Supporting Information

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Model Reduction—Minimal Descriptions of Models M1 and M3

Here, we consider models M1 and M3—both vast oversimplifications of the true hematopoietic system—from a different angle: robustness to the specification of the model. That is, we investigate how varying the number of species affects model response.

Model M1 contains three healthy species and two leukemic species. The healthy progenitor species (intermediate layer) has been included to capture some of the effects produced by the large number of layers contained in the hematopoietic system. The number of leukemic species reflects evidence for at least two layers in the leukemia lineage, but not necessarily more than this; a model with three leukemic species has been analyzed previously and the qualitative changes introduced by the addition of this species were found to be negligible (1).

Model M3 has four layers of cell types for each lineage, which are described as stem cells, progenitor cells and differentiated cells and terminally differentiated cells (2). The justification for this model hierarchy is based on early characterizations of the hematopoietic lineage (3, 4). Hematopoietic species do make up a multilevel hierarchy, but whether this number of species is required in a model used to analyze data for only the terminally differentiated cell population is questionable. To test this, we ran a similar posterior comparison analysis to that performed above for reduced versions of M3 with only two or three layers in the hierarchy. The results of this are shown in Fig. S1.

For remission we see that trajectories of the three- and four-layer models are very similar, so we could omit one layer without changing the model behavior. For two layers, however, we observe changes: now the dynamics of differentiated leukemia cells are constrained, as are the dynamics of their parent (LSC) population (Fig. S1*B*). These trajectories show similarities to those obtained for model M1 in the case of remission. The shared feature between model M1 and two-layer M3 is that the niche exerts its influence over all nondifferentiated cells. The remaining difference between these models is the number of niche competitors cells: all species in M1 vs. only stem cell species in two-layer M3 (Fig. 1*C*). For relapse the healthy and the leukemic differentiated cells follow restricted trajectories in all versions of model M3: in no cases do we see significant mechanistic differences between the different versions of M3.

In summary, this analysis demonstrates that a hierarchy of four layers is not necessary to capture the observed CML dynamics within the context of model (or model family) M3. The main difference between models M1 and M3 is the level to which cells in the hematopoietic system experience the influence of the hematopoietic stem cell niche (Fig. 1*C*). The version of M3 with a two-layer hierarchy thus naturally resembles the dynamics of M1 where differentiation occurs inside the niche.

1. MacLean AL, Lo Celso C, Stumpf MPH (2013) Population dynamics of normal and leukaemia stem cells in the haematopoietic stem cell niche show distinct regimes where leukaemia will be controlled. *J R Soc Interface* 10(81):20120968.
2. Michor F, et al. (2005) Dynamics of chronic myeloid leukaemia. *Nature* 435(7046):1267–1270.
3. Spangrude GJ, Heimfeld S, Weissman IL (1988) Purification and characterization of mouse hematopoietic stem cells. *Science* 241(4861):58–62.
4. Morrison SJ, Uchida N, Weissman IL (1995) The biology of hematopoietic stem cells. *Annu Rev Cell Dev Biol* 11:35–71.

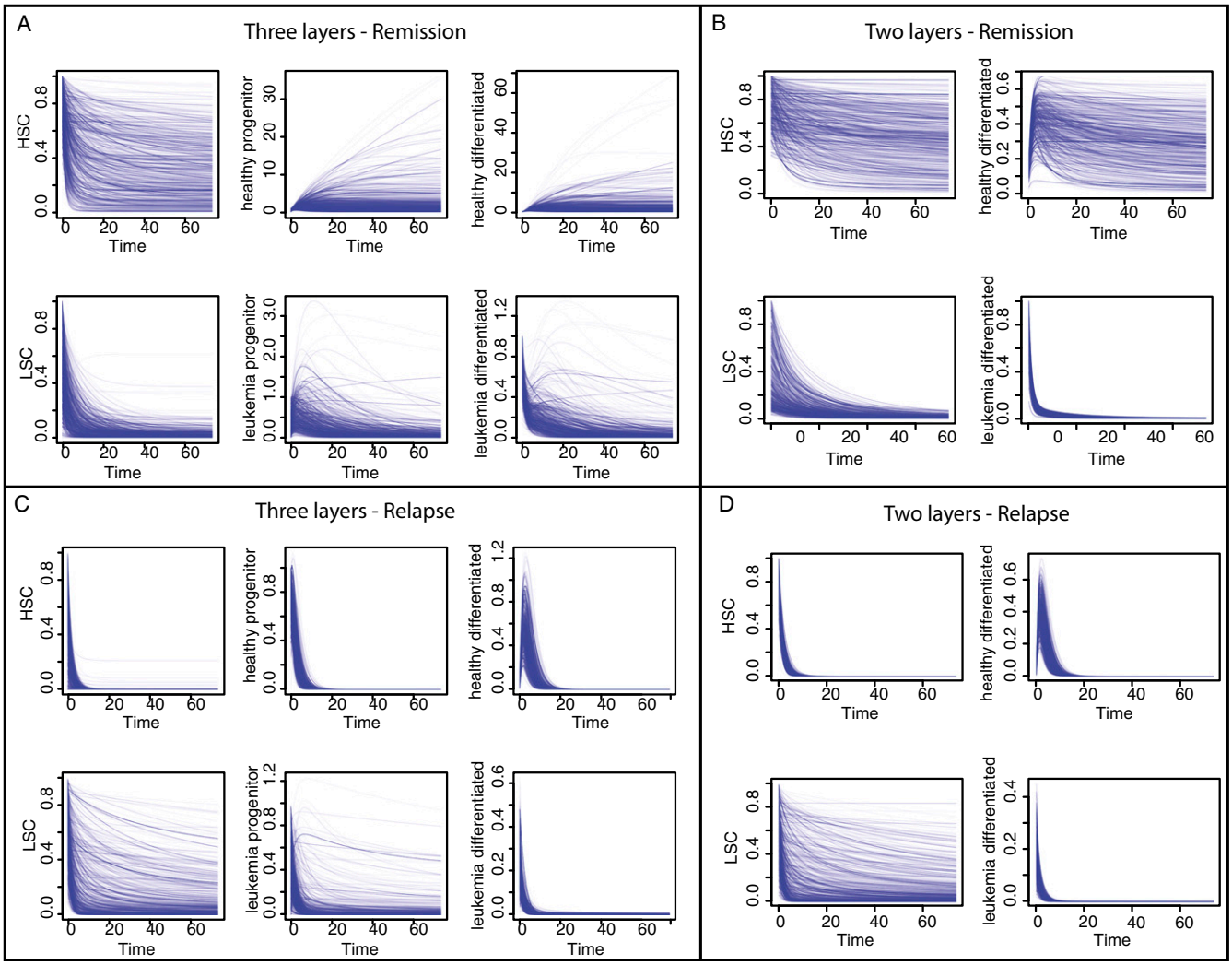

Fig. S1. Predicted evolution of each species for both outcomes—(*A* and *B*) remission and (*C* and *D*) relapse—under two reduced versions of model M3: (*A* and *C*) three-layer and (*B* and *D*) two-layer hierarchies, respectively. For each model and each outcome, 1,000 parameter sets were sampled from the posterior distribution and each line corresponds to the simulated trajectory for one of these parameter sets.

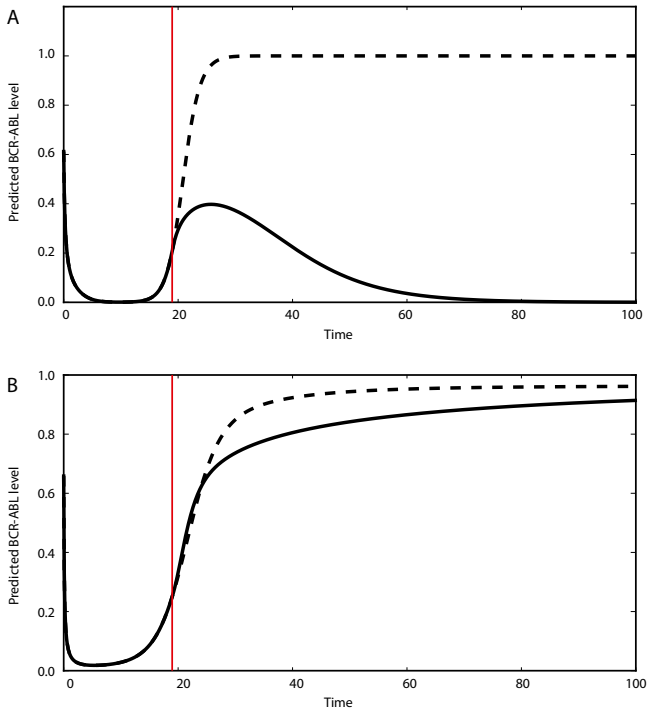

Fig. S2. In silico interventions predict that for M1 (but not M3) relapse can be avoided. (*A*) Response of model M1 to treatment intervention. Model is simulated using the maximum a posteriori parameter for relapse until 19 mo, at which point the LSC growth parameter (a_y) is decreased from 0.92 to 0.07, and the model predicts that the patient returns to remission (bold line). The dashed line represents the predicted level of the CML-related BCR-ABL fusion gene product without intervention. (*B*) Response of model M3 to treatment intervention. Model is simulated using the maximum a posteriori parameter for relapse until 19 mo, at which point the progenitor cell death parameter (δ_2) is decreased from 0.47 to 0.01. In this case the predicted time until relapse increases, but the outcome is not changed. As above, the bold line represents the intervention and the dashed line represents original relapse parameters.

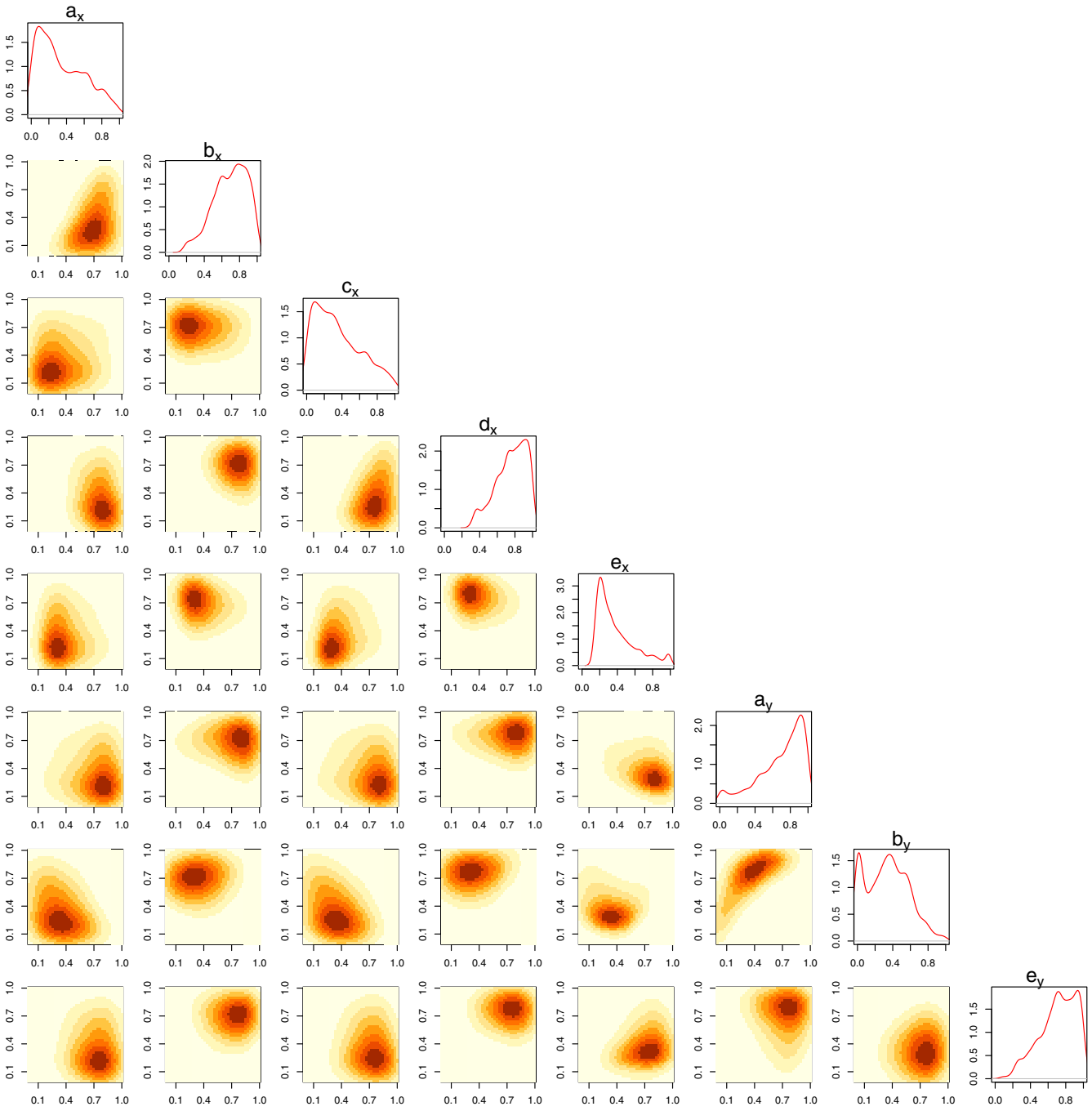

Fig. S3. Posterior distributions for model M1 under remission condition. Marginal posterior distributions for each parameter are shown along the diagonal and surface density plots for each pair of parameters are given as heat maps.

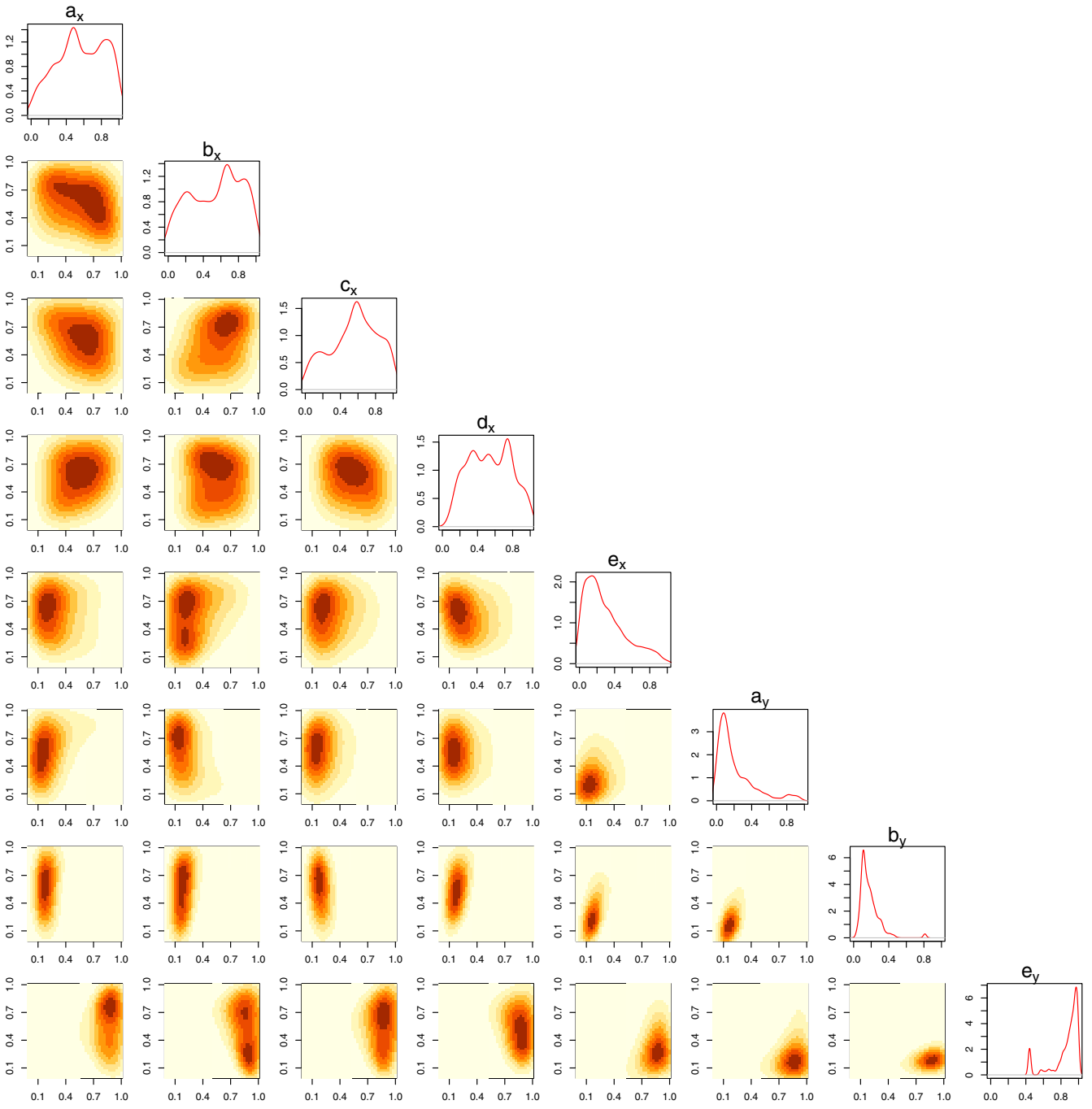

Fig. S4. Posterior distributions for model M1 under relapse condition. Marginal posterior distributions for each parameter are shown along the diagonal and surface density plots for each pair of parameters are given as heat maps.

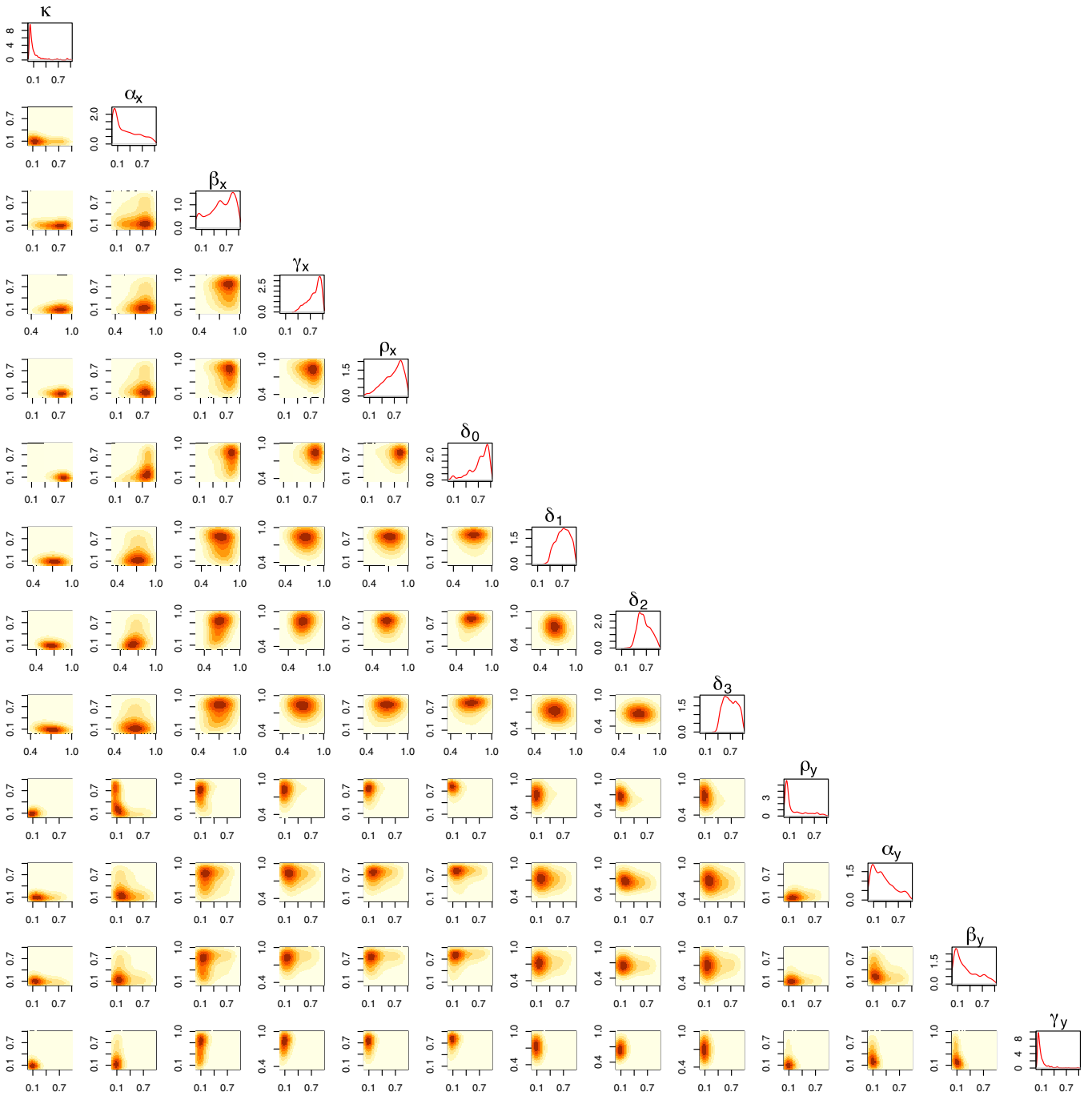

Fig. S5. Posterior distributions for model M3 under remission condition. Marginal posterior distributions for each parameter are shown along the diagonal and surface density plots for each pair of parameters are given as heat maps.

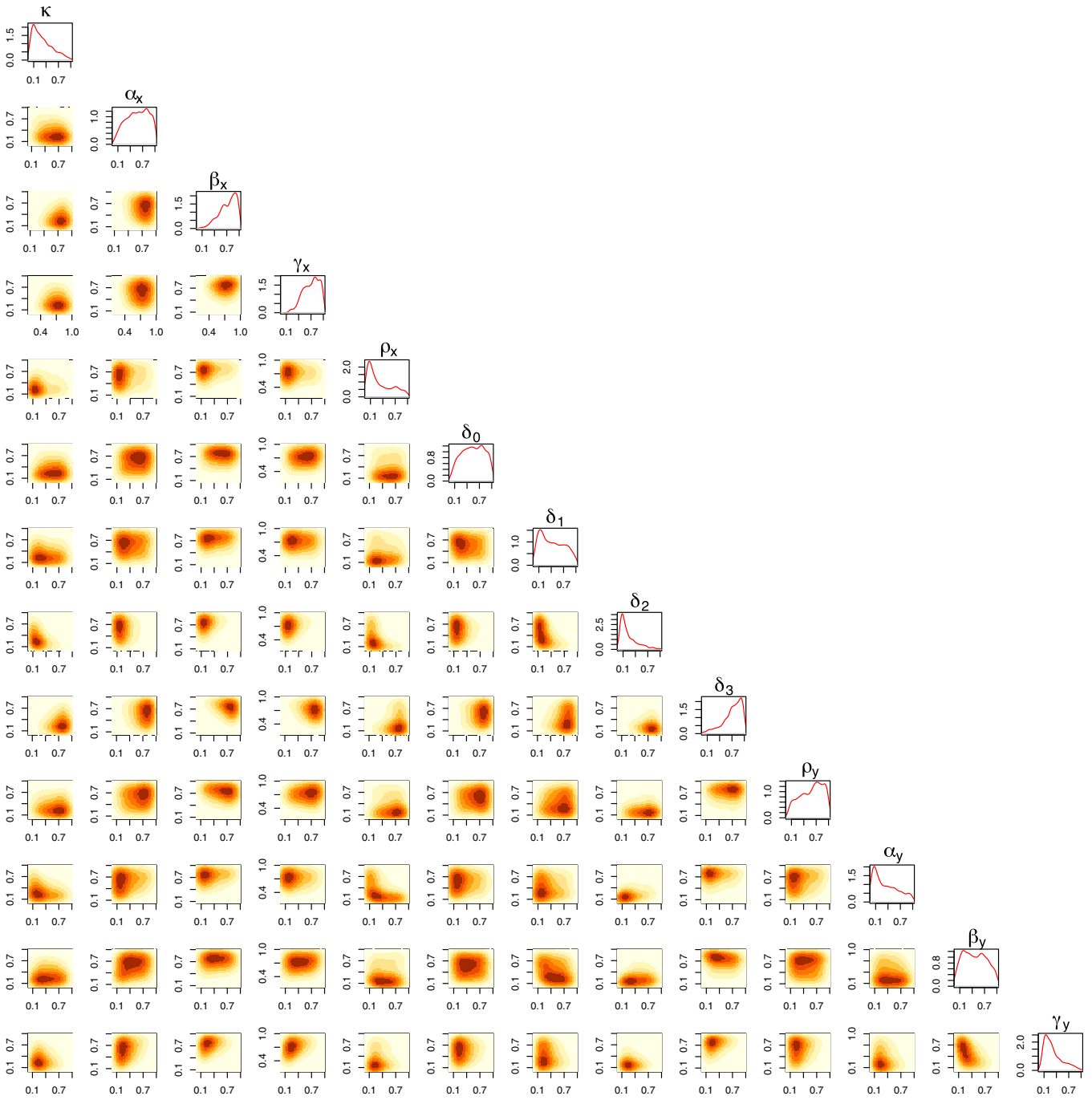

Fig. S6. Posterior distributions for model M3 under relapse condition. Marginal posterior distributions for each parameter are shown along the diagonal and surface density plots for each pair of parameters are given as heat maps.