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A Family of Additive-Multiplicative Frailty Models using the Inverse Gaussian as Frailty Distribution

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Abstract

Traditionally, frailty models are built with the assumption that frailty influences the baseline hazard function in a multiplicative manner, known as a multiplicative frailty model. An alternate model available in the literature is the additive frailty model, in which the frailty variable is linearly related to the baseline hazard function. Although both models are popular, there is a need for a model that incorporates both multiplicative and additive models, especially in epidemiological data where neither the multiplicative nor the additive model adequately describes the data. This paper aims to address this gap by developing a family of models that include both multiplicative and additive frailty models under the inverse Gaussian frailty distribution. The paper also discusses the inference procedure for estimating model parameters using the MCMC method and applies the proposed model to real-life datasets.

Keywords: Additive frailty; Multiplicative frailty; Additive-Multiplicative frailty; Inverse Gaussian distribution; MCMC.

AMS Subject Classifications: 62C10, 62F15, 62N02.

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1. Introduction

The proportional hazard model becomes the workhorse of survival analysis. In these models, we include explanatory variables or covariates to study the effect of these variables on the hazard function. The covariates can have a multiplicative or additive effect on the hazard function. The resulting models are commonly referred to as multiplicative and additive hazard models, respectively. These models are popular because of their ease of interpretation and inference-making. Despite their popularity, Lin and Ying (1997) argued that a compromise between these models is desirable. Furthermore, to illustrate the need for compromise between these models, Lin and Ying (1997) referenced the British doctor's

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study by Breslow and Day (1987). The data concern the effects of smoking on mortality. The data suggested that the difference between the two hazard functions increases over time, whereas their ratio decreases. Thus, neither additive nor multiplicative model adequately describes the data. Aranda-Ordaz (1983) proposed a Box-Cox type transformation family,

$$\frac{h^p(t \mid \underline{x}) - 1}{p} = h_0(t) + \underline{\beta}^T \underline{x}$$

in which $p \to 0$ corresponds to multiplicative and $p = 1$ corresponds to additive hazard models. In addition, Lin and Ying (1995) proposed an alternate extension given by

$$h(t \mid \underline{x}_a, \underline{x}_m) = e^{\underline{\beta}^T \underline{x}_m} \left\{ h_0(t) + \gamma^T \underline{x}_a \right\}$$

The covariates in the additive part $\underline{x}_a$ can be the same as, related to, or different from that of the multiplicative part $\underline{x}_m$.

In proportional hazard models, the assumption is that the population is homogeneous. However, heterogeneity can arise from unknown factors that influence the hazard function. For example, in a family disease study, the risk of disease occurrence varies according to genetic predisposition or shared environmental factors. Vaupel *et al.* (1979) were the first to introduce the term frailty to describe the population's heterogeneity. Duchateau and Janseen (2008), Hanagal (2019), Hougaard (2000), and Wienke (2011) are good references for the frailty models.

Several frailty models are currently being developed. The most common approach to define frailty models is to assume that frailty interacts multiplicatively with the baseline hazard function, called the multiplicative frailty model. Following the introduction of additive models by Aalen (1980), many additive frailty models have been developed in the literature as an alternative to the multiplicative frailty models. Recent advances in additive frailty models include contributions from Silva and Amarmal-Turkman (2004), Hanagal and Pandey (2016, 2017) and Hanagal (2022). In this model, frailty acts additively with the baseline hazards function.

In the case of frailty models, frailty represents the effect of some unknown factors that affect the hazard function. These unknown factors can affect the hazard function either additively or multiplicatively. For example, Kheiri *et al.* (2005) analyzed corneal transplant data in which the event of interest is graft rejection. The unknown causes that increase the rate of graft rejection may involve recipient-related, donor-related, surgery-related, or environmental-related factors. Some of these factors may have an additive effect, and others may have a multiplicative effect. Aalen and Tretli (1999) analyzed data on testicular cancer. Men who develop cancer after the hormonal process of puberty has started, receive damage during a critical period of their fetal development. The damage may result from the mother's exposure to environmental factors, an excessive estrogenic burden, or genetic factors. These causes may additively or multiplicatively affect the hazard function. However, it is challenging to determine which factors have an additive effect and which ones have a multiplicative effect, as frailty is unobservable. The usual approach is to fit the additive, multiplicative and additive-multiplicative models and select the best among them.

According to the literature review, no previous study has considered incorporating frailty with both additive and multiplicative effects into a model. This research aims to

bridge this gap. This paper introduces the concept of the additive-multiplicative frailty model, where the frailty random variable is assumed to follow an inverse Gaussian distribution. The paper is structured as follows: Section 2 presents the general univariate additive and multiplicative frailty models. Further, the Section continues to introduce additive-multiplicative frailty models. Section 3 explores the inverse Gaussian distribution, as well as additive, multiplicative, and additive-multiplicative inverse Gaussian frailty models. Section 4 discusses the baseline distribution. Section 5 outlines the Bayesian inferential procedure. Sections 6 and 7 are respectively dedicated to the simulation study and real-life data analysis. Finally, Section 8 concludes the paper with a summary of the findings.

2. Univariate frailty models

2.1. Univariate multiplicative frailty models

Let T be a lifetime random variable and Z_m be a non-negative frailty random variable. The conditional hazard function under the multiplicative frailty (MF) model for given frailty $Z_m = z_m$ and known covariates $\underline{X}_m = \underline{x}_m$ at time $t > 0$ is given by

$$h_m(t \mid \underline{x}_m, z_m) = \begin{cases} z_m h_0(t)\eta_m & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{1}$$

where $h_0(t)$ is the baseline hazard function; $\eta_m = e^{\underline{\gamma}^T \underline{x}_m}$ is the link function and $\underline{\gamma}$ is a vector of regression coefficients. Using the relation between the survival function and the hazard function, the conditional survival function for given frailty is

$$S_m(t \mid \underline{x}_m, z_m) = \begin{cases} exp\left(-z_m H_0(t)\eta_m\right) & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{2}$$

where $H_0(t)$ is the cumulative baseline hazard function at time $t > 0$. Suppose that the frailty random variable Z_m follows a continuous distribution defined over the positive half part of the real line with probability density function $f_{Z_m}(\cdot)$ and Laplace transform $L_{Z_m}(\cdot)$. Integrating over the range of the frailty random variable, the survival function of the lifetime random variable T is,

$$S_m(t \mid \underline{x}_m) = \begin{cases} L_{Z_m}(H_0(t)\eta_m) & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{3}$$

The probability density function of T is given by

$$\psi_m(t \mid \underline{x}_m) = \begin{cases} h_0(t)\eta_m L^{(1)}_{Z_m}(H_0(t)\eta_m) & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{4}$$

where $L^{(1)}_{Z_m}(s) = -\int_0^\infty z e^{-zs} f_{Z_m}(z) dz$.

2.2. Univariate additive frailty models

If Z_a is a frailty random variable that affects the hazard function additively having the probability density function $f_{Z_a}(\cdot)$ and the Laplace transform $L_{Z_a}(\cdot)$, then the conditional

hazard function for given frailty $Z_a = z_a$ and known covariates $\underline{X}_a = \underline{x}_a$ under the additive frailty (AF) model is

$$h_a(t \mid \underline{x}_a, z_a) = \begin{cases} h_0(t) + z_a\eta_a & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{5}$$

where $\eta_a = e^{\underline{\beta}^T \underline{x}_a}$ and $\underline{\beta}$ is a vector of regression coefficients. The conditional survival function for given frailty and covariates is

$$S_a(t \mid \underline{x}_a, z_a) = \begin{cases} exp\left(-H_0(t)\right) exp\left(-z_a t\eta_a\right) & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{6}$$

After integrating over the range of the frailty random variable, the survival and probability density functions of T are given by

$$S_a(t \mid \underline{x}_a) = \begin{cases} e^{-H_0(t)} L_{Z_a}(t\eta_a) & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{7}$$

$$\psi_a(t \mid \underline{x}_a) = \begin{cases} h_0(t) S_a(t) + \eta_a e^{-H_0(t)} L^{(1)}_{Z_a}(t\eta_a) & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{8}$$

The MF and AF models can be extended as shared and correlated for multivariate cases. In shared frailty models, the frailty variable is shared by all individuals in a family. In contrast, in correlated frailty models, frailty variables associated with all individuals in a family are correlated. This article considers only univariate frailty models, so shared and correlated frailty models are not discussed further.

2.3. Univariate additive-multiplicative frailty models

Suppose $\underline{Z} = (Z_a, Z_m)$ is a frailty random vector with joint probability density function $f_{\underline{Z}}(\cdot, \cdot)$ and Laplace transform $L_{\underline{Z}}(\cdot, \cdot)$ in which Z_a and Z_m are non-negative frailty random variables that act additively and multiplicatively on the hazard function, respectively. Furthermore, suppose $\underline{X}_a$ and $\underline{X}_m$ are vectors of covariates acting additively and multiplicatively on the hazards function. The conditional hazard function given $\underline{z} = (z_a, z_m)$ and $\underline{x} = (\underline{x}_a, \underline{x}_m)$ under the additive-multiplicative frailty (AMF) model is

$$h(t \mid \underline{x}, \underline{z}) = \begin{cases} z_a\eta_a + z_m h_0(t)\eta_m & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{9}$$

The conditional survival function given $\underline{x}$ and $\underline{z}$ is

$$S(t \mid \underline{x}, \underline{z}) = \begin{cases} exp\left[-\left(z_a t\eta_a + z_m H_0(t)\eta_m\right)\right] & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{10}$$

The survival and probability density functions of the lifetime random variable T at $t > 0$ are, respectively,

$$S(t \mid \underline{x}) = \begin{cases} L_{\underline{Z}}\left(t\eta_a, H_0(t)\eta_m\right) & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{11}$$

$$\psi(t \mid \underline{x}) = \begin{cases} \eta_a L^{(a)}_{\underline{Z}}(t\eta_a, H_0(t)\eta_m) + h_0(t)\eta_m L^{(m)}_{\underline{Z}}(t\eta_a, H_0(t)\eta_m) & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases} \tag{12}$$

where $L_{\underline{Z}}^{(i)}(s_1, s_2) = -\int_0^\infty \int_0^\infty z_i e^{-[z_a s_1 + z_m s_2]} f_{\underline{Z}}(z_a, z_m)\, dz_a dz_m \ ;\ i = a, m.$

If Z_a has a degenerate distribution at zero, then Equation (9) reduces to Equation (1), and hence, AMF model reduces to the MF model similarly if Z_m is degenerate at one, then the AMF model reduces to the AF model. In particular, if $\eta_m = 1$ then Equation (9) reduces to Equation (5).

3. Inverse Gaussian frailty models

3.1. Inverse Gaussian distribution

The gamma distribution is the most common and simple frailty distribution due to its mathematical convenience. However, it has some drawbacks (*see* Kheiri *et al.* (2007)). For example, it may weaken the effect of covariates. Another choice of frailty distribution that can be considered is the inverse Gaussian distribution, as it shares many striking similarities with the most popular statistical distribution, the normal distribution (*see* Chhikara *et al.* 1986). Hougaard (1984) introduced the inverse Gaussian as a frailty distribution.

Let a continuous random variable X follows inverse Gaussian (IG) distribution with parameters μ and α, denoted by $IG(\mu, \alpha)$, then the probability density function of X is

$$f(x) = \begin{cases} \sqrt{\dfrac{\alpha}{2\pi x^3}}\ exp\left[-\dfrac{\alpha(x-\mu)^2}{2x\mu^2}\right] & ;\ x > 0, \alpha > 0, \mu > 0 \\ 0 & ;\ otherwise. \end{cases}$$

Hougaard (2000) given a re-parameterization of $f(\cdot)$ from an exponential family point of view as;

$$f(x) = \sqrt{\frac{\psi}{2\pi}} exp\left(\sqrt{\psi\phi}\right) x^{-3/2} exp\left\{-\frac{\phi x}{2} - \frac{\psi}{2x}\right\} \ ;\ x > 0$$

where $\psi = \alpha$ and $\phi = \frac{\alpha}{\mu^2}$.

The Laplace transform of inverse Gaussian distribution is,

$$L_X(s) = exp\left[\frac{\alpha}{\mu}\left(1 - \sqrt{1 + \frac{2\mu^2 s}{\alpha}}\right)\right];\ \ s \geq 0 \tag{13}$$

Differentiating the Laplace transform with respect to s and evaluating at $s = 0$, the first- and second-order moments are

$$E\left[X\right] = \mu \ \text{ and } \ \text{var}\left[\text{X}\right] = \frac{\mu^3}{\alpha}.$$

Frailty models suffer from the identifiability problem. So, the expected value of the frailty random variable is always restricted to one. For inverse Gaussian frailty models, the restriction on parameters is $\mu = 1$, under this restriction, the variance of X is, $\sigma^2 = \dfrac{1}{\alpha}$. The

Laplace transform and probability density function of X then reduce to

$$\begin{aligned} f(x) &= \begin{cases} \sqrt{\frac{1}{2\pi\sigma^2 x^3}} exp\left[-\frac{(x-1)^2}{2x\sigma^2}\right] & ;\ x>0, \sigma^2>0 \\ 0 & ;\ otherwise. \end{cases} \\ L_Z(s) &= exp\left[\frac{1}{\sigma^2}\left(1-\sqrt{1+2\sigma^2 s}\right)\right];\ \ s\geq 0 \end{aligned} \tag{14}$$

3.2. Additive and multiplicative IG frailty models

Suppose the multiplicative and additive frailty random variables $Z_i \sim IG(\mu_i, \alpha_i)$, $i = a, m$. Under the restriction for identifiability $\mu_a = 1$ and $\mu_m = 1$ the Laplace transform of Z_a and Z_m is as given in Equation (14). Substituting this Laplace transform (Equation (14)) in Equations (3) and (7), we get the survival function of the lifetime random variable T under the multiplicative inverse Gaussian frailty (MIGF) and additive inverse Gaussian frailty (AIGF) models as

$$S_m(t \mid \underline{x}_m) = \begin{cases} exp\left[\frac{1}{\sigma_m^2}\left(1-\sqrt{1+2\sigma_m^2 H_0(t)\eta_m}\right)\right] & ;\ t>0 \\ 1 & ;\ \text{otherwise} \end{cases} \tag{15}$$

$$S_a(t \mid \underline{x}_a) = \begin{cases} exp\left(-H_0(t)\right) exp\left[\frac{1}{\sigma_a^2}\left(1-\sqrt{1+2\sigma_a^2 t\eta_a}\right)\right] & ;\ t>0 \\ 1 & ;\ \text{otherwise} \end{cases} \tag{16}$$

The respective probability density functions are given by

$$f_m(t \mid \underline{x}_m) = \begin{cases} \frac{h_0(t) S_m(t \mid \underline{x}_m)\eta_m}{\sqrt{1+2\sigma_m^2 H_0(t)\eta_m}} & ;\ t>0 \\ 0 & ;\ \text{otherwise} \end{cases}$$

$$f_a(t \mid \underline{x}_a) = \begin{cases} S_a(t \mid \underline{x}_a)\left\{h_0(t) + \frac{\eta_a}{\sqrt{1+2\sigma_a^2 t\eta_a}}\right\} & ;\ t>0 \\ 0 & ;\ \text{otherwise} \end{cases}$$

3.3. Additive-Multiplicative IG frailty models

First, to obtain the additive-multiplicative inverse Gaussian frailty (AMIGF) model, assume that frailty random variables Z_a and Z_m are independent but not identical. Suppose $Z_i \sim IG(\mu_i, \alpha_i)$, $i = a, m$. Again, under the restriction for identifiability, we assume $\mu_a = \mu_m = 1$ and Laplace transform of Z_m and Z_a is given by Equation (14). Using Equation (11) and the fact that if X and Y are independent random variables, then $L_{(X,Y)}(s_1, s_2) = L_X(s_1) \cdot L_Y(s_2)$, the survival function of lifetime random variable is given by

$$S(t \mid \underline{x}) = \begin{cases} L_{Z_a}(t\eta_a) L_{Z_m}(H_0(t)\eta_m) & ;\ t>0 \\ 1 & ;\ \text{otherwise} \end{cases} \tag{17}$$

Substituting the Laplace transform of IG distribution (14) the survival function (17) becomes

$$S(t \mid \underline{x}) = \begin{cases} exp\left[\frac{1}{\sigma_a^2}\left(1 - D_a(t \mid \underline{x}_a)\right)\right] \cdot exp\left[\frac{1}{\sigma_m^2}\left(1 - D_m(t \mid \underline{x}_m)\right)\right] & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{18}$$

and the probability density function is given by

$$\psi(t \mid \underline{x}) = \begin{cases} S(t)\left\{\frac{\eta_a}{D_a(t \mid \underline{x}_a)} + \frac{h_0(t)\eta_m}{D_m(t \mid \underline{x}_m)}\right\} & ; \quad t > 0 \\ 0 & ; \quad \text{otherwise} \end{cases}$$

where $D_a(t \mid \underline{x}_a) = \sqrt{1 + 2\sigma_a^2 t\eta_a}$, $D_m(t\underline{x}_m) = \sqrt{1 + 2\sigma_m^2 H_0(t)\eta_m}$.

Now, we consider the case where Z_a and Z_m are not independent. To obtain the survival function of the lifetime random variable under the AMIGF model when Z_a and Z_m are not independent, the Laplace transform of frailty random vector $\underline{Z}$ needs to be obtained. In this paper, it is obtained using the concept of trivariate reduction (*see* Kocherlakota and Kocherlakota (1992)). The idea is to create a pair of dependent random variables from three or more possibly independent initial random variables. Let U_i, $i = 0, 1, 2$ be independently distributed continuous random variables, then the trivariate reduction method consists of defining a pair of correlated random variables V_1 and V_2 by relation,

$$V_1 = \tau(U_0, U_1); \qquad V_2 = \tau(U_0, U_2)$$

Define the function $\tau(x, y) = c\,(dx + y)$ so that the variable $V_j = c_j(d_j U_0 + U_j), j = 1, 2$. If $L_{U_j}(\cdot)$ is the Laplace transform of $U_j, j = 0, 1, 2$ then the Laplace transform of V_j and $\underline{V} = (V_1, V_2)$ are easily shown to be respectively.

$$L_{V_j}(s) = L_{U_0}(c_j d_j s) L_{U_j}(c_j s)\ ; \qquad j = 1, 2 \tag{19}$$

$$L_{\underline{V}}(\underline{s}) = L_{U_0}(c_1 d_1 s_1 + c_2 d_2 s_2) L_{U_1}(c_1 s_1) L_{U_2}(c_2 s_2) \tag{20}$$

Now, to obtain the Laplace transform of the frailty vector $\underline{Z}$ using the trivariate reduction method, let Y_0, Y_a, Y_m be independent positive valued random variables following $IG(\mu_i, \alpha_i), i = 0, a, m$ having Laplace transform as given in Equation (13). Define a random variable $Z_j = \frac{\alpha_j}{\alpha_0 + \alpha_j}\left(\frac{\alpha_0}{\alpha_j} Y_0 + Y_j\right)$, $j = a, m$. Putting $c_j = \frac{\alpha_j}{\alpha_0 + \alpha_j}; d_j = \frac{\alpha_0}{\alpha_j}$ and using Equation (19) the Laplace transform of the frailty random variable Z_j, $j = a, m$ is given by

$$L_{Z_j}(s) = exp\left[\frac{\alpha_0 + \alpha_j}{\mu}\left(1 - \sqrt{1 + \frac{2\mu^2 s}{\alpha_0 + \alpha_j}}\right)\right]; \quad s \geq 0 \tag{21}$$

Hence, each Z_j marginally follows $IG(\mu, \alpha_0 + \alpha_j)$; $j = a, m$. The moments of Z_j's are given by

$$E\left[Z_j\right] = \mu; \quad var\left[Z_j\right] = \frac{\mu^3}{\alpha_0 + \alpha_j}; \quad j = a, m.$$

Theorem 1: The correlation coefficient between Z_a and Z_m is

$$\rho = \frac{\alpha_0}{\sqrt{\alpha_0+\alpha_a}\sqrt{\alpha_0+\alpha_m}}$$

Proof: Given in Appendix I

The Laplace transform of $\underline{Z}$ for $s_1 \geq 0, s_2 \geq 0$ using Equation (20), is given by,

$$\begin{aligned} L_{\underline{Z}}(s_1,s_2) &= exp\left[\frac{\alpha_0}{\mu}\left(1-\sqrt{1+2\mu^2\left(\frac{s_1}{\alpha_0+\alpha_a}+\frac{s_2}{\alpha_0+\alpha_m}\right)}\right)\right]\cdot \\ & \quad exp\left[\frac{\alpha_a}{\mu}\left(1-\sqrt{1+\frac{2\mu^2 s_1}{\alpha_0+\alpha_a}}\right)\right]\cdot exp\left[\frac{\alpha_m}{\mu}\left(1-\sqrt{1+\frac{2\mu^2 s_2}{\alpha_0+\alpha_m}}\right)\right] \end{aligned} \tag{22}$$

Restricting Z_j to have the mean one, for the identifiability problem, the restriction on the parameter is $\mu = 1$, so that the Laplace transform in Equation (22) reduces to

$$\begin{aligned} L_{\underline{Z}}(s_1,s_2) &= exp\left[\alpha_0\left(1-\sqrt{1+2\left(\frac{s_1}{\alpha_0+\alpha_a}+\frac{s_2}{\alpha_0+\alpha_m}\right)}\right)\right]\cdot exp\left[\alpha_a\left(1-\sqrt{1+\frac{2s_1}{\alpha_0+\alpha_a}}\right)\right] \\ & \quad \cdot exp\left[\alpha_m\left(1-\sqrt{1+\frac{2s_2}{\alpha_0+\alpha_m}}\right)\right]; s_1 \geq 0, s_2 \geq 0 \end{aligned}$$

and from Equation (11), the survival function of the lifetime random variable T is

$$S(t \mid \underline{x}) = \begin{cases} exp\left[\alpha_0\left(1-\sqrt{G(t \mid \underline{x})}\right)\right]\cdot exp\left[\alpha_a\left(1-\sqrt{G_a(t \mid \underline{x}_a)}\right)\right] & \\ \qquad exp\left[\alpha_m\left(1-\sqrt{G_m(t \mid \underline{x}_m)}\right)\right] & ; \quad t>0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{23}$$

where $G(t \mid \underline{x}) = 1 + 2A(t \mid \underline{x}_a) + 2B(t \mid \underline{x}_m)$; $G_a(t \mid \underline{x}_a) = 1 + 2A(t \mid \underline{x}_a)$; $G_m(t \mid \underline{x}_m) = 1 + 2B(t \mid \underline{x}_m)$; $A(t \mid \underline{x}_a) = \dfrac{t\eta_a}{\alpha_0+\alpha_a}$, $B(t \mid \underline{x}_m) = \dfrac{H_0(t)\eta_m}{\alpha_0+\alpha_m}$ and the probability density function is

$$\psi(t \mid \underline{x}) = \begin{cases} S(t \mid \underline{x})\left\{\dfrac{\alpha_a}{\alpha_0+\alpha_a}E_1(t \mid \underline{x}_a) + \dfrac{\alpha_m}{\alpha_0+\alpha_m}E_2(t \mid \underline{x}_m) + \alpha_0 E(t \mid \underline{x})\right\} & ; \quad t>0 \\ 0 & ; \quad \text{otherwise} \end{cases}$$

where $E_1(t \mid \underline{x}_a) = \dfrac{\eta_a}{\sqrt{1+2A(t \mid \underline{x}_a)}}$, $E_2(t \mid \underline{x}_m) = \dfrac{h_0(t)\eta_m}{\sqrt{1+2B(t \mid \underline{x}_m)}}$ and $E(t \mid \underline{x}) = \dfrac{\left(A^{(1)}(t \mid \underline{x}_a) + B^{(1)}(t \mid \underline{x}_m)\right)}{\sqrt{1+2A(t \mid \underline{x}_a)+2B(t \mid \underline{x}_m)}}$

$A^{(1)}(t \mid \underline{x}_a)$ and $B^{(1)}(t \mid \underline{x}_m)$ are first-order derivatives of $A(t \mid \underline{x}_a)$ and $B(t \mid \underline{x}_m)$ respectively with respect to t.

Furthermore, expressing the parameters α_0, α_a and α_m in terms of σ_a^2, σ_m^2 and ρ we have

$$\alpha_0 = \frac{\rho}{\sigma_a \sigma_m}; \qquad \alpha_a = \frac{1}{\sigma_a^2}\left[1 - \frac{\sigma_a}{\sigma_m}\rho\right]; \qquad \alpha_m = \frac{1}{\sigma_m^2}\left[1 - \frac{\sigma_m}{\sigma_a}\rho\right].$$

Defining $\kappa_0 = \frac{\rho}{\sigma_a \sigma_m}$; $\kappa_a = \left[1 - \frac{\sigma_a}{\sigma_m}\rho\right]$ and $\kappa_m = \left[1 - \frac{\sigma_m}{\sigma_a}\rho\right]$ and rewriting Equation (23) in terms of $\sigma_a^2, \sigma_m^2, \kappa_0, \kappa_a$ and κ_m the survival function of the lifetime random variable T becomes

$$S(t \mid \underline{x}) = \begin{cases} exp\left[\kappa_0 \left(1 - F(t \mid \underline{x})\right)\right] \cdot exp\left[\frac{\kappa_a}{\sigma_a^2}\left(1 - F_a(t \mid \underline{x}_a)\right)\right] & \\ \quad exp\left[\frac{\kappa_m}{\sigma_m^2}\left(1 - F_m(t \mid \underline{x}_m)\right)\right] & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases}$$

where $F(t \mid \underline{x}) = \sqrt{1 + 2\sigma_a^2 \eta_a t + 2\sigma_m^2 \eta_m H_0(t)}$, $F_a(t \mid \underline{x}_a) = \sqrt{1 + 2\sigma_a^2 \eta_a t}$ and $F_m(t \mid \underline{x}_m) = \sqrt{1 + 2\sigma_m^2 \eta_m H_0(t)}$. From Equations (15) and (16) we can write

$$\sqrt{1 + 2\sigma_a^2 \eta_a t} = 1 - \sigma_a^2 \ln\left[S_a(t \mid \underline{x}_a) e^{H_0(t)}\right] \text{ and } \sqrt{1 + 2\sigma_{\mathrm{m}}^2 \eta_{\mathrm{m}} \mathrm{t}} = 1 - \sigma_{\mathrm{m}}^2 \ln \mathrm{S_m(t \mid \underline{x}_m)}$$

Hence, the survival function can be expressed as

$$S(t \mid \underline{x}) = \begin{cases} exp\left\{\kappa_0 \left[1 - \sqrt{D(t \mid \underline{x}) - 1}\right]\right\} \cdot \left[S_a(t \mid \underline{x}_a) e^{H_0(t)}\right]^{\kappa_a} \cdot S_m(t \mid \underline{x}_m)^{\kappa_m} & ; \quad t > 0 \\ 1 & ; \quad \text{otherwise} \end{cases} \tag{24}$$

where $D(t \mid \underline{x}) = \left[1 - \sigma_a^2 \ln\left(S_a(t \mid \underline{x}_a) e^{H_0(t)}\right)\right]^2 + \left[1 - \sigma_m^2 \ln S_m(t \mid \underline{x}_m)\right]^2$.

If we compare the survival functions in Equations (24) and (18) then the first factor and powers to $S_a(t \mid \underline{x}_a), S_m(t \mid \underline{x}_m)$ in Equation (24) are due to the non-independence between Z_a and Z_m. When $\rho = 0$, $\kappa_a = 1 = \kappa_m$ and $\kappa_0 = 0$, Equation (24) reduces to Equation (18).

Thus, the family of AMIGF models is $\left\{S(t, \underline{\theta}),\ t > 0;\ \underline{\theta} = \left(\underline{\tau}, \underline{\omega}, \underline{\beta}\right)\right\}$, where $S(t, \underline{\theta})$ is the survival function given by Equation (24) or (23) and $\underline{\tau}, \underline{\omega}$ and $\underline{\beta}$ are respectively vectors of the baseline parameters, frailty parameters and regression parameters. By considering different baseline distributions, one can develop different AMIGF models.

4. Baseline specification

To complete the form of the survival function this paper considers the baseline hazard function to be the hazard function of the generalized exponential distribution. Gupta and Kundu (1999) suggested that the generalized exponential distribution can be used effectively in analyzing many lifetime data sets, particularly as an alternative to the gamma and Weibull distributions. A continuous random variable X is said to follow the generalized exponential distribution if its survival function is,

$$S_0(x) = \begin{cases} 1 - (1 - e^{-x/\theta_2})^{\theta_1} & ;\ x > 0, \theta_1 > 0, \theta_2 > 0 \\ 1 & ;\ \text{otherwise.} \end{cases}$$

where θ_1 and θ_2 are, respectively, the shape and scale parameters of the distribution. The hazard function and the cumulative hazard function are, respectively,

$$h_0(x) = \begin{cases} \frac{\theta_1 e^{-x/\theta_2}(1-e^{-x/\theta_2})^{\theta_1-1}}{\theta_2\left[1-(1-e^{-x/\theta_2})^{\theta_1}\right]} & ; \ x>0, \theta_1>0, \theta_2>0 \\ 0 & ; \text{ otherwise.} \end{cases}$$

$$H_0(x) = \begin{cases} -ln[1-(1-e^{-x/\theta_2})^{\theta_1}] & ; \ x>0, \theta_1>0, \theta_2>0 \\ 0 & ; \text{ otherwise.} \end{cases}$$

When $\theta_1 = 1$ distribution reduces to the one-parameter exponential distribution and has constant failure rate $\frac{1}{\theta_2}$. When $\theta_1 > 1$, the hazard function is an increasing function of time, and for $\theta_1 < 1$, the hazard function is a decreasing function of time.

5. Bayesian inferential procedure

Suppose n individuals are observed with lifetimes $\underline{t} = (t_1, t_2, \cdots, t_n)$; censoring times $c_1, c_2, \cdots, c_n$ and censoring indicators $\underline{\delta} = (\delta_1, \delta_2, \cdots, \delta_n)$ with

$$\delta_j = \begin{cases} 1 & ; \text{ if j}^{\text{th}} \text{ individual is observed} \\ 0 & ; \text{ if j}^{\text{th}} \text{ individual is censored} \end{cases}$$

Also, suppose that x_{auj} and x_{mvj}, are the observed covariate values of u^{th} additive covariate and v^{th} multiplicative covariate, $u = 1, 2, \cdots, k_a$; $v = 1, 2, \cdots, k_m$; $j = 1, 2, \cdots, n$. Assuming the independence between censoring times and lifetimes, the likelihood function is

$$L\left(\underline{\tau}, \underline{\omega}, \underline{\beta} \mid (\underline{t}, \underline{\delta})\right) = \prod_{j=1}^{n} \left\{\psi(t_j)^{\delta_j} S(t_j)^{1-\delta_j}\right\}$$

The commonly used estimation method is the maximum likelihood method, which involves solving simultaneous likelihood equations, namely the first-order partial derivatives of the log-likelihood function with respect to the parameters. The likelihood equations for the proposed models could not provide an analytical solution. As a result, an iterative procedure such as Newton-Raphson has to be used to solve likelihood equations. Unfortunately, in frailty models, the maximum likelihood method fails to converge to the true parameters due to a large number of parameters and heavy censoring. (*see* Kheiri *et al.* (2005), Hanagal (2021)). Hence, a computational Bayesian approach is adopted to estimate the model parameters in this paper. The joint posterior density function of the parameters $\left(\underline{\tau}, \underline{\omega}, \underline{\beta}\right)$ for given data $\underline{t}, \underline{\delta}$ is given by

$$\pi(\underline{t}, \underline{\delta} | \underline{\tau}, \underline{\omega}, \underline{\beta}) \ \propto \ L(\underline{\tau}, \underline{\omega}, \underline{\beta} | \underline{t}, \underline{\delta}) \times \prod_{i=1}^{n_b} g_i(a_i) \times \prod_{i=1}^{n_f} h_i(b_i) \times \prod_{i=1}^{k} p_i(\beta_i)$$

where $g_i(\cdot), h_i(\cdot), p_i(\cdot)$ are the prior density functions of the baseline, frailty, and regression parameters with known hyperparameters. The number of baseline, frailty, and regression parameters are represented by n_b, n_f and $k = k_a + k_m$, respectively. Here, independence is assumed between all model parameters. The posterior density function of a specific parameter can be obtained by integrating over other parameters.

When no information about the parameters is available, one can choose an empirical approach to determine prior distributions or use non-informative distributions as priors. In this paper, the latter approach is used. A widely used prior distribution for frailty parameters is $Gamma(shape = \phi, scale = \phi)$ with a small choice of ϕ so that the distribution will have mean one and a large variance. For the regression coefficients, $N(0, \sigma^2)$ with a large value of σ^2 is a popular choice. This paper examines two sets of prior distributions to investigate the impact of prior distributions on estimators. The first set is

$$\begin{aligned} \theta_1, \theta_2 &\sim Gamma(shape = 1, scale = 0.0001) \\ \alpha_0, \alpha_1, \alpha_2 &\sim Gamma(shape = 1, scale = 0.0001) \\ \underline{\beta} &\sim Normal(mean = 0, sd = 1000) \end{aligned}$$

and second set based on $U(a, b)$ is

$$\begin{aligned} \theta_1, \theta_2 &\sim U(0, 100) \\ \alpha_0, \alpha_1, \alpha_2 &\sim U(0, 100) \\ \underline{\beta} &\sim U(-50, 50) \end{aligned}$$

The probability density functions of the prior distributions in both sets are flat, providing very little information about the parameters.

A computational Bayesian approach was used to generate two Markov chains, each comprising $N = 50000$ iterations, using the Gibbs sampler and the Metropolis-Hastings algorithm with two sets of prior distributions. A normal transition kernel was considered to generate the chains. The burn-in period (B) was determined using coupling from the past plots, and the convergence of chains to a stationary distribution was monitored using the Gelman-Rubin convergence statistic and the Geweke test. The plots of the sample autocorrelation function were used to determine the autocorrelation lag (k). Once the values of B and k were decided, a pseudorandom sample of size n (where n is less than or equal to $(N - B)/k$) was obtained, and the model parameters were estimated using the sample posterior mean. The posterior variances of the estimators, along with credible intervals, were also obtained.

A Deviance Information Criteria (DIC) was used to compare the fitted models. As Spiegelhalter *et al.* (2002) noted, DIC is a good measure for comparing the Bayesian models, where analysis is carried out via MCMC methods to assess the posterior distribution. Instead, the advantage of the DIC is that it can be easily calculated from a posterior summary, unlike the other information criterion. Log-likelihood and Bayes' factor (*see* Kass and Raftery (1995)) were also used to compare the models.

6. Simulation study

A simulation study was conducted to evaluate the performance of the estimation procedure. In this comprehensive study, data were generated from the AMIGF model with two covariates: one having an additive effect (x_a) and the other having a multiplicative effect (x_m) on the hazard function. Both these variables were generated from a normal distribution with different parameters. The inverse transform technique was used to generate lifetimes, which involves equating the survival function for given frailties z_a, z_m and covariates x_a, x_m

to a random number R. By equating the Equation (10) to R, we get

$$z_a\eta_a t + z_m\eta_m H_0(t) = -log(R) \tag{25}$$

Solving the Equation (25), one can generate lifetimes, but unfortunately, the equation cannot be expressed as an explicit function of R, so it must be generated using the Newton-Raphson iterative procedure. Table 1 provides an algorithm for generating data. The frailties were

Table 1: Simulation algorithm

step 1	Generate x_a, x_m from $N(\mu_a, \sigma_a^2)$ and $N(\mu_m, \sigma_m^2)$ respectively.
step 2	Generate frailties z_a, z_m from $IG(\mu = 1, \alpha_0 + \alpha_a)$ and $IG(\mu = 1, \alpha_0 + \alpha_m)$ respectively.
step 3	Generate lifetime t by solving the Equation (25) using generated values z_a, z_m, x_a, x_m.

generated from IG using the R package 'statmod'. The true values of the parameters were $\theta_1 = 1.0; \theta_2 = 42, \alpha_0 = \alpha_a = \alpha_m = 2.5, \beta_1 = 3.0 = \beta_2$.

The generated data was used to fit three models: AIGF, MIGF, and AMIGF. The AIGF model considered both covariates to have an additive effect, while MIGF considered a multiplicative effect. For the AMIGF model, the actual model (x_a additive and x_m multiplicative) was first fitted (AMIGF I). The second model (AMIGF II) was then fitted by reversing the positions of the covariates (x_a multiplicative and x_m additive) to test the model's sensitivity to the position of the covariates.

The trace plots depicting the parameters of the AMIGF I model are shown in Figure 1. The plots do not show a trend or pattern, suggesting that the parameter values generated are randomly distributed throughout the parameter space. The same observations were made for the other model parameters.

The Gelman-Rubin convergence statistic values were quite close to one for all the models' parameters, and the p-values of the Geweke tests were significant enough to indicate that the chains have attained a stationary distribution. A similar pattern was observed regarding the posterior summary in both chains and with both prior sets. Hence, results are presented here for only one chain and with only one prior set of distributions. The posterior summaries for the AIGF and MIGF models are presented in Table 2, and Table 3 represents the posterior summaries for the AMIGF models. Figures 2 to 4 represent the posterior distribution of the parameters of the AIGF, MIGF, AMIGF I and AMIGF II models. The Table 4 shows the DIC values and log-likelihood for all fitted models. Twice the logarithm of Bayes' factor with AMIGF I as the numerator model and the other three models AIGF, MIGF, and AMIGF II as denominator are, respectively, $16.5830, 22.9156$ and 1.4136. All these measures indicate that the fitted model (AMIGF I) estimates the parameters unbiasedly when the fitted model is the actual model. This performance of the estimation strategy underscores its reliability and ability to fit the data accurately.

7. Data analysis

The AMIGF model presented in this research is demonstrated using two datasets: Kidney Infection (KI) data from McGilchrist and Aisbett (1999) and Acute Myelogenous

Leukemia (AML) data as reported in Miller (1997).

7.1. Kidney infection data

The data pertain to the time it took for an infection to recur after catheter insertion in 38 kidney patients who used portable dialysis equipment. For each patient, the first and second recurrence times (in days) of infection from the time of catheter insertion until it had to be removed due to infection were recorded. It's essential to note that the catheter may have been removed for reasons unrelated to the kidney infection, which should be considered as censoring. The actual data includes the first and second infection times or censoring times for a patient represented by T_1, T_2 respectively, along with censoring indicators and five covariates: age, gender (Male(0), Female(1)), and presence (1) or absence (0) of disease type GN, AN, PKD represented by x_1, x_2, x_3, x_4, and x_5 respectively, where GN, AN and PKD are short forms of Glomerulo Neptiritis, Acute Neptiritis and Polycyatic Kidney Disease. Since this paper addresses a univariate case, only the first infection time is considered for the analysis.

All three models were fitted to the first infection time using a self-written program in R. When fitting the AIGF model; all covariates were considered to have an additive effect, whereas when fitting the MIGF model, they were all considered to have a multiplicative effect. The AMIGF models were attempted by considering different combinations of covariates as either additive or multiplicative to determine whether the effects of covariates were additive or multiplicative. In total, there were 30 such combinations.

The two chains, generated using the Bayesian inference procedure, demonstrated similar results. Additionally, both sets of prior distributions yielded matching results. Therefore, only the results from one chain, using the first set of prior distributions, are discussed here. The Gelman-Rubin convergence statistic values were close to one, indicating convergence and the Geweke test values were relatively small, with corresponding p-values that were significant enough to suggest the chain had reached a stationary distribution.

Table 5 contains the posterior summary for the AIGF and MIGF models. Figures 5 and 6 display the histogram of the posterior distribution for the AIGF and MIGF models, respectively. Table 6 provides the DIC and log-likelihood values for all the fitted 30 AMIGF models, including AIGF and MIGF models. In the case of AMIGF models, the covariates listed in the first column of Table 6 indicate additive covariates, while the remaining covariates were considered multiplicative. Table 6 shows that the MIGF model has a lower DIC than the AIGF model. Although the log-likelihood values are not significantly different, the twice the log of Bayes' factor with MIGF as the numerator model is 17.0077, indicating that the MIGF is a better model. Additionally, it's worth noting that some AMIGF models have less DIC and larger log-likelihood values than the MIGF model. The model with x_2 as an additive covariate stands out among these similar models. Therefore, including x_2 into the model additively may be a better choice than multiplicatively. Furthermore, AMIGF models with x_2 and x_5 as additive covariates and x_1, x_3, and x_4 as multiplicative covariates (AMIGF-25) have a lower DIC value than all other models, including AIGF and MIGF. The log-likelihood value is also slightly higher than all other models, indicating that the AMIGF-25 model performs better than the MIGF model. Moreover, twice the log of Bayes' factor with AMIGF-25 as the numerator model and MIGF as the denominator model is 4.6016,

suggesting that the AMIGF-25 model is the best model for modeling the first recurrence time.

Figure 7 shows the trace plots for the parameters of the best model AMIGF-25. The plot shows the random behavior of generated values. The posterior summary for model AMIGF-25 is provided in Table 7. Figure 8 displays the posterior distribution.

The estimate to standard error ratios for β_2 and β_5 are significantly different from one. Specifically, these ratios are -5.4782 and -1.4486 respectively. This suggests that gender (x_2) and PKD disease type (x_5) have a significant impact on kidney infection development. The negative values of both regression coefficients indicate that they have a reverse effect on infection. Therefore, for female patients, the frequency of infection is lower than for male patients who suffer from PKD.

7.2. Acute myelogenous leukemia data

The study aimed to assess the efficacy of maintenance chemotherapy for AML patients. Once the patients achieved remission through chemotherapy, those who continued the study were randomly divided into two groups. One group received maintenance chemotherapy, while the other did not receive any further treatment. The data include the survival or censoring time (t), censoring indicators (δ), and covariate x, which indicates whether the patient received maintenance chemotherapy (1) or not (0). There were 23 patients in total, with 5 of them censored.

All three models (AIGF, MIGF, and AMIGF) were used to analyze the data. Two AMIGF models were fitted to the data to determine whether the covariate effect is additive or multiplicative. The first model (AMIGF I) considered the covariate to have an additive effect, while the second model (AMIGF II) considered it to have a multiplicative effect. Similar results were observed from both chains and both sets of prior distributions, so the discussion focuses on the results from one chain with the first set of prior distributions.

The Gelman-Rubin convergence statistic values were close to one, the Geweke test values were relatively small, and the corresponding p-values were significant enough to confirm that the chain had attained a stationary distribution. The Figure 9 displays trace plots for the AMIGF I model. A similar random pattern was observed in the trace plots of other models. The posterior summaries for the AIGF and MIGF models are presented in Table 8, and the posterior summaries for AMIGF I and AMIGF II models are presented in Table 9. The posterior distribution for the AIGF, MIGF, AMIGF I, and AMIGF II models are shown in Figures 10 and 11. Table 10 provides DIC and log-likelihood values for all fitted models. The results indicate that the MIGF model fits better than the AIGF model. The twice log of Bayes' factor with MIGF as the numerator model is 5.7282, which confirms the conclusion. While comparing AMIGF models, both models exhibited similar behavior, suggesting no difference in whether the covariate is included in the model as having an additive or multiplicative effect. Furthermore, these models showed slightly larger log-likelihood values and smaller DIC values than the MIGF models. The twice the log of the Bayes' factor with the AMIGF I and AMIGF II models as the numerator and MIGF as the denominator is 8.4439 and 9.1167. These findings collectively indicate that the AMIGF models outperform the AIGF and MIGF models.

The absolute ratio of the estimate to the standard error of β in both models, AMIGF I and AMIGF II, is slightly larger than one. The credible interval contains zero, indicating that the treatment has a significant effect on remission time. However, the negative value of β indicates that maintained chemotherapy does not help to increase the remission period. Further research on testing the significance of β can provide a better understanding of this.

8. Conclusion

The additive and multiplicative hazard models are commonly used regression models to analyze the impact of covariates on failure time. The additive hazard model examines the relationship between covariates and the hazard function in terms of risk difference, while the multiplicative model focuses on the risk ratio. Although these models are straightforward and practical, researchers have identified a need for a compromise model incorporating covariates with both additive and multiplicative effects, as proposed by Lin and Ying (1997). Furthermore, to account for heterogeneity within the population, it is necessary to include frailty variables in the model. These frailty variables may affect the hazard function additively (additive frailty model) or multiplicatively (multiplicative frailty model). The additive and multiplicative frailty models are well-studied in the literature. Since frailty variables are unobservable, one can not decide whether frailty is acting additively or multiplicatively. Some of the unknown factors may affect the hazard additively, while others may affect it multiplicatively. Therefore, it is essential to explore additive-multiplicative frailty models.

This study aims to present a new family of models that incorporates both additive and multiplicative frailty variables. This model can capture the additive and multiplicative relationships between the frailty random variable and the hazard function. In this article, to complete the parametric form, the inverse Gaussian distribution is considered as the frailty distribution, and the generalized exponential distribution, introduced by Gupta and Kundu (1999), is used as the baseline distribution. One can define various AMIGF models by considering more advanced baseline distributions.

The proposed AMIGF model was applied to real-world data, the first infection time of kidney infection data, and acute myelogenous leukemia data. It was then compared with the traditional MIGF and AIGF models using a self-written program in R. Based on the DIC criteria, log-likelihood, and Bayes' factor, the best model that emerged was the AMIGF model. This practical application emphasizes the importance of the proposed model and also highlights the need for frailty to have additive and multiplicative effects.

Further research can involve exploring and comparing different frailty distributions, such as the gamma, power variance, compound Poisson, and compound negative binomial distributions. The AMIGF model can also be expanded to include shared and correlated frailty models.

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Conflict of interest

The author has no financial or non-financial conflict of interest to declare for the research work included in this article.

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Appendix I
Proof of Theorem 1

Proof: As $Z_a = c_a(d_aY_0 + Y_a)$ and $Z_m = c_m(d_mY_0 + Y_m)$ we have,

$$E\left[Z_a\right] = c_a(d_aE\left[Y_0\right] + E\left[Y_a\right]) \quad \text{and } \mathrm{E}\left[\mathrm{Z_m}\right] = \mathrm{c_m}(\mathrm{d_m}\mathrm{E}\left[\mathrm{Y_0}\right] + \mathrm{E}\left[\mathrm{Y_m}\right])$$

Consider

$$\begin{aligned} cov\left(Z_a, Z_m\right) &= E\left[\left(Z_a - E(Z_a)\right)\left(Z_m - E(Z_m)\right)\right] \\ &= c_ac_md_ad_mvar(Y_0) + c_ac_md_mcov(Y_0, Y_a) + c_ac_md_acov(Y_0, Y_m) + c_ac_mcov(Y_a, Y_m) \\ &= c_ac_md_ad_mvar(Y_0) \qquad \text{since} \mathrm{Y_0}, \mathrm{Y_a} \text{ and } \mathrm{Y_m} \text{ are independent} \end{aligned}$$

substituting c_j, d_j, $j = a, m$ and $var(Y_0)$ we have

$$cov\left(Z_a, Z_m\right) = \frac{\mu^3\alpha_0}{\left(\alpha_0 + \alpha_a\right)\left(\alpha_0 + \alpha_m\right)}$$

Therefore

$$\rho = \frac{cov\left(Z_a, Z_m\right)}{\sqrt{var\left(Z_a\right)}\sqrt{var\left(Z_m\right)}} = \frac{\alpha_0}{\sqrt{\alpha_0 + \alpha_a}\sqrt{\alpha_0 + \alpha_m}}$$

□

Appendix II: Tables and figures

Table 2: Simulation results for AIGF and MIGF models

Parameter	True values	AIGF				MIGF			
		Mean	Standard error	Credible Interval Lower	Credible Interval Upper	Mean	Standard error	Credible Interval Lower	Credible Interval Upper
θ_1	1.0	1.24	0.73	0.37	2.89	0.30	0.05	0.22	0.42
θ_2	42	55.72	23.36	21.29	97.69	26.66	9.25	20.15	50.22
α_a (α_m)	2.5	3.16	1.17	0.74	4.90	3.63	0.91	1.78	4.95
β_1	3.0	2.84	0.42	2.02	3.64	1.23	0.43	0.54	2.08
β_2	3.0	0.49	0.29	0.02	1.13	0.33	0.26	0.01	0.92

Table 3: Simulation results for AMIGF models

Parameter	True values	AMIGF I				AMIGF II			
		Mean	Standard error	Credible Interval Lower	Credible Interval Upper	Mean	Standard error	Credible Interval Lower	Credible Interval Upper
θ_1	1.0	1.02	0.28	0.57	1.59	0.61	0.12	0.38	0.84
θ_2	42	42.27	19.88	20.56	91.04	44.33	21.46	20.99	96.96
α_0	2.5	2.56	1.43	0.17	4.89	0.67	0.82	0.02	3.21
α_a	2.5	2.54	1.43	0.10	4.84	0.74	0.99	0.02	4.26
α_m	2.5	2.63	1.41	0.21	4.91	2.89	1.35	0.27	4.85
β_1	3.0	3.24	0.35	2.45	3.89	3.62	0.76	2.22	4.91
β_2	3.0	3.61	0.99	1.37	4.94	1.77	0.50	0.77	2.82

Table 4: Model comparison values for simulation study

Model	AIGF	MIGF	AMIGF I	AMIGF II
DIC	7.93	44.29	-2.81	18.48
log likelihood	-2.42	-19.97	3.59	-8.01

Table 5: Posterior summary for AIGF and MIGF models fitted to KI data

Parameter	AIGF Model				MIGF Modle			
	mean	standard error	Credible Intervals Lower	Upper	mean	standard error	Credible Intervals Lower	Upper
θ_1	2.72	1.12	0.93	4.83	0.95	0.21	0.55	1.43
θ_2	203.90	49.43	121.93	294.67	143.57	52.61	101.64	298.31
$\alpha_a(\alpha_m)$	0.03	0.02	0.001	0.071	5.97	2.37	1.25	9.68
β_1	0.42	0.54	-0.53	1.61	-0.15	0.25	-0.58	0.33
β_2	-2.48	0.49	-2.99	-0.99	-1.04	0.51	-2.02	0.14
β_3	-0.46	1.19	-2.71	1.92	1.14	0.63	-0.19	2.19
β_4	0.47	1.09	-1.69	2.66	1.68	0.59	0.36	2.74
β_5	-1.45	1.01	-2.88	0.91	0.39	0.65	-1.07	1.65

Table 6: DIC and log-likelihood values for the models fitted to KI data

Additive covariates	log likelihood	DIC	Additive covariates	log likelihood	DIC
Model: AMIGF					
-	-185.36	390.89	x_1	-188.67	379.82
x_2	-183.99	374.49	x_3	-189.39	383.49
x_4	-189.52	384.76	x_5	-188.68	379.65
x_1, x_2	-183.74	374.89	x_1, x_3	-189.09	382.74
x_1, x_4	-189.16	384.43	x_1, x_5	-187.53	377.95
x_2, x_3	-183.69	374.64	x_2, x_4	-184.14	377.04
x_2, x_5	-180.06	370.13	x_3, x_4	-189.57	386.57
x_3, x_5	-188.75	381.97	x_4, x_5	-189.18	384.69
x_1, x_2, x_3	-183.60	374.95	x_1, x_2, x_4	-184.04	377.33
x_1, x_2, x_5	-183.10	372.70	x_1, x_3, x_4	-189.49	387.26
x_1, x_3, x_5	-188.47	382.09	x_1, x_4, x_5	-188.73	384.06
x_2, x_3, x_4	-183.85	377.11	x_2, x_3, x_5	-182.84	373.71
x_2, x_4, x_5	-183.31	375.69	x_3, x_4, x_5	-189.37	386.46
x_1, x_2, x_3, x_4	-183.78	376.82	x_1, x_2, x_3, x_5	-182.85	373.67
x_1, x_2, x_4, x_5	-183.16	375.93	x_1, x_3, x_4, x_5	-189.09	386.00
x_2, x_3, x_4, x_5	-183.08	375.85	x_1, x_2, x_3, x_4, x_5	-183.21	376.44
Model: MIGF			Model: AIGF		
-	-181.49	374.89	x_1, x_2, x_3, x_4, x_5	-182.68	377.03

Table 7: Posterior summary for AMIGF-25 model fitted to KI data

parameter	mean	standard error	Credible Intervals	
			Lower	Upper
θ_1	2.0454	0.5415	1.0603	2.9363
θ_2	209.8744	50.9649	116.1107	293.6556
α_0	0.0098	0.0053	0.0008	0.0192
α_a	0.0094	0.0055	0.0007	0.0192
α_m	2.0033	1.1084	0.2547	3.8709
β_1	0.0435	0.3386	-0.7293	0.4889
β_2	-2.4608	0.4492	-2.9851	-1.3263
β_3	-0.3596	1.2644	-2.7740	2.1238
β_4	1.0061	1.4008	-2.5124	2.8934
β_5	-1.4067	0.9711	-2.8853	0.7154

Table 8: Posterior summary for AIGF and MIGF models fitted to AML data

parameter	mean	standard error	Credible Intervals	
			Lower	Upper
AIGF Model				
θ_1	2.2076	0.9644	1.1761	4.8805
θ_2	40.7607	15.5808	16.9704	95.1269
α_a	0.0038	0.0039	0.0001	0.0163
β_1	-1.1354	0.8959	-1.9652	0.2658
MIGF Model				
θ_1	3.1361	1.2108	1.1264	4.8691
θ_2	14.4335	4.6274	17.5399	94.0934
α_m	1.7154	1.0976	0.0001	0.0163
β_1	-0.6188	0.3396	-1.9620	0.1611

Table 9: Posterior summary for AMIGF I and AMIGF II models fitted to AML data

parameter	mean	standard error	Credible Intervals Lower	Upper
AMIGF I Model				
θ_1	2.7997	1.0354	1.0509	4.8087
θ_2	40.2723	20.8904	16.6114	93.0445
α_0	0.0042	0.0040	9.46×10^{-5}	1.53×10^{-2}
α_a	0.0043	0.0039	0.0001	0.0156
α_m	2.3590	1.3707	0.1925	4.7937
β_1	-0.7880	0.5790	-1.1886	0.3373
AMIGF II Model				
θ_1	2.8090	1.0433	1.1264	4.8691
θ_2	46.2515	21.5199	17.5399	94.0934
α_0	0.0047	0.0041	0.0001	0.0151
α_a	0.0048	0.0042	0.0001	0.0156
α_m	2.7134	1.3423	0.3410	4.8755
β_1	-1.1019	0.5925	-1.9619	0.1611

Table 10: DIC and log-likelihood values for the models fitted to AML data

Model	AIGF	MIGF	AMIGF I	AMIGF II
log-likelihood	-84.7276	-80.6346	-79.3018	-79.3251
DIC values	173.0994	167.2703	164.5656	164.6036

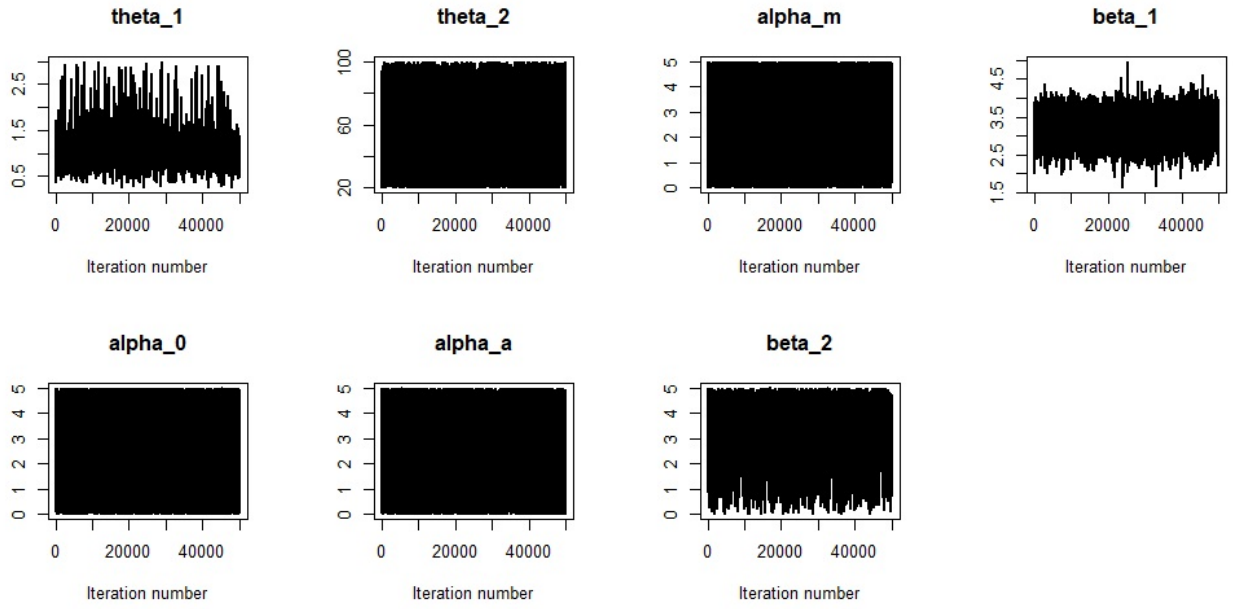

Figure 1: Trace plots of AMIGF I model parameters for simulated data

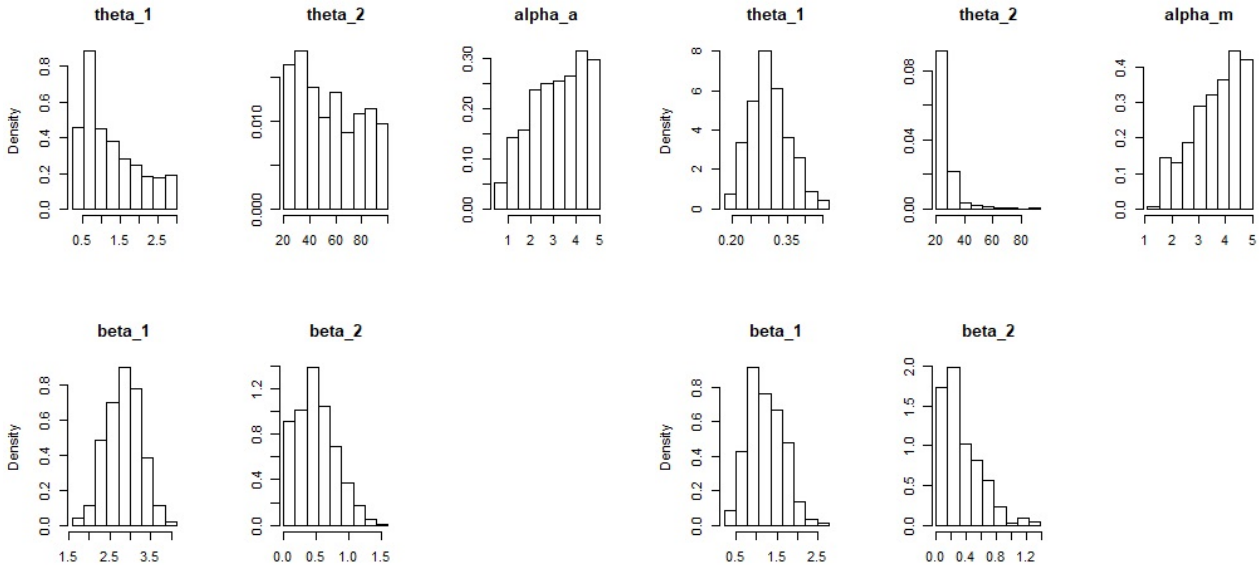

Figure 2: Posterior distribution of AIGF (left) and MIGF (right) model parameters for simulated data

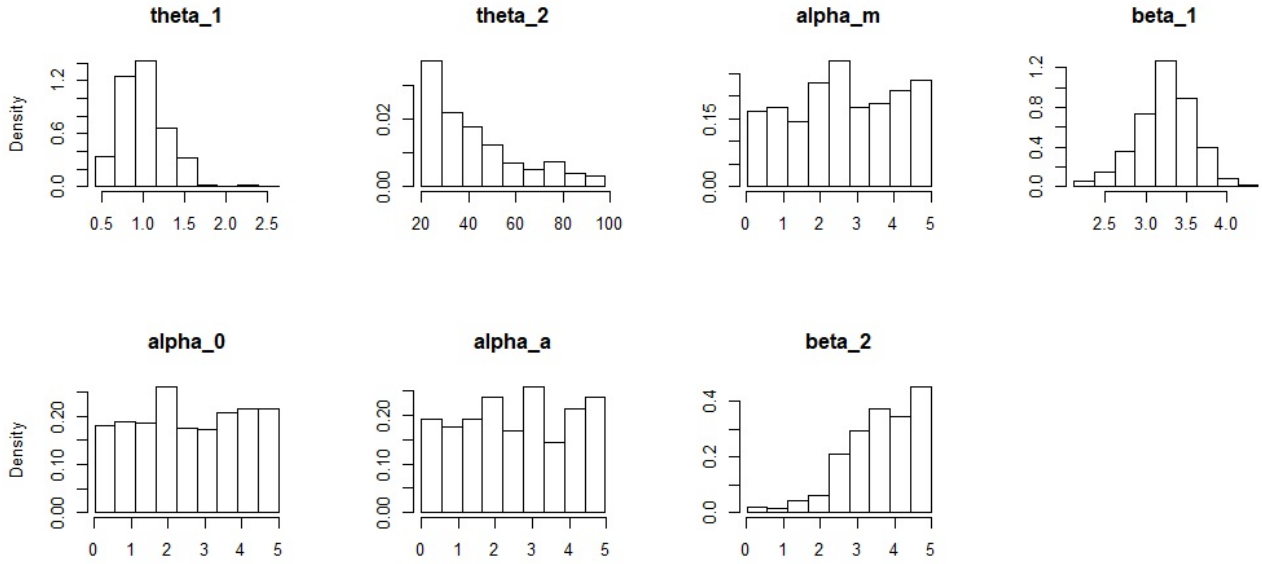

Figure 3: Posterior distribution of AMIGF I model parameters for simulated data

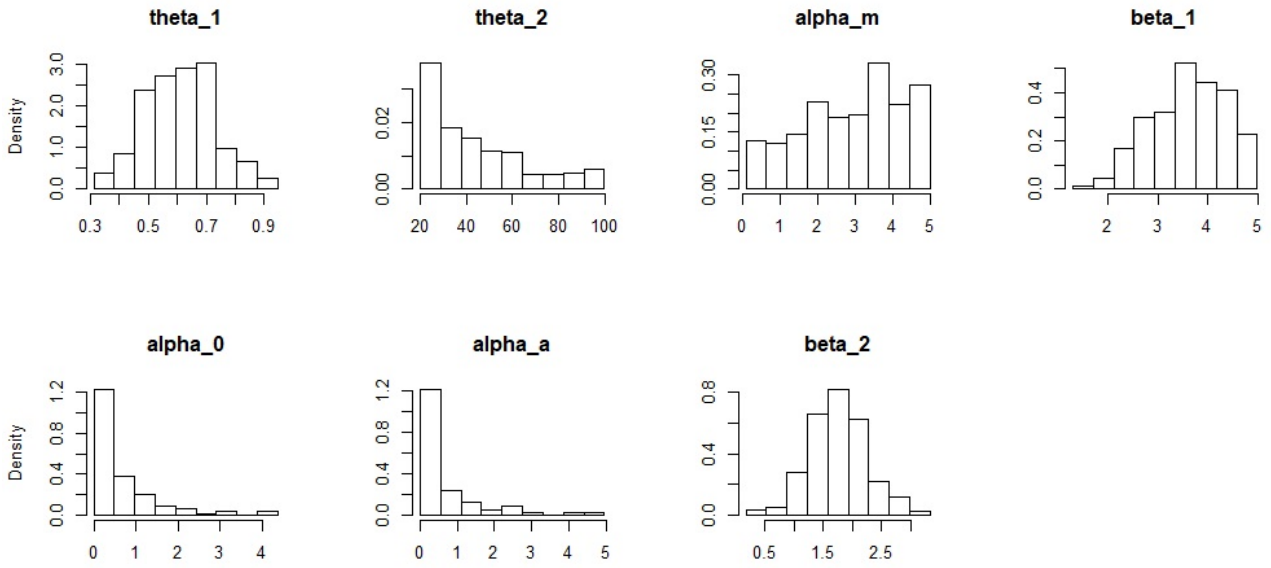

Figure 4: Posterior distribution of AMIGF II model parameters for simulated data

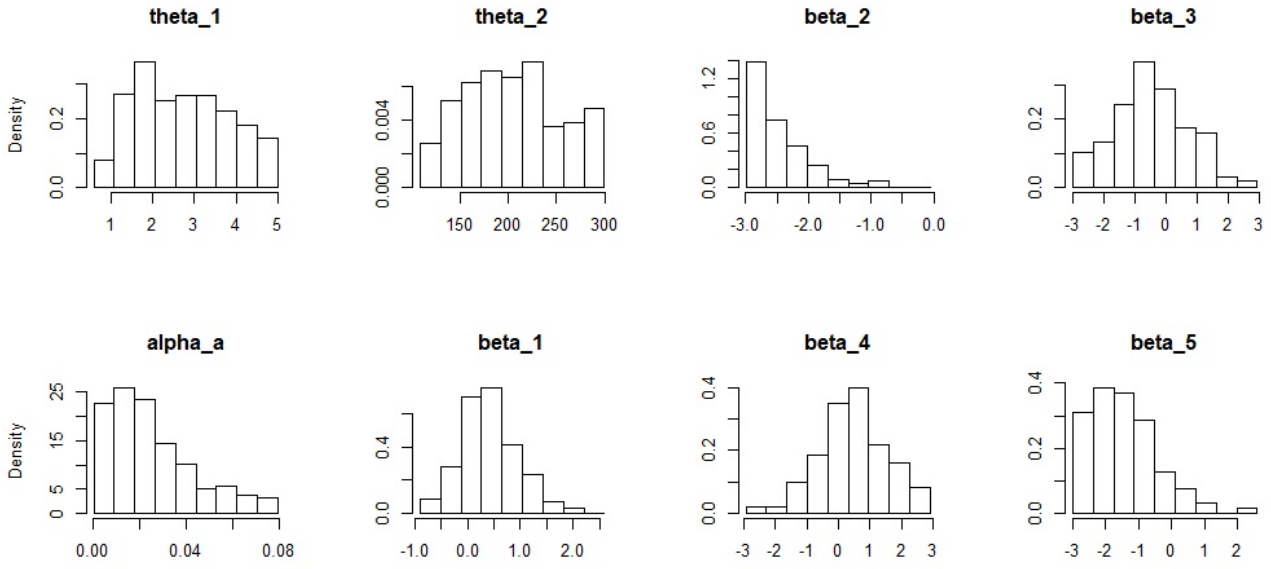

Figure 5: Posterior distribution of AIGF model parameters for KI data

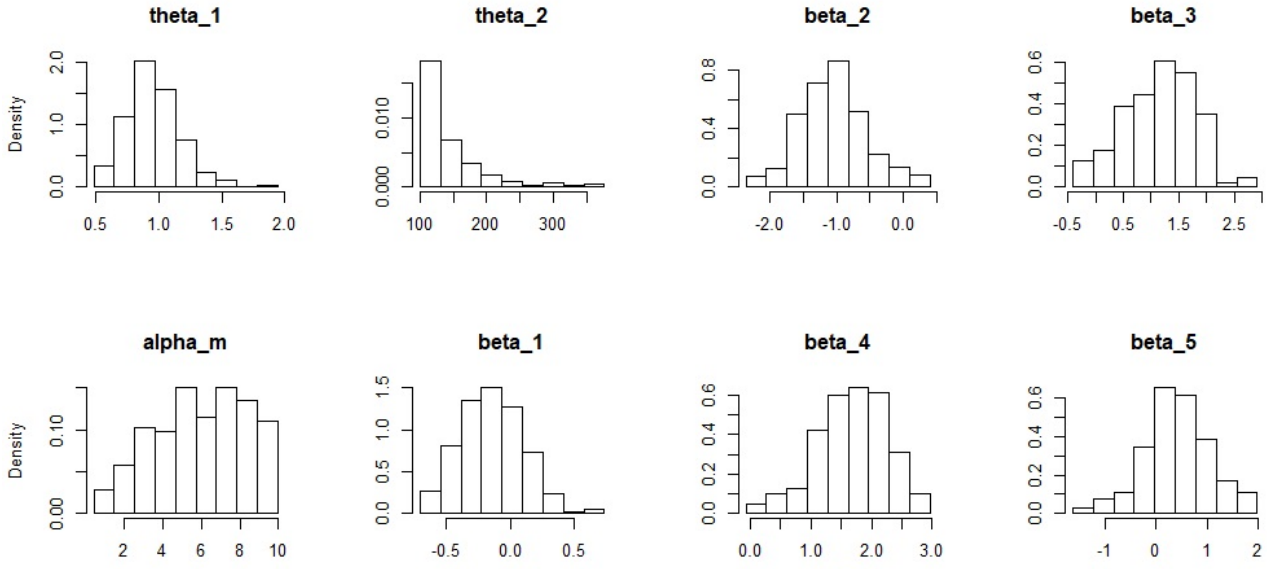

Figure 6: Posterior distribution of MIGF model parameters for KI data

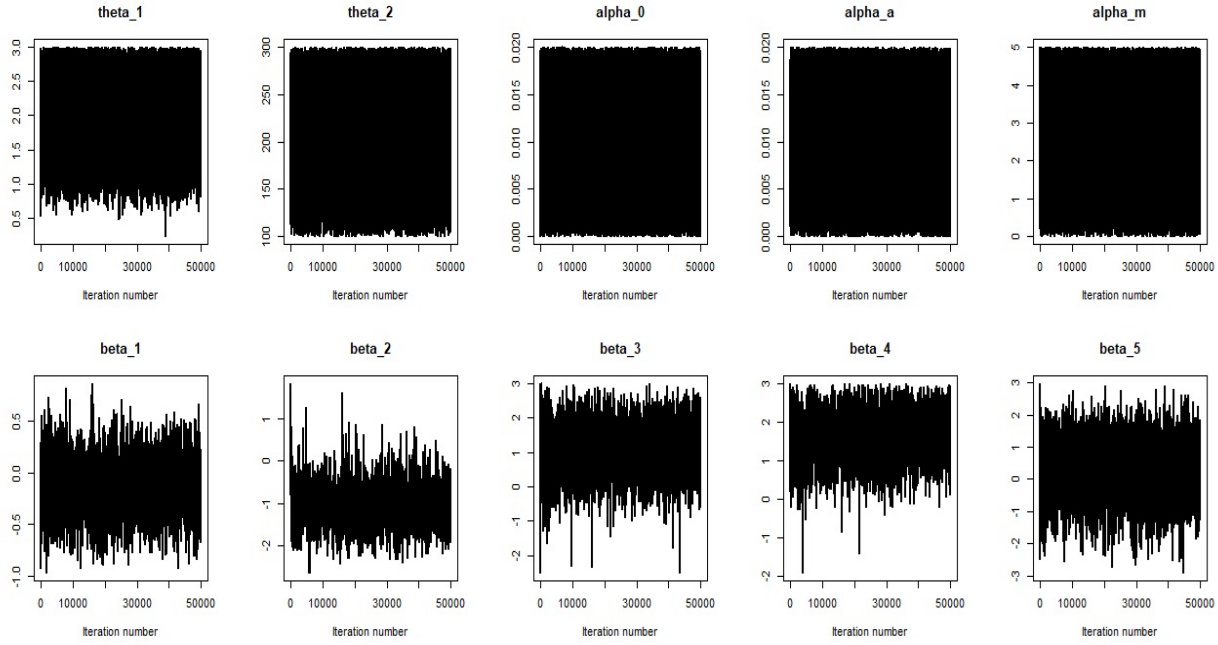

Figure 7: Trace plots of the AMIGF-25 model parameters fitted to KI data

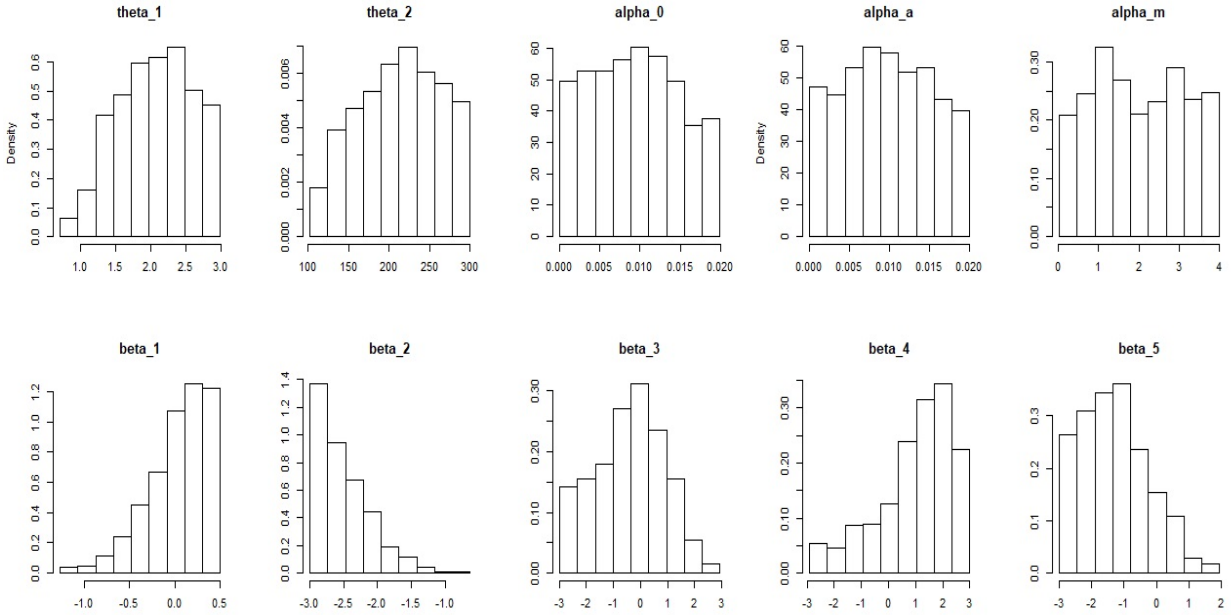

Figure 8: Posterior distribution of AMIGF-25 model parameters for KI data

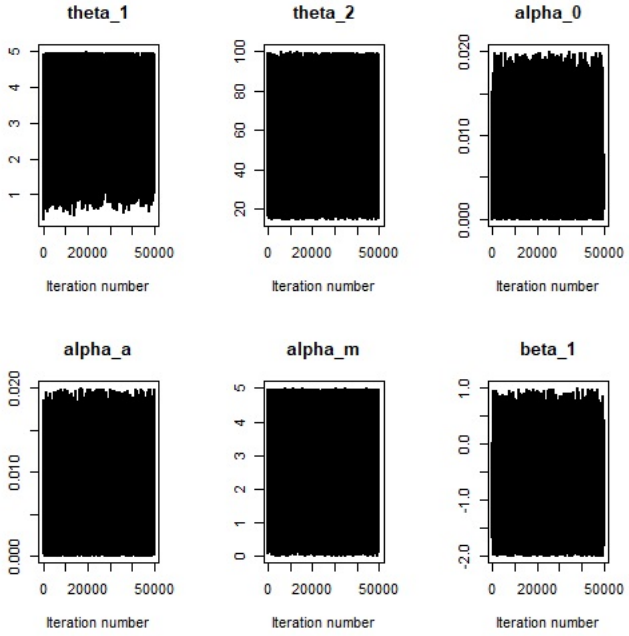

Figure 9: Trace plots of AMIGF I model parameters for AML data

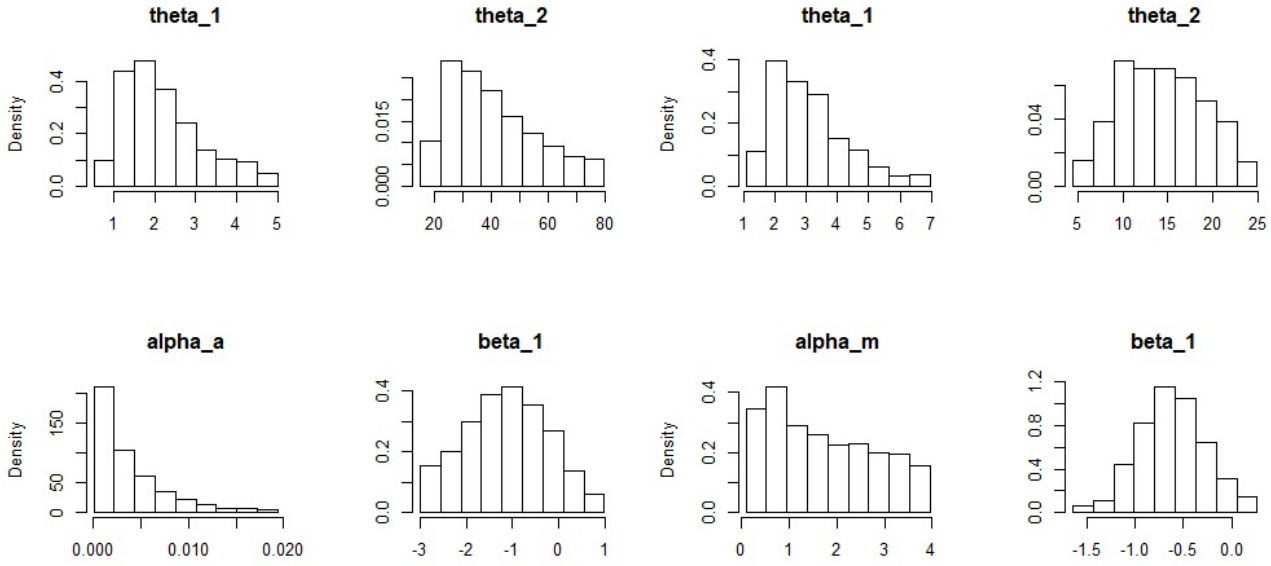

Figure 10: Posterior distribution for AIGF (left), MIGF (right) model parameters for AML data

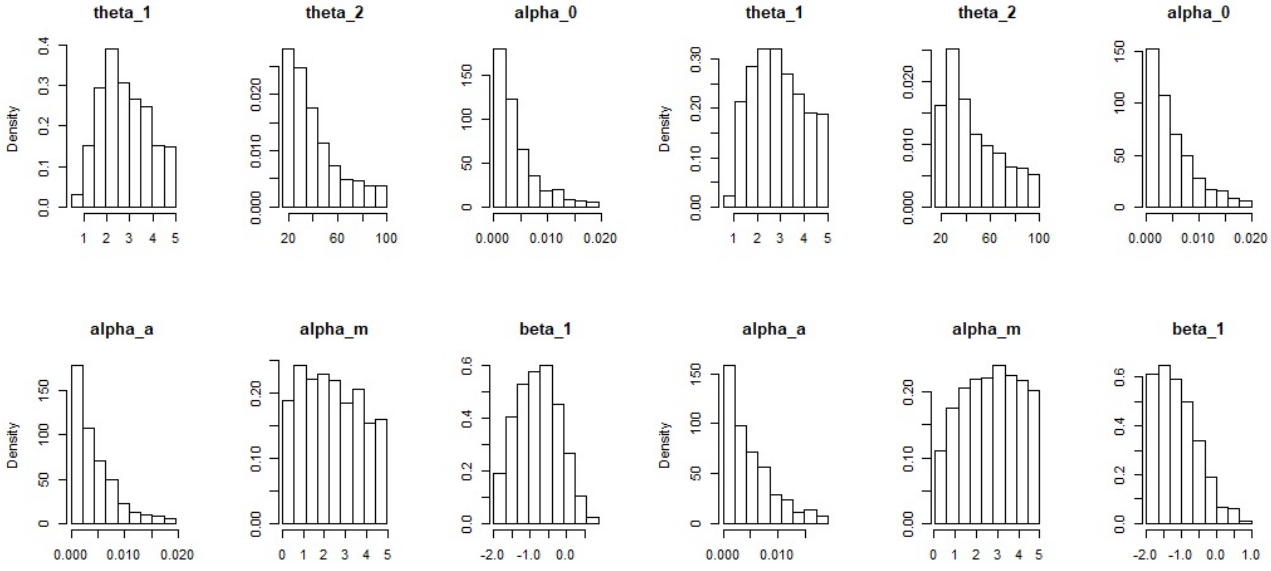

Figure 11: Posterior distribution for AMIGF I (left), AMIGF II (right) model parameters for AML data