.488753e-01	rho	-0.06801359	$\Sigma_{1,1}$	3.3233352	p2	0.5758543
rho	-0.2039	DIC	-124,162	$\Sigma_{1,2}$	-0.2310581	DIC	15,4795
DIC	-124,113			$\Sigma_{1,3}$	-0.4414663		
				$\Sigma_{1,4}$	0.0793336		
				$\Sigma_{2,2}$	0.6194683		
				$\Sigma_{2,3}$	-0.2737424		
				$\Sigma_{2,4}$	0.1886902		
				$\Sigma_{3,3}$	2.4113149		
				$\Sigma_{3,4}$	-0.5026431		
				$\Sigma_{4,4}$	1.1907894		
				DIC	62,350		

Figure 1:

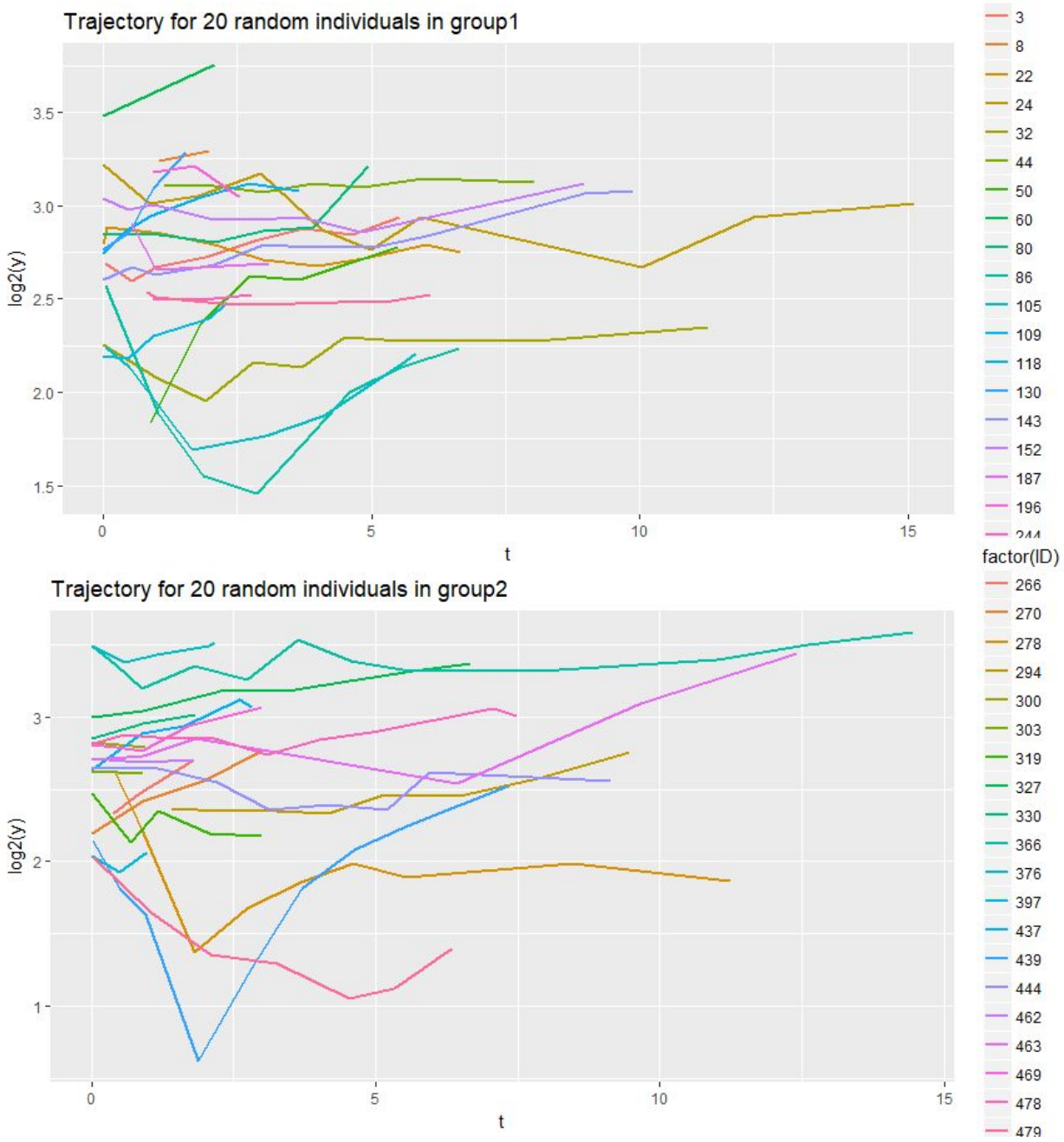
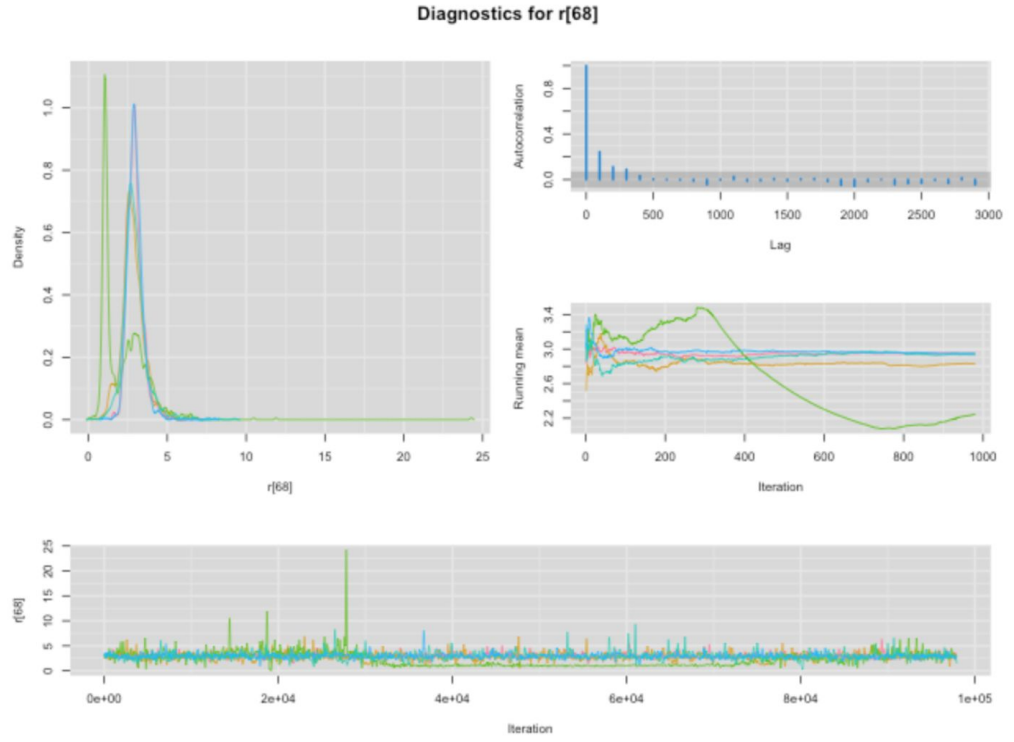
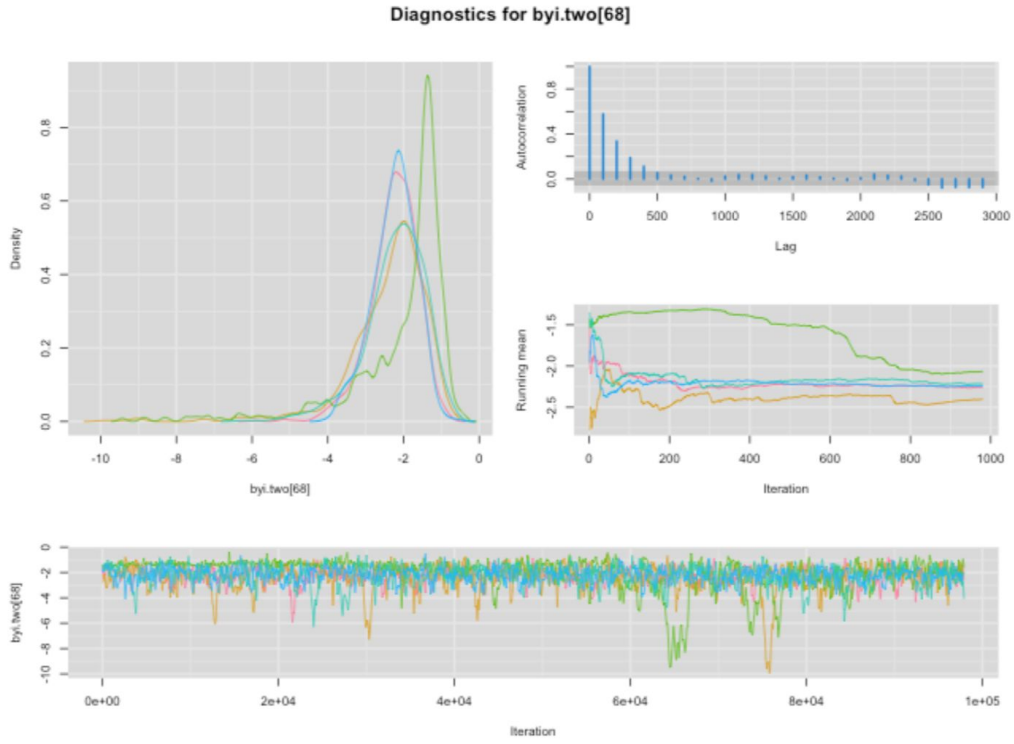
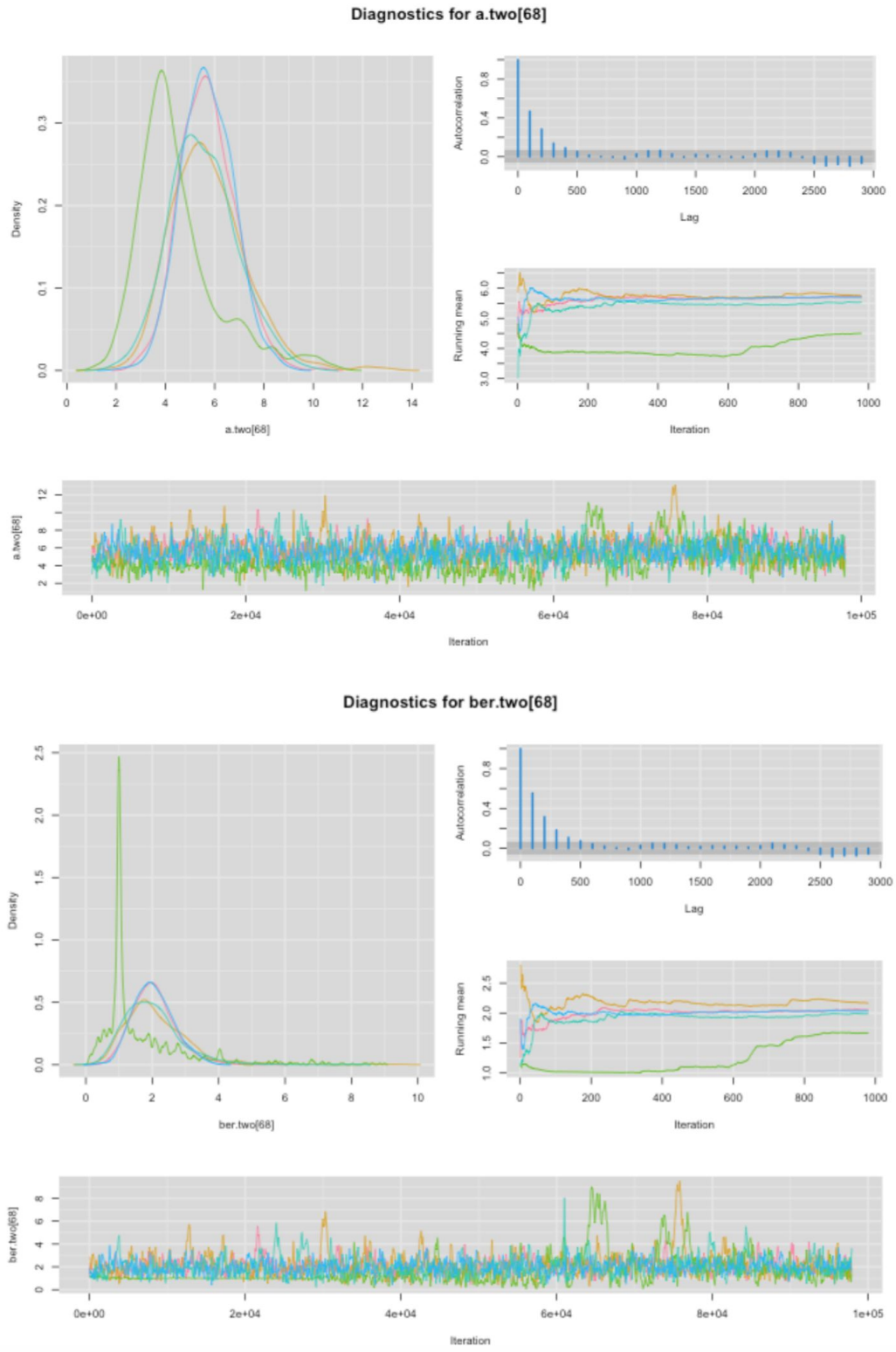


Figure 2. MCMC Plots

Randomly picked person, z=1, model 2:







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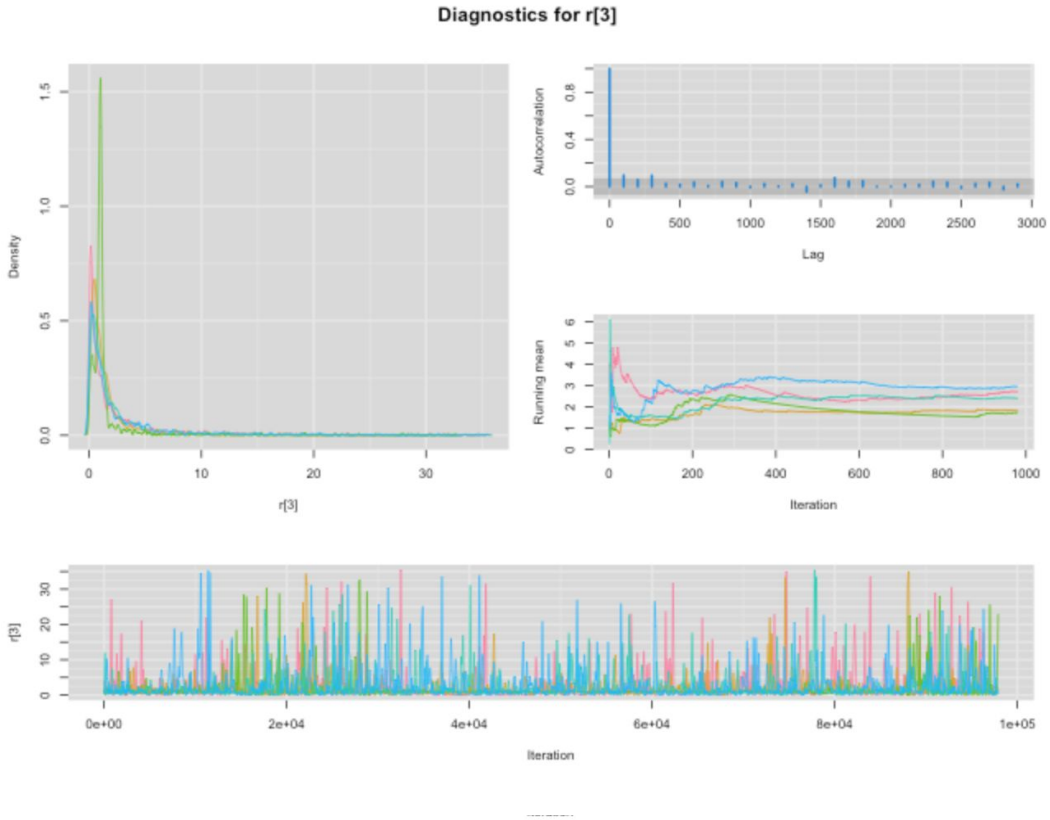
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Iteration
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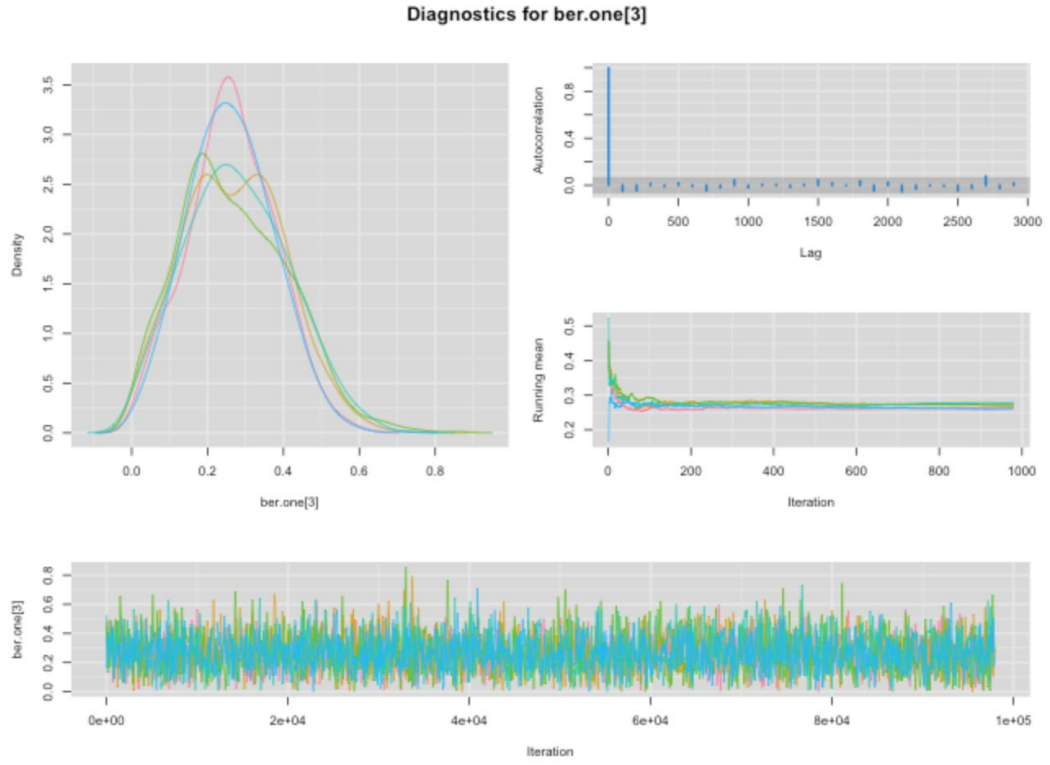
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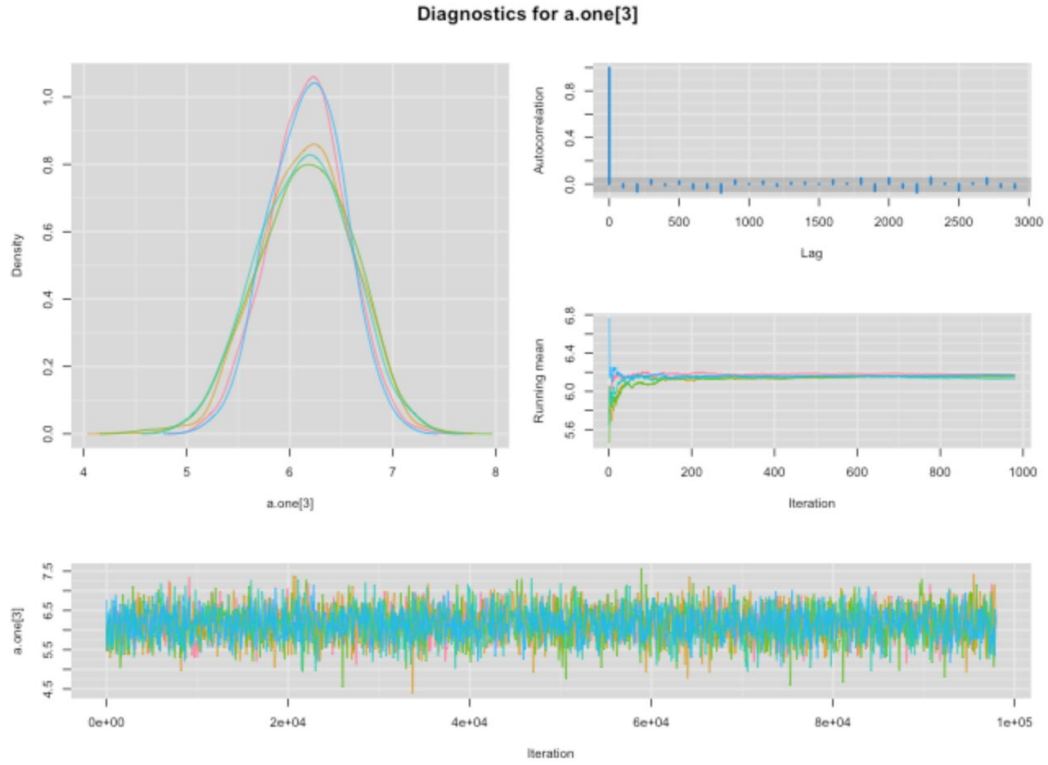
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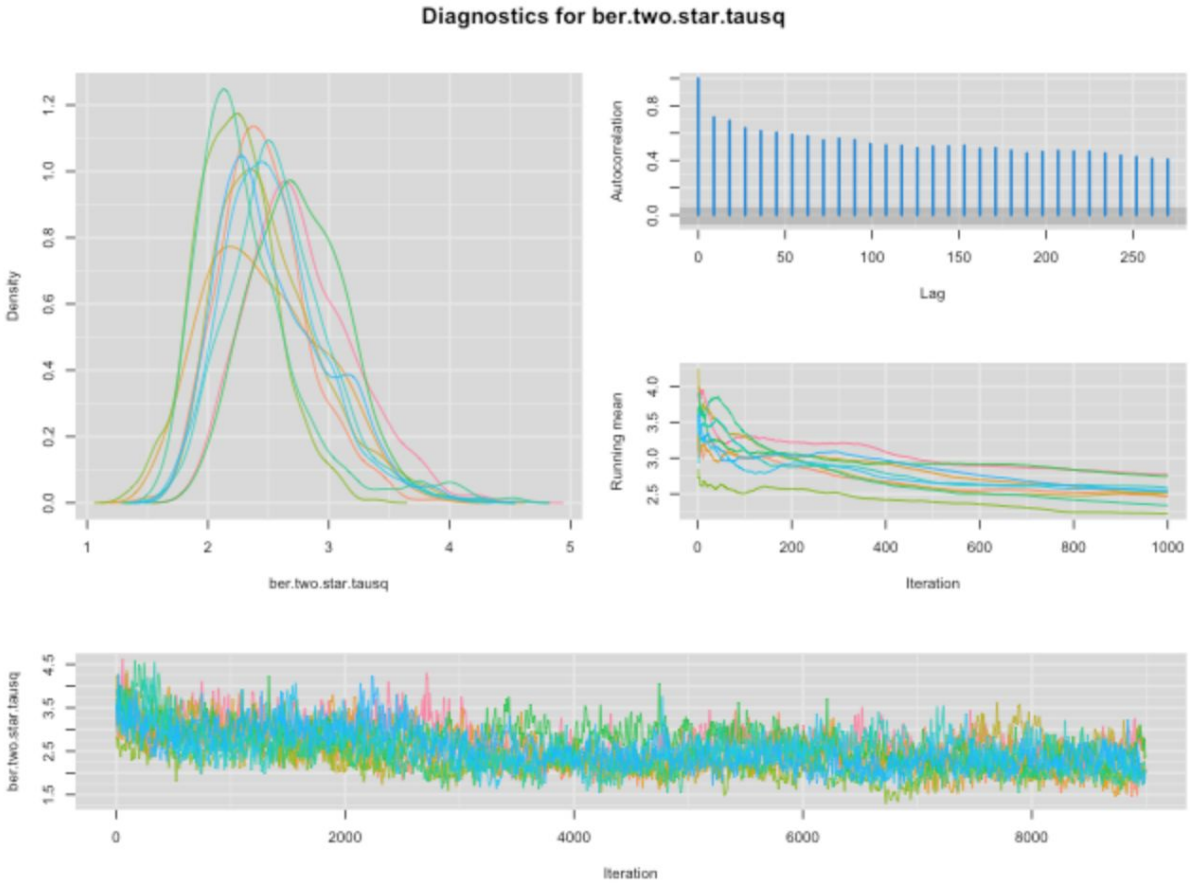
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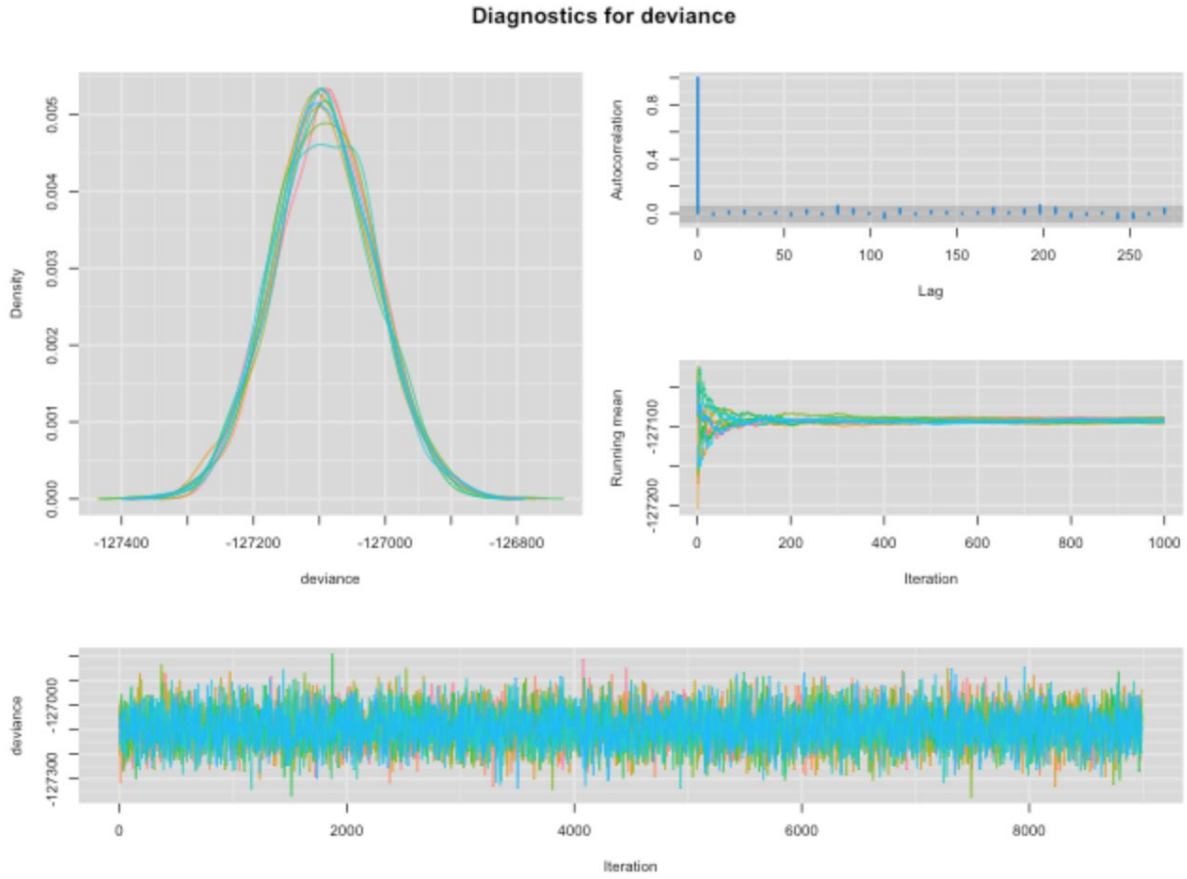
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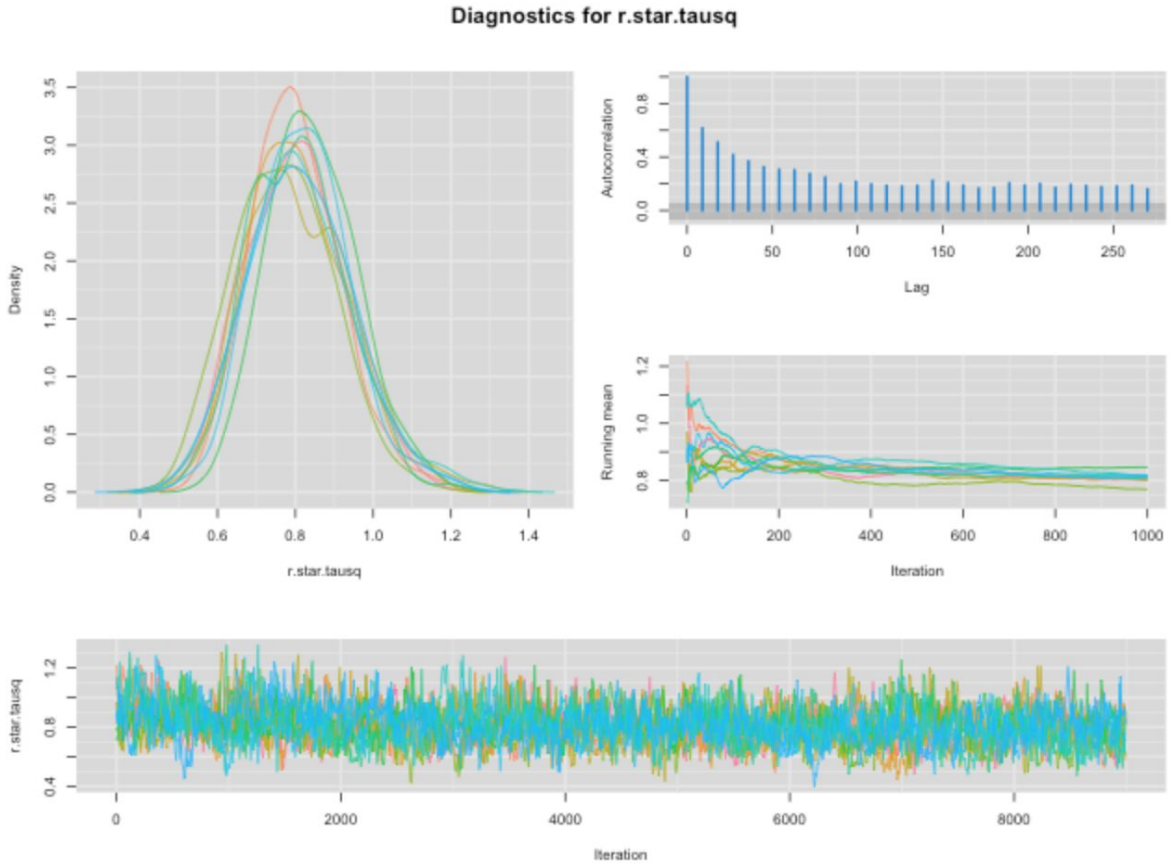
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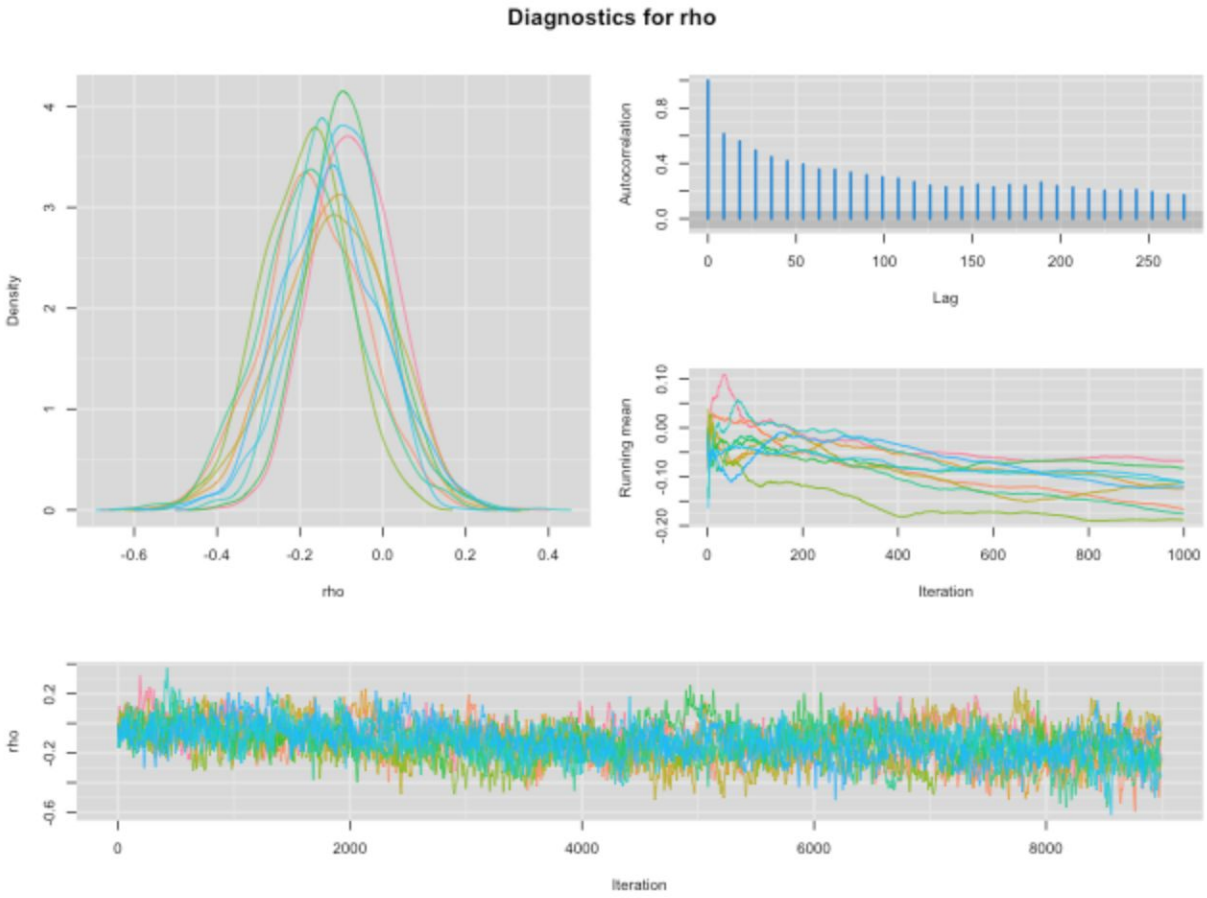
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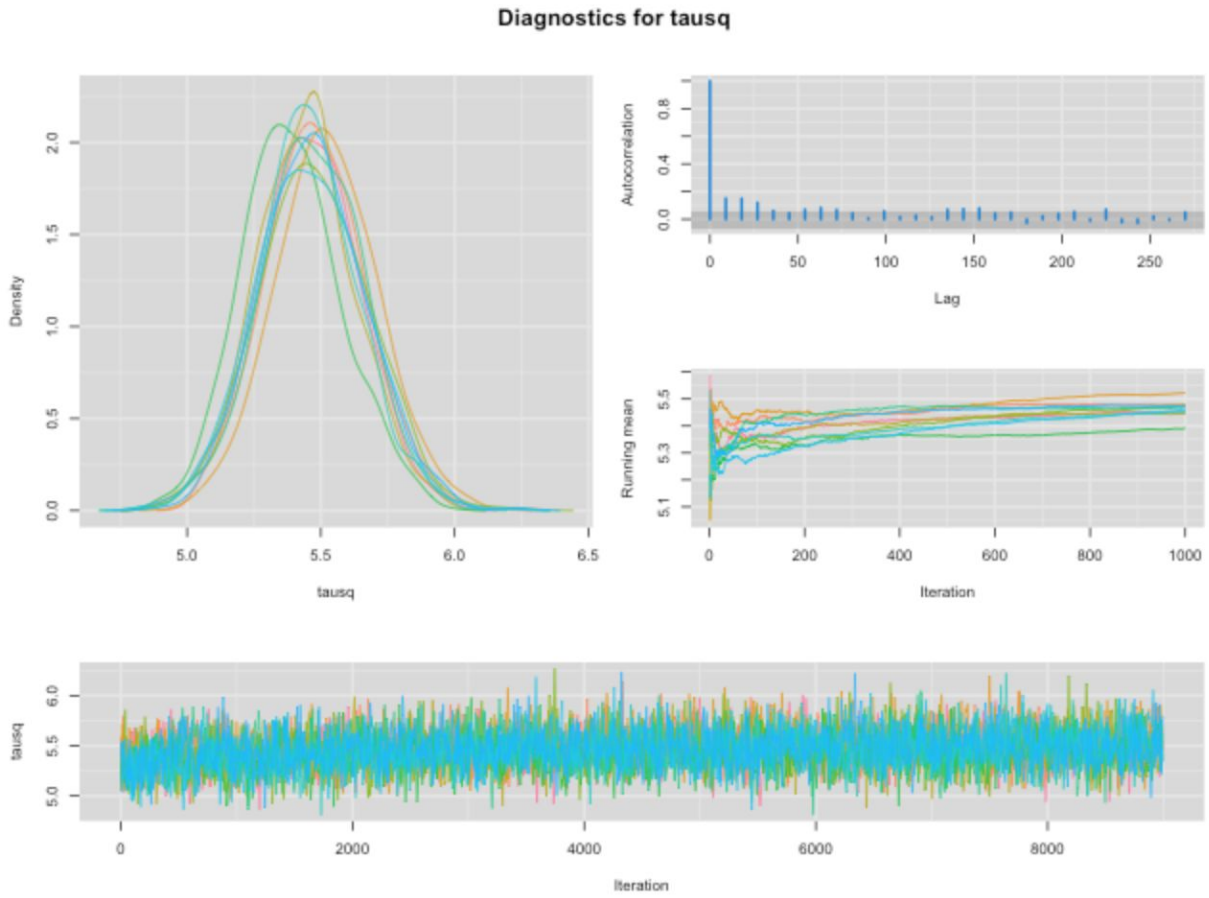
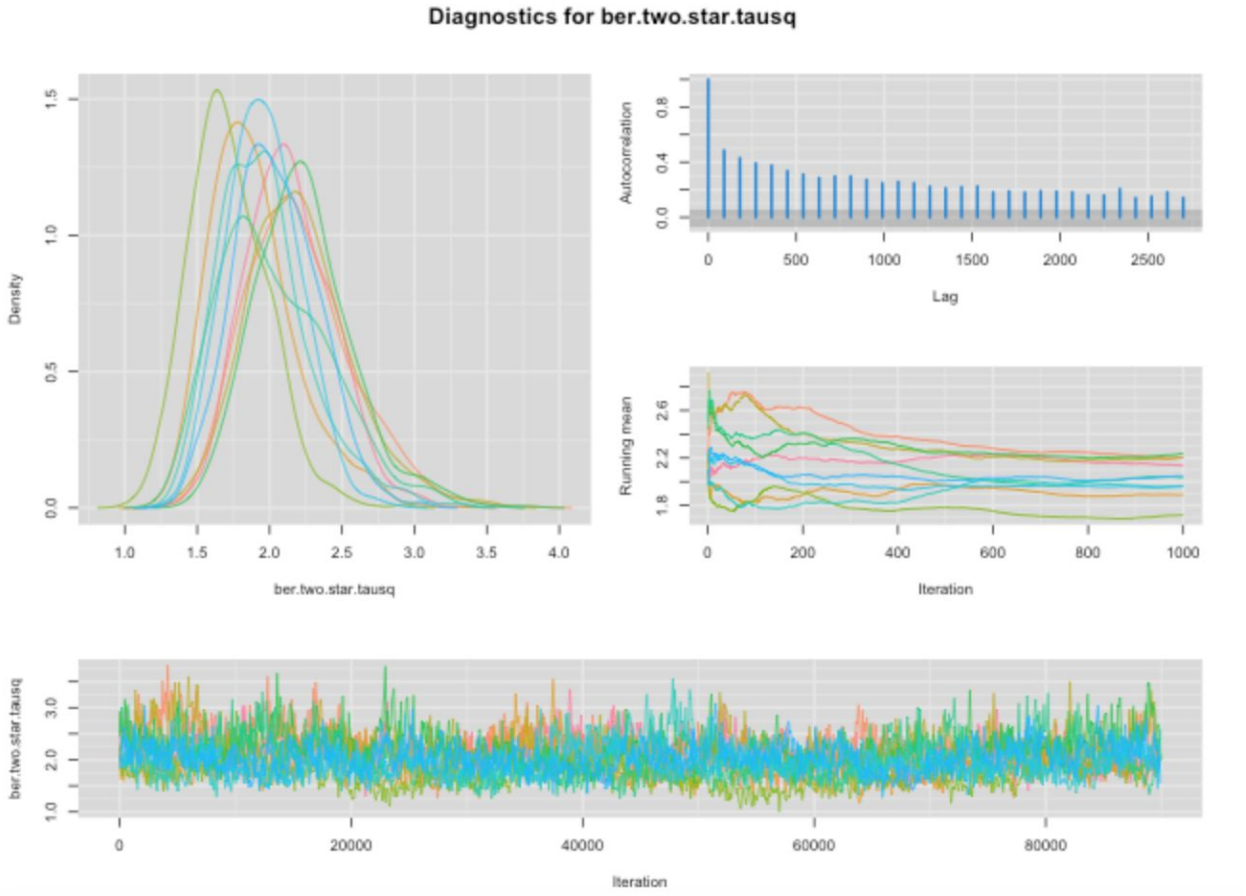


Additional figures in Model1, with larger iteration number: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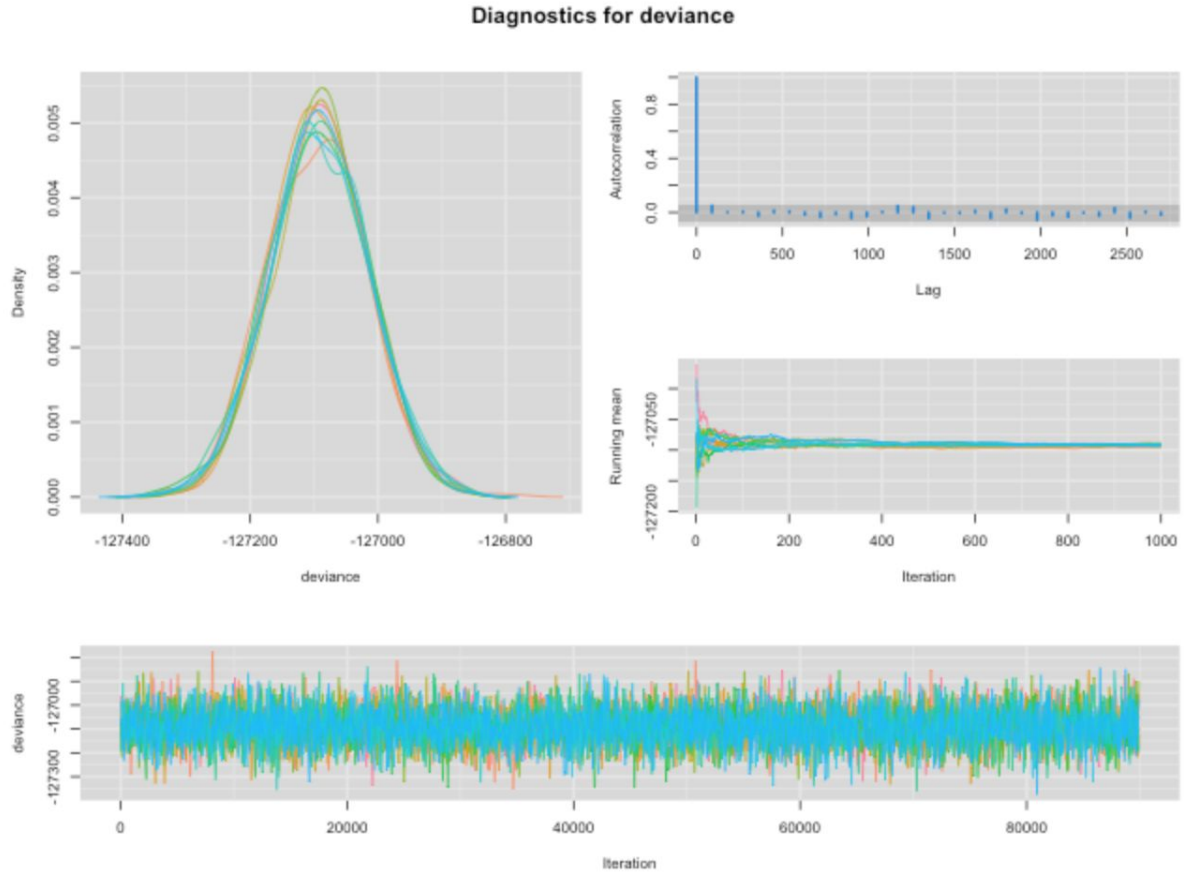
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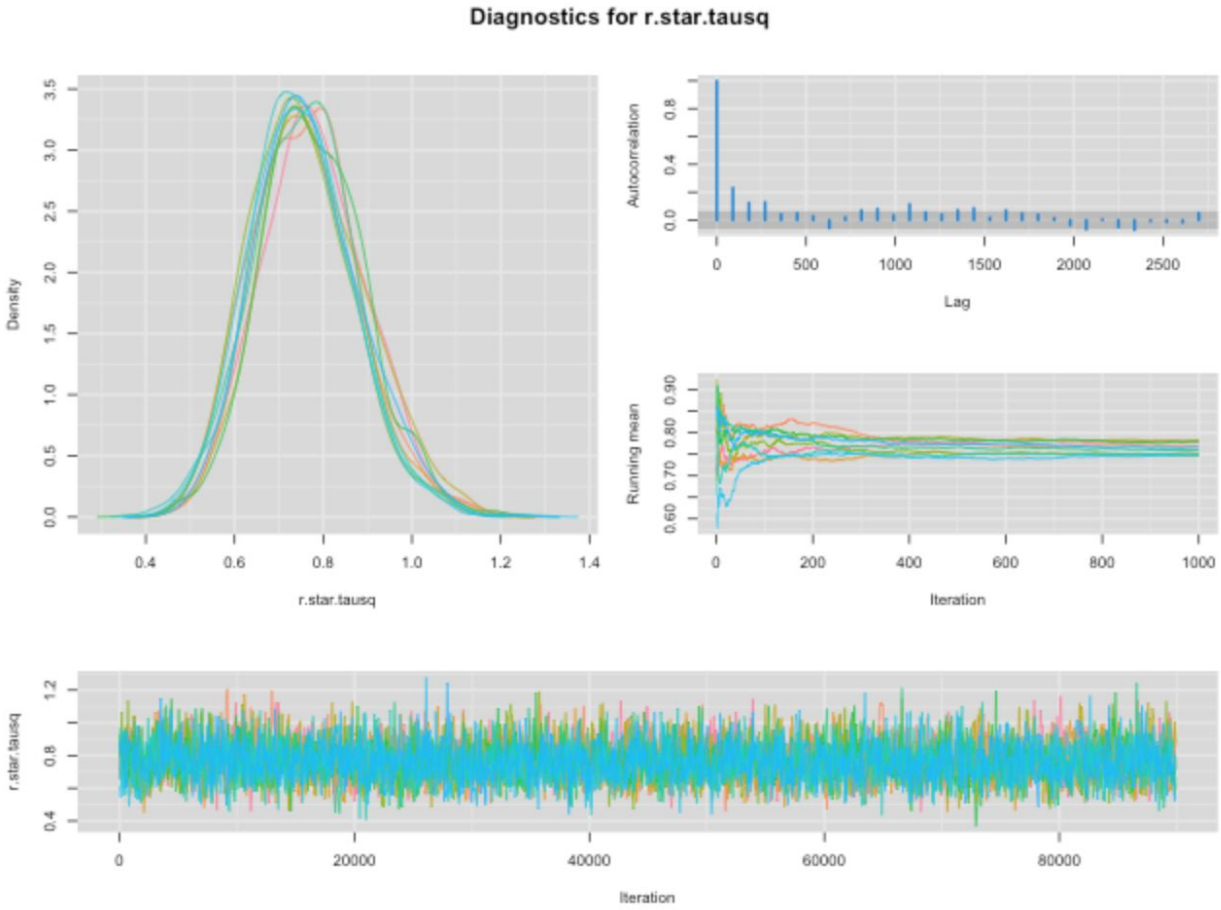
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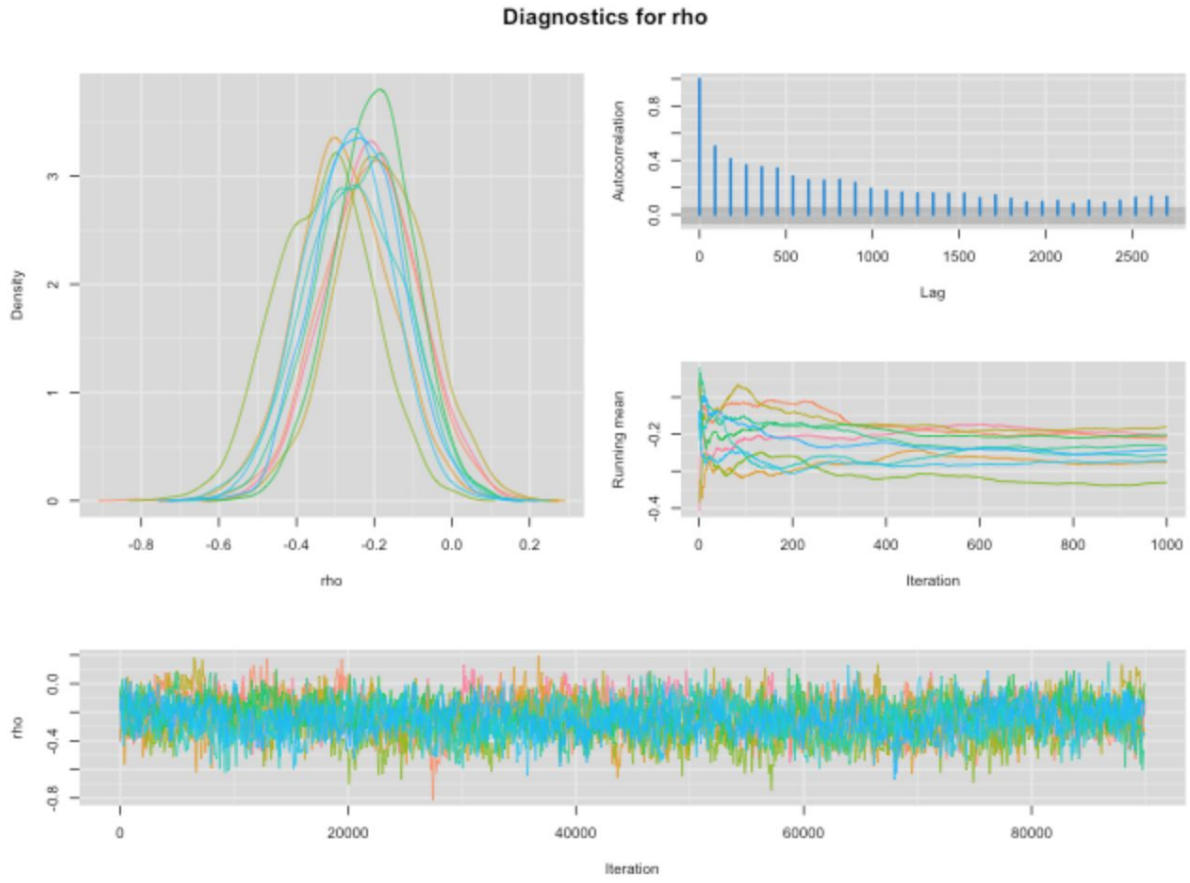
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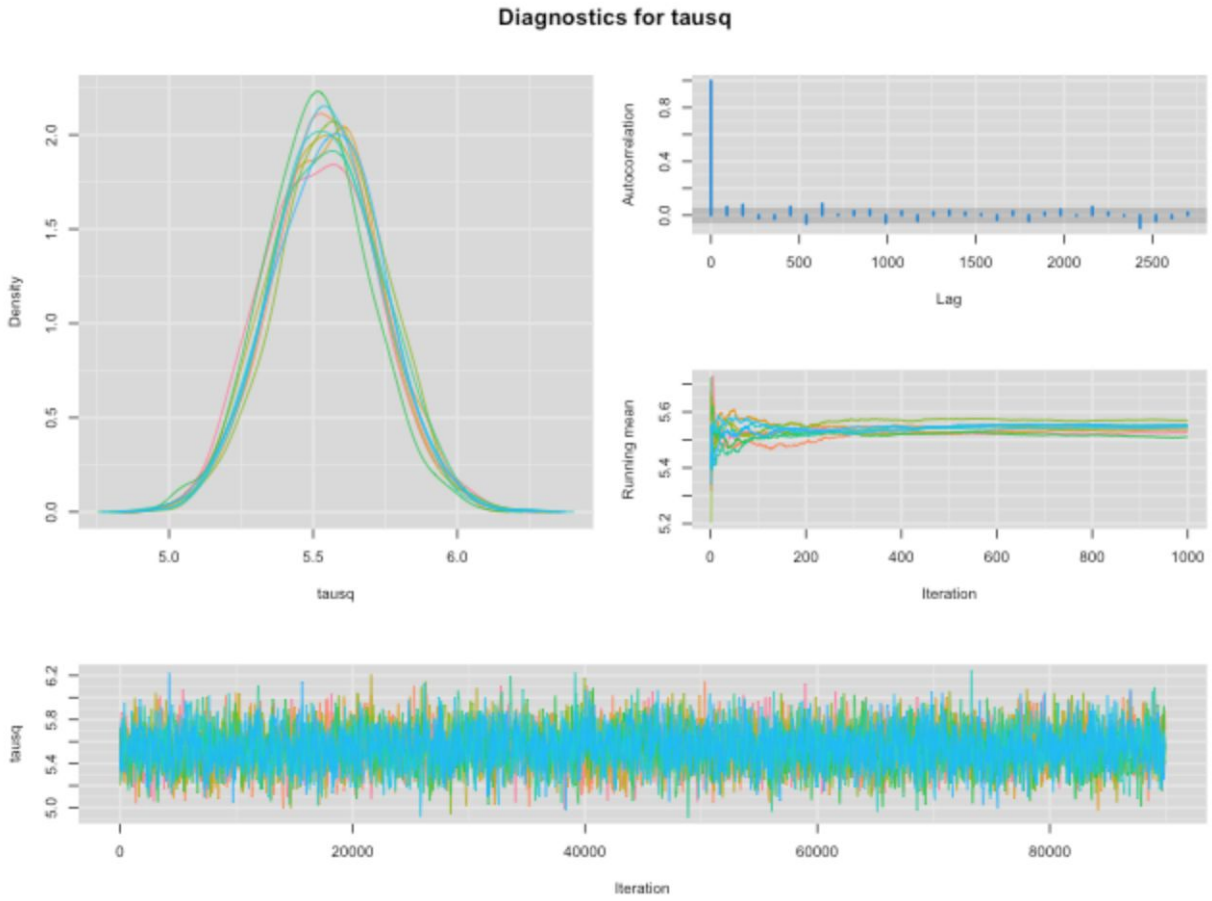
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Figure 3.a. PSA Trajectories for Individuals with Changepoint

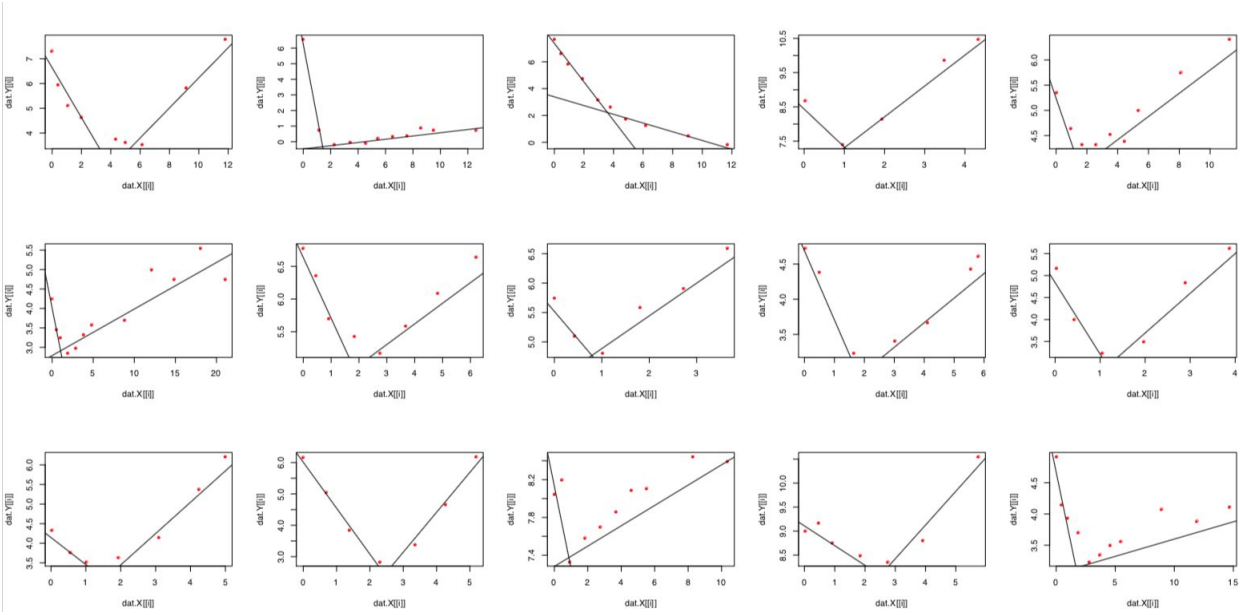

Figure 3.b. PSA Level Trajectories for Individuals without Changepoint