

# Numerical Evaluation of Gamma Inequalities

John Cook

Department of Biostatistics, Box 447  
The University of Texas, M. D. Anderson Cancer Center  
1515 Holcombe Blvd., Houston, Texas 77030, USA  
`cook@mdanderson.org`

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## Abstract

This paper addresses the problem of numerically evaluating the probabilities  $P(X > Y)$ ,  $P(X > \max(Y, Z))$ , and  $P(X < \min(Y, Z))$  where  $X$ ,  $Y$ , and  $Z$  are independent gamma or inverse gamma random variables.

**Keywords:** gamma distribution, stochastic inequalities, Appell F2 function, generalized order statistics

## 1 Introduction

In adaptively randomized clinical trials, the probability of assigning a treatment increases as evidence accumulates in favor of that treatment being better than its competitors. Such a design will, on average, assign more patients to more effective treatments while retaining the benefits of randomization.

When the primary endpoint of the trial is survival time, a common method of conducting adaptively randomized trials requires calculating

$$P(X_1 > X_2)$$

or

$$P(X_1 > \max(X_2, X_3))$$

for independent inverse gamma random variables  $X_i$ . When the primary end point is time to a desirable event, say transplant engraftment, one needs to calculate

$$P(X_1 < X_2)$$

or

$$P(X_1 < \min(X_2, X_3)).$$

One may also consider trials with binary end points. These commonly require evaluating similar stochastic inequalities, but for beta random variables. See [2] and [3] for more on calculating beta inequalities. In this note we focus on (inverse) gamma random variables.

See [4] and [8] for more on the application of stochastic inequalities to clinical trials. See [9] for clinical trial simulation software that employs the algorithms given in this paper.

Note that these inequality probabilities are of interest outside of medical applications. For example, in reliability engineering one may be interested in survival times of mechanical devices rather than survival times of cancer patients.

## 2 Preliminaries

### 2.1 Distribution parameterizations

There are two common parameterizations for both the gamma and inverse gamma distribution. To avoid confusion, we state our parametrization conventions as follows. A gamma random variable with shape parameter  $a > 0$  and scale  $b > 0$ , abbreviated  $G(a, b)$ , has PDF

$$\frac{1}{\Gamma(a)b^a} x^{a-1} e^{-x/b}.$$

And inverse gamma random variable with shape  $a > 0$  and scale  $b > 0$ , abbreviated  $IG(a, b)$ , has PDF

$$\left( \frac{b^a}{x^{a+1}\Gamma(a)} \right) e^{-b/x}.$$

With these parameterizations,  $X \sim G(a, b)$  iff  $1/X \sim IG(a, 1/b)$ .

## 2.2 Reductions

Since

$$P(X_1 > X_2) = 1 - P(X_2 > X_1)$$

and

$$P(X_1 < \min(X_2, X_3)) = 1 - P(X_1 > X_2) - P(X_1 > X_3) + P(X_1 > \max(X_2, X_3))$$

we need only consider how to compute inequality probabilities of one random variable being greater than another or the maximum of others.

Also, if  $X_i \sim \text{IG}(a_i, b_i)$  and  $Y_i = 1/X_i$ ,

$$P(X_1 > X_2) = P(Y_1 < Y_2)$$

and

$$P(X_1 > \max(X_2, X_3)) = P(Y_1 < \min(Y_2, Y_3)).$$

Therefore we may restrict our attention to gamma random variables.

## 3 Two variables

In a two-arm trial, we need to evaluate  $g_2(a_1, b_1, a_2, b_2)$  defined as the probability  $P(X_1 > X_2)$  where  $X_i \sim G(a_i, b_i)$ .

In [2] we show that

$$g_2(a_1, b_1, a_2, b_2) = I_{b_1/(b_1+b_2)}(a_2, a_1)$$

where  $I_x(a, b)$  is the incomplete beta function.

## 4 Three variables

In a three-arm trial, we need to evaluate  $g_3(a_1, b_1, a_2, b_2, a_3, b_3)$  defined as  $P(X_1 > \max(X_2, X_3))$  where  $X_i \sim G(a_i, b_i)$ .

## 4.1 Analytical representations

In [4] we show that

$$g_3 = \frac{\Gamma(a_1 + a_2 + a_3)}{a_2 a_3 \Gamma(a_1) \Gamma(a_2) \Gamma(a_3)} \left(\frac{b_1}{b_2}\right)^{a_2} \left(\frac{b_1}{b_3}\right)^{a_3} \times F_2 \left( \begin{matrix} a_1 + a_2 + a_3, a_2, a_3 \\ a_2 + 1, a_3 + 1 \end{matrix} \middle| -\frac{b_1}{b_2}, -\frac{b_1}{b_3} \right) \quad (1)$$

where  $F_2$  denotes the Appell function of the second kind. Note that a  $G(a, b)$  random variable in the notation of this note corresponds to a  $G(1/b, a)$  in the parameterization used in [4].

See [6] for numerically evaluating  $F_2$  for general arguments. Here, however, we take advantage of the special form of the arguments of  $F_2$  needed for our application.

Note that equation (1) only depends on the ratios  $b_1/b_2$  and  $b_1/b_3$  and not on the  $b$ 's individually. This is because if  $X \sim G(a, b)$ ,  $kX \sim G(a, kb)$  for any positive constant  $k$ . Thus we can multiply all the  $b$ 's by a positive constant and not change the inequalities. We now simplify notation slightly by assuming without loss of generality that  $b_1 = 1$ .

Appell's  $F_2$  function is defined in terms of a double series, though the series representation is only valid for arguments  $(x, y)$  satisfying  $|x| + |y| < 1$ . However, using results from section 206D of [7], one can express  $F_2$  as a double integral obtaining

$$g_3 = \frac{\Gamma(a_1 + a_2 + a_3)}{\Gamma(a_1) \Gamma(a_2) \Gamma(a_3) b_2^{a_2} b_3^{a_3}} \int_0^1 \int_0^1 \frac{u^{a_2-1} v^{a_3-1}}{(1 + u/b_2 + v/b_3)^{a_1+a_2+a_3}} du dv. \quad (2)$$

This integral representation gives an analytic continuation valid for all arguments we need.

## 5 Upper and lower bounds

For any independent random variables  $X_i$ ,

$$P(X_1 > X_2 \text{ and } X_1 > X_3) \leq P(X_1 > X_2).$$

By symmetry one can reverse  $X_2$  and  $X_3$  and so

$$P(X_1 > X_2 \text{ and } X_1 > X_3) \leq \min(P(X_1 > X_2), P(X_1 > X_3)).$$

Also,

$$\begin{aligned} P(X_1 > X_2 \text{ and } X_1 > X_3) &= P(X_1 > X_2)P(X_1 > X_3 | X_1 > X_2) \\ &\geq P(X_1 > X_2)P(X_1 > X_3). \end{aligned}$$

Therefore if we let  $p_j = P(X_1 > X_j)$  then

$$p_2 p_3 \leq P(X_1 > \max(X_2, X_3)) \leq \min(p_2, p_3) \quad (3)$$

## 6 Numerical considerations

Routines for accurate and efficient evaluation of the incomplete beta function are readily available. See for example [1] and [5]. Therefore the evaluation of  $g_2$  is a solved problem. However, I am not aware of software any other software to evaluate  $g_3$ .

The integral (2) is easy to evaluate numerically if  $a_2$  and  $a_3$  are larger than 1, but we only know that these parameters are positive. If either were less than 1, the integrand would be singular along an edge of its domain. To obtain a well-behaved integrand for all positive values of  $a_2$  and  $a_3$  we integrate by parts twice. Let  $s = a_1 + a_2 + a_3$  and denote

$$I = \int_0^1 \int_0^1 \frac{u^{a_2-1} v^{a_3-1}}{(1 + u/b_2 + v/b_3)^s} du dv.$$

Then integration by parts show that

$$\begin{aligned} a_2 a_3 I &= \frac{s(s+1)}{b_2 b_3} \int_0^1 \int_0^1 \frac{u^{a_2} v^{a_3}}{(1 + u/b_2 + v/b_3)^{s+2}} du dv \\ &\quad + \frac{s}{b_3} \int_0^1 \frac{v^{a_3}}{(1 + 1/b_2 + v/b_3)^s} dv \\ &\quad + \frac{s}{b_2} \int_0^1 \frac{u^{a_2}}{(1 + u/b_2 + 1/b_3)^s} dv \\ &\quad + \frac{1}{(1 + 1/b_2 + 1/b_3)^s} \end{aligned} \quad (4)$$

We obtain an accurate and efficient algorithm for evaluating the integrals given in the appendix using Gaussian (product) quadrature with 32 nodes. The integrals in equation (4) have no singularities and Gaussian quadrature works quite well. However, one must be careful about numerical overflow and underflow. In application, the shape parameters  $a_i$  can be large enough that the factor

$$\frac{\Gamma(a_1 + a_2 + a_3)}{\Gamma(a_1)\Gamma(a_2)\Gamma(a_3)} \quad (5)$$

will overflow or that the integrals in equation (4) underflow. The solution to this problem is to first evaluate the logarithm of expression (5) by using a routine for  $\log \Gamma(x)$ . Then in the routines for evaluating the integrands in equation (4) first evaluate the logarithm of the integrands, add the logarithm of expression (5), and then exponentiate.

This procedure becomes less accurate when one of the random variables  $X_i$  is very likely to be larger than one of the others. Fortunately, this is precisely when inequality (3) becomes tighter. For our application to clinical trial randomization, we are interested in controlling absolute error rather than relative error: we do not need to know small probabilities to many significant figures.

Define  $p_i$  as in (3). Furthermore, let  $p_{\min} = \min(p_2, p_3)$  and  $p_{\max} = \max(p_2, p_3)$ . Then

$$p_{\min} p_{\max} \leq g_3 \leq p_{\min}$$

and so if  $p_{\min}(1 - p_{\max}) < 2\varepsilon$  then the error in the approximation

$$g_3 \approx \frac{p_{\min}(1 - p_{\max})}{2} \quad (6)$$

is less than  $\varepsilon$ .

## 7 Testing the algorithm

We implemented the algorithm in this report, using the approximation (6) whenever one of the probabilities on the right was either below  $\varepsilon = 0.001$  or above  $1 - \varepsilon$ . We generated 100,000 vectors of the form  $(u_1, \dots, u_6)$  with each  $u_i$  being a uniform random sample from  $(0.1, 90)$ . For each such vector, we evaluated  $g_3(u_1, u_2, u_3, u_4, u_5, u_6)$ ,  $g_3(u_3, u_4, u_5, u_6, u_1, u_2)$ , and  $g_3(u_5, u_6, u_1, u_2, u_3, u_4)$ . In theory, these values should sum to 1.

The average absolute error was  $5.477 \times 10^{-5}$  and the maximum error was 0.00343. The largest errors occur when one of the three probabilities is very small. If we throw out cases where one of the probabilities is less than 0.005, the average error drops to  $1.016 \times 10^{-6}$  and the maximum error to 0.00261.

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