

A Stopped Negative Binomial Distribution

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Abstract

We introduce a discrete distribution suggested by curtailed sampling rules common in early-stage clinical trials. We derive the distribution of the smallest number of independent and identically distributed Bernoulli trials needed to observe either s successes or t failures. This report provides a closed-form expression for the mass function and illustrates limiting approximations.

Keywords: discrete distribution, curtailed sampling

1. Introduction and Motivation

Consider a prototypical early phase, single-arm clinical trial in which 17 patients are enrolled and treated. The binomial probability of a patient responding to treatment is $p = 0.2$ under the null hypothesis that the treatment is not effective. If seven or more patients out of these 17 respond to the treatment then we reject this hypothesis and the treatment is deemed successful at a significance level of 0.1. If fewer than seven respond then the null hypothesis is not rejected and the treatment is deemed ineffective.

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If all 17 patients are enrolled at once, as in the classic design, then the sample size is 17. However, in most clinical trials the patients are enrolled sequentially over time. In the present example, observing seven successful patients is one endpoint and the number of enrollees required could be as small as seven. Similarly 11 observed treatment failures also ends the trial. This sampling mechanism, in which the experiment ends as soon as any predefined endpoint is reached, is called *curtailed sampling*. Under curtailed sampling, the range of the sample size for this trial is seven through 17.

Let us assume each patient outcome can be modeled as an independent, identically distributed Bernoulli(p) random variable. The trial is realized as a sequence of Bernoulli samples stopping when either a specified number of responders or non-responders has been reached.

A hypothetical sample path is illustrated in Fig. 1. The vertical axis denotes the number of successful outcomes. The horizontal axis counts the number of patients enrolled. The horizontal and vertical boundaries represent endpoints for the trial. In this case, a seventh response was reached on the 15th enrollment. Since the success boundary is reached, we say the treatment succeeds.

More generally the distribution of the number of trial enrollments is shown in Fig. 2 (a). There is relatively little probability mass for values of sample size equal to seven through 10 since p is small and it is unlikely the treatment will succeed quickly. Fig. 2 (b) shows the expected value and variance for the number

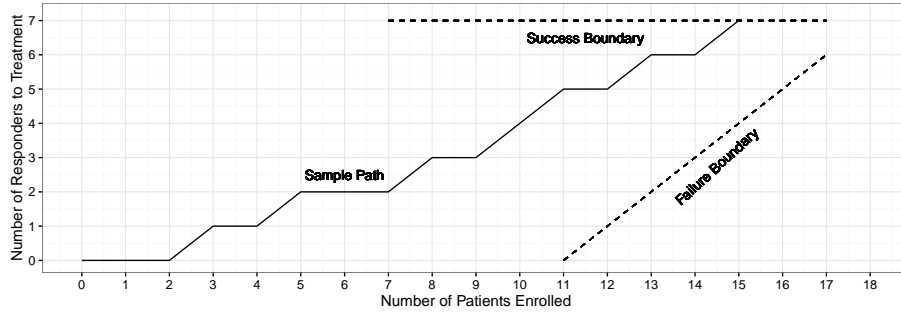


Figure 1: A hypothetical realization of the trial.

of trial enrollments varying p between zero and one. When p is small then the treatment is more likely to fail shortly after the 11th enrollment. When p is large then the treatment is more likely to succeed and the number of enrollees approaches seven from above.

When $p = 0$ or 1 the processes are deterministic and variance is zero. Values between zero and one change the mixing proportions of the two endpoints. The saddle around $p = 0.25$ results from inequality in the size of the support of the two endpoints.

In the rest of this work, we derive the distribution of the number of enrollees needed to observe either s successes or t failures. We refer to this distribution as the Stopped Negative Binomial (SNB). This paper derives this distribution and explores its properties. Section 2 derives the distribution function based on a defined Bernoulli process and gives some basic properties. Section 3 shows how the distribution is related to other standard distributions and connects the SNB tail probability to the binomial tail probability. Section 4 derives the moment

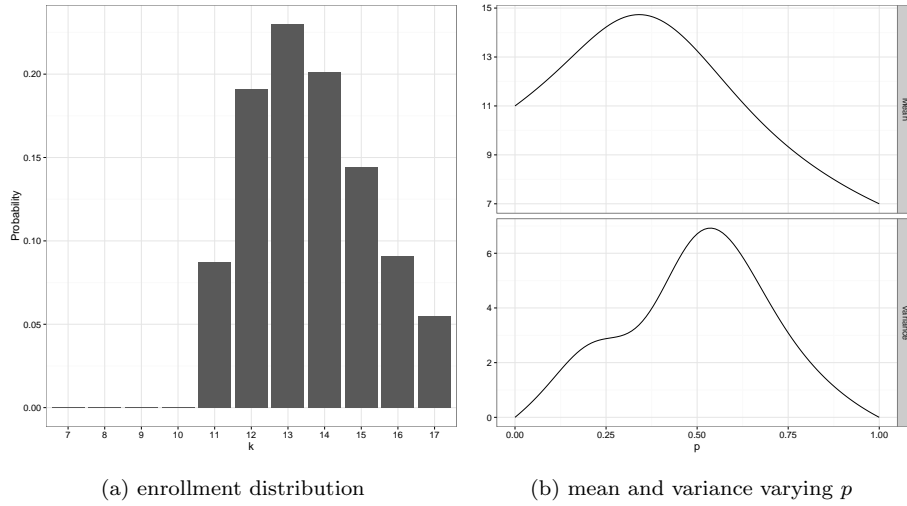


Figure 2: The distribution of a trial that stops after seven patients respond to treatment or 11 patients do not. Panel (a) shows the distribution when $p = 0.2$. The mean and variance of the distribution varying p between zero and one are shown in panel (b).

45 generating function. Section 5 derives the predictive and posterior distributions when p has a beta prior distribution.

2. Probability Mass Function

Let b_1, b_2, \dots denote a sequence of independent, identically distributed, Bernoulli random variables with $\mathbb{P}[b_i = 1] = p$ and $\mathbb{P}[b_i = 0] = 1 - p$, for
 50 probability parameter $0 \leq p \leq 1$. In the clinical trial setting $b_i = 1$ corresponds to a patient responding to treatment. Let s and t be positive integers. Define the SNB random variable Y as the smallest integer value such that $\{b_1, \dots, b_Y\}$ contains *either* s responders *or* t non-responders. That is, the SNB distribution of Y is the smallest integer such that either $\sum_i^Y b_i = s$ or $\sum_i^Y 1 - b_i = t$.

The distribution of Y has support on integer values in the range

$$\min(s, t) \leq Y \leq s + t - 1.$$

The probability mass function is

$$\mathbb{P}[Y = k] = S(k, p, s) I_{\{s \leq k \leq s+t-1\}} + S(k, 1-p, t) I_{\{t \leq k \leq s+t-1\}} \quad (1)$$

where $I_{\{f\}}$ is the *indicator function*, taking the value of one if f is true and zero otherwise, and

$$S(k, p, s) = \binom{k-1}{s-1} p^s (1-p)^{k-s} \quad (2)$$

55 is the negative binomial probability mass.

To prove (1), consider the process $\mathbf{X} = \{X(k) : k = 0, 1, \dots\}$ with $X(0) = 0$ and

$$X_{k+1} = X_k + b_{k+1} I_{\{k-t < X_k < s\}}.$$

At each step a patient's outcome is measured. In Fig. 1 we consider a graphical illustration of the plot X_k against k . If the outcome of the k th patient responds to treatment then the process advances diagonally in the positive horizontal and vertical direction. If the k th patient does not respond then the sample path
 60 advances in the positive horizontal direction only. The process continues until either $X_k = s$ or $X_k = k - t$ corresponding to the success and failure boundaries in Fig. 1, respectively.

Proposition 1. *The distribution of the stopping time*

$$Y = \underset{k}{\operatorname{argmin}} [X_k \geq s \cup X_k \leq k - t]$$

is given at (1).

Proof. The probability a given realization of \mathbf{X} reaches s at the k th outcome is
 65 the probability that, at time $k - 1$, there are $s - 1$ successful outcomes and $k - s$
 unsuccessful outcomes multiplied by the probability of a final success at time
 k . This expression is given in (2). Similarly, the probability a given realization
 reaches $k - t$ is the probability that, at outcome $k - 1$, there are $k - t$ successful
 outcomes and $t - 1$ unsuccessful outcomes multiplied by the probability of a
 70 final unsuccessful outcome at time k .

To show that (1) sums to one, define

$$R = \sum_{k=s}^{s+t-1} S(k, p, s) + \sum_{k=t}^{s+t-1} S(k, 1-p, t).$$

If we substitute $i = k - s$ in the first summation and $j = k - t$ in the second
 then R can be written as the cumulative distribution function of two negative
 binomial distributions:

$$R = \sum_{i=0}^{t-1} \binom{i+s-1}{i} p^s (1-p)^i + \sum_{j=0}^{s-1} \binom{j+t-1}{j} p^j (1-p)^t. \quad (3)$$

Let $\mathcal{I}_p(s, t)$ be the *regularized incomplete beta function* [1]. This function
 satisfies $\mathcal{I}_p(s, t) = 1 - \mathcal{I}_{1-p}(t, s)$ [2]. Then

$$\begin{aligned} R &= \sum_{i=0}^{t-1} \binom{i+s-1}{i} p^s (1-p)^i + \sum_{j=0}^{s-1} \binom{j+t-1}{j} p^j (1-p)^t \\ &= 1 - \mathcal{I}_p(s, t) + 1 - \mathcal{I}_{1-p}(t, s) \\ &= 1. \end{aligned}$$

This completes the proof that (1) is the distribution of the stopping time and
 is a valid probability mass function. \square

Next, we consider an interim analysis of a clinical trial after s' patients
 respond to treatment and t' fail to respond for $s' < s$ and $t' < t$.

75 **Corollary 1.** *The number of subsequent enrollments needed to reach either s or t endpoints behaves as $SNB(p, s - s', t - t')$.*

Having observed s' responders and t' non-responders, there are $s - s'$ more responders needed to reach the success endpoint and $t - t'$ more non-responders needed to reach the failure endpoint.

80 **3. Connections and Approximations to Other Distributions**

The SNB is a generalization of the negative binomial distribution. When t is large then $Y - s$ has a negative binomial distribution with

$$\mathbb{P}[Y = s + j \mid t \text{ is large}] = \binom{s + j - 1}{s - 1} p^s (1 - p)^j$$

for $j = 0, 1, \dots$. A similar statement can be made when s is large and t is moderate. As a result, with proper parameter choice, the SNB can mimic other probability distributions in a manner similar to those described in [3] and [4]. Examples are shown in in Fig. 3.

85 The SNB generalizes both the minimum (riff-shuffle) and maximum negative binomial distributions up to a translation of the support. For the special case of $s = t$, the distribution of Y is the riff-shuffle, or minimum negative binomial distribution [2, 5]. The maximum negative binomial [6, 7, 5] is the smallest number of outcomes necessary to observe at least s responders *and* s non-responders and is equivalent to a translated version of the riff-shuffle.

There is an equivalence between the probability of reaching an endpoint in the SNB model and the tail probability of the binomial distribution. That is, the probability that the number of responders is at least s in the binomial model is the same as the probability the treatment succeeds (reaches s) in the SNB model.

95 **Proposition 2.** *Let Y be distributed as $SNB(p, s, t)$ and let X_Y correspond to the number of responders at the end of the trial. Let B be distributed binomial with size $n = s + t - 1$ and response probability p . Then*

$$\mathbb{P}[B \geq s] = \mathbb{P}[X_Y = s]. \quad (4)$$

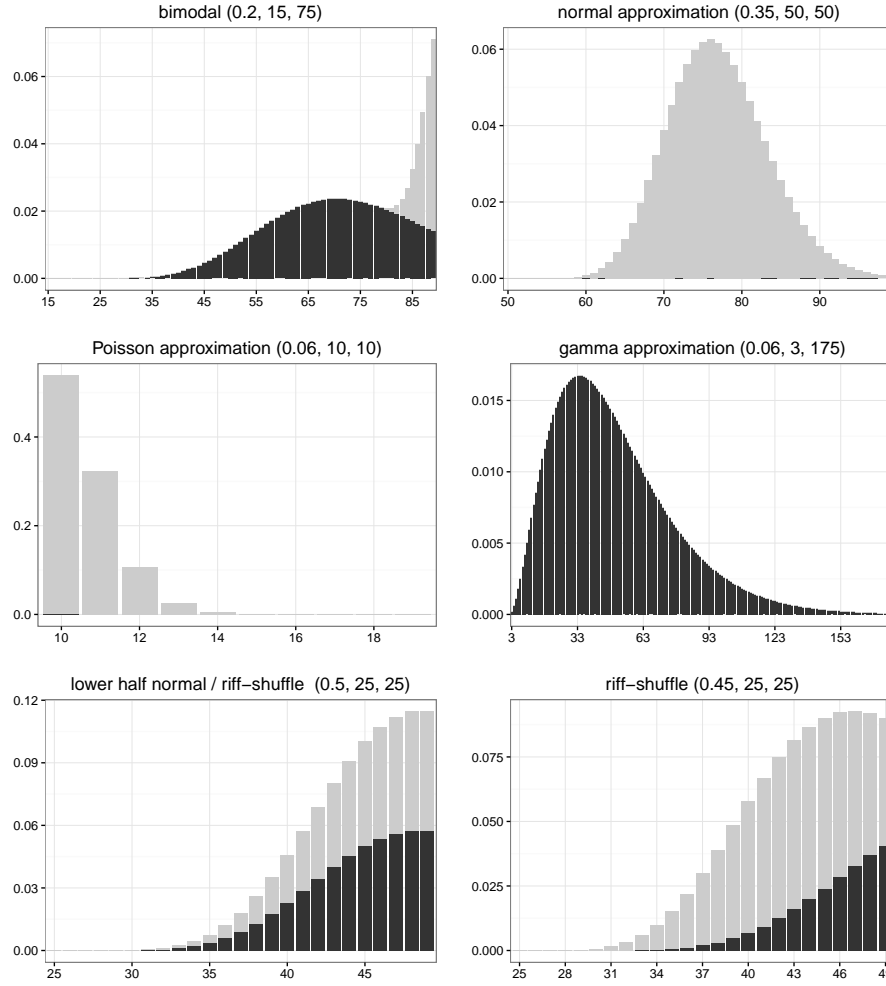


Figure 3: Different shapes of the SNB distribution with parameters (p, s, t) , as given. Black indicates mass contributed by reaching s responders before t non-responders. Grey indicates mass contributed by reaching t non-responders first.

Proof. The binomial tail probability is

$$\mathbb{P}[B \geq s] = 1 - \mathcal{I}_{1-p}(s, t)$$

where $\mathcal{I}_{1-p}(s, t)$ is the *regularized incomplete beta function*. The corresponding success probability is

$$\mathbb{P}[X_Y = s] = \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} p^s (1-p)^{k-s}. \quad (5)$$

Let $i = k - s$. Since

$$\binom{i+s-1}{s-1} = \binom{i+s-1}{i},$$

the summation in (5) can be rewritten as

$$\begin{aligned} \mathbb{P}[X_Y = s] &= \sum_{i=0}^{t-1} \binom{i+s-1}{i} p^s (1-p)^i \\ &= 1 - \mathcal{I}_{1-p}(t, s) \end{aligned}$$

completing the proof. \square

To illustrate this result, let us return to our initial example where $s = 7$, $t = 11$, and $p = 0.2$. The probability masses in Fig. 4 represented in black are equal in panels (a) and (b) as are the masses in grey. The probability that s responders are reached in the SNB process is the same as the binomial probability of at least seven responders. Likewise, the probability that t non-responders are reached in the SNB process is the same as the binomial probability of zero through six responders.

4. The Moment Generating Function

The moment generating function for the SNB is calculated in a manner similar to that of two negative binomial distributions.

Proposition 3. *Let Y be distributed SNB with parameters p , s , and t . Then the moment generating function (MGF) of Y is*

$$\mathbb{E} e^{xY} = \left(\frac{pe^x}{1-qe^x} \right)^s \mathcal{I}_{1-qe^x}(s, t) + \left(\frac{qe^x}{1-pe^x} \right)^t \mathcal{I}_{1-pe^x}(t, s) \quad (6)$$

for $q = 1 - p$ and is defined for $x < \min \{\log(1/p), \log(1/q)\}$.

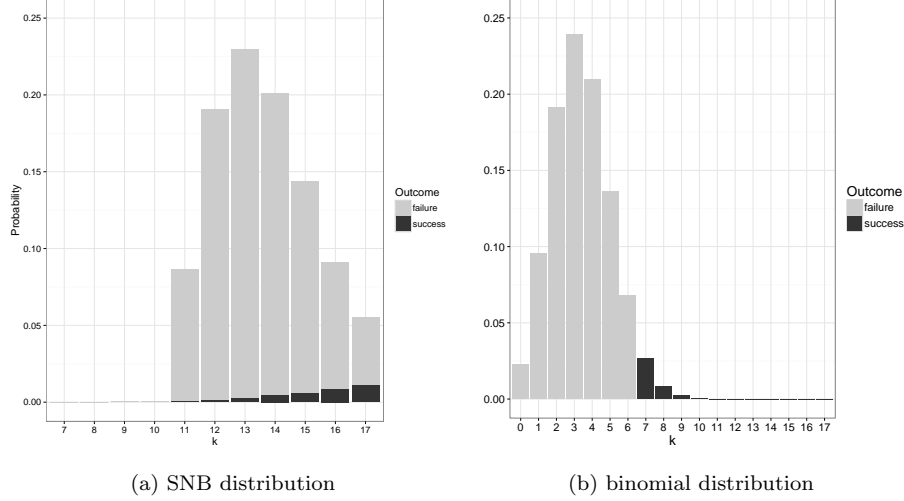


Figure 4: SNB(0.2, 7, 11) with mass contributed from 7 responders (black) or 11 non-responders (grey) along with Binomial(0.2, 17) with at least 2 responders (black) or fewer (grey).

Proof. The MGF of the SNB is:

$$\mathbb{E} e^{xY} = \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} p^s q^{k-s} e^{kx} + \sum_{k=t}^{s+t-1} \binom{k-1}{t-1} p^{k-t} q^t e^{kx}$$

and can be rewritten as:

$$\mathbb{E} e^{xY} = \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} (pe^x)^s (qe^x)^{k-s} + \sum_{k=t}^{s+t-1} \binom{k-1}{t-1} (qe^x)^t (pe^x)^{k-t}. \quad (7)$$

The first summation in (7) satisfies

$$\begin{aligned} \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} (pe^x)^s (qe^x)^{k-s} &= \left(\frac{pe^x}{1-qe^x} \right)^s \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} (qe^x)^{k-s} (1-qe^x)^s \\ &= \left(\frac{pe^x}{1-qe^x} \right)^s \mathcal{I}_{1-qe^x}(s, t). \end{aligned}$$

Since the regularized incomplete beta function's subscript parameter has support on zero to one, we have $0 \leq qe^x < 1$. This implies $x < -\log(q)$. A similar
110 expression can be derived for the second summation in (7) and results in the constraint $x < -\log(p)$. \square

The SNB's ability to approximate the geometric, normal, gamma, and Poisson distributions follow from it generalizing the negative binomial distribution.

Proposition 4. *The MGF of the SNB converges to that of the negative binomial when either s or t gets large. That is*

$$\mathbb{E}e^{xY} \rightarrow \left(\frac{pe^x}{1 - qe^x} \right)^s$$

as $t \rightarrow \infty$. The analogous result holds when $s \rightarrow \infty$.

Proof. The second regularized incomplete beta term in (6) can be written in terms of a cumulative binomial distribution

$$\mathcal{I}_{1-pe^x}(t, s) = \mathbb{P}[B \leq s - 1]$$

where B is distributed as Binomial($t - k, pe^x$). By Chebychev's inequality it follows that

$$\mathbb{P}[B \leq s - 1] \leq \frac{(t - k)pe^x(1 - pe^x)}{(s - (t - k)pe^x)^2} \quad (8)$$

As t gets large $\mathcal{I}_{1-pe^x}(t, s)$ goes to zero Likewise, $\mathcal{I}_{1-qe^x}(s, t)$ goes to one. The proof follows by realizing

$$0 < \frac{qe^x}{1 - pe^x} < 1$$

115 over the support of x . □

When $s = 1$ (and t is still large) the SNB's MGF is approximately the same as that of the geometric distribution. The negative binomial can therefore be seen as a sum of i.i.d. geometric distributions. For an appropriately large number of samples, the central limit theorem yields a normal approximation.

120 Drawing connections to the gamma and Poisson distributions are more complicated. However a connection to the gamma distribution well-studied problem in the literature (see [8, 9, 4] for examples). A connection to the Poisson appears in [10] where it is shown that if the mean of a Poisson is proportional to a chi-square distribution with $2k$ degrees of freedom then the negative binomial is
125 obtained. Both of these approximations work by equating cumulants and then

showing that differences between the cumulant generating functions converge to zero.

The lower-half normal distribution can be approximated by setting $s = t$ for appropriately large s and t and $p = 0.5$. In this case, the SNB can be viewed
130 as identical, negative binomials approximating a normal and truncated at the median.

5. The Posterior and Predictive Probability Distribution

Let us consider the case where the rate parameter is distributed as Beta(α , β) and denoted P . The prior times the likelihood is given by the function

$$f_P(p, \alpha, \beta) f_{Y|P}(p, k, s, t) = \frac{\binom{k-1}{s-1}}{B(\alpha, \beta)} p^{\alpha+s-1} (1-p)^{k+\beta-s-1} + \frac{\binom{k-1}{t-1}}{B(\alpha, \beta)} p^{k+\alpha-t-1} (1-p)^{\beta+t-1} \quad (9)$$

where $0 \leq p \leq 1$, $s \leq k \leq s+k-1$, and $t \leq k \leq s+k-1$. This result can be found directly by multiplying the probability mass function in (1) by the
135 density of the Beta distribution.

The predictive distribution of the SNB can be found by integrating p over the interval zero to one and applying the definition of the beta function.

$$f_Y(k, s, t, \alpha, \beta) = \int_0^1 f_P(p|\alpha, \beta) f_{Y|P}(p, k, s, t) dp \\ = \binom{k-1}{s-1} \frac{B(\alpha+s, k-s+\beta)}{B(\alpha, \beta)} + \binom{k-1}{t-1} \frac{B(\alpha+k-t, t+\beta)}{B(\alpha, \beta)}. \quad (10)$$

If both α and β are non-negative integers then the predictive distribution is a mixture of hypergeometric distributions.

$$f_Y(k, s, t, \alpha, \beta) = \frac{\binom{k-1}{s-1} \binom{\alpha+\beta}{\alpha}}{\binom{\alpha+\beta+k-1}{\alpha+s}} \frac{\alpha}{\alpha+\beta} \frac{\beta}{k-s+\beta} + \frac{\binom{k-1}{t-1} \binom{\alpha+\beta}{\beta}}{\binom{\alpha+\beta+k-1}{t+\beta}} \frac{\beta}{\alpha+\beta} \frac{\alpha}{k-t+\alpha}$$

The ratio of combinations in the first term can be interpreted as the probability of $s-1$ responders from $k-1$ patients in $\alpha+s$ draws from a population size of $\alpha+\beta+k-1$. This value is multiplied by $\alpha/(\alpha+\beta)$, the expected response rate of the prior. The final term in the product weights the prior based on the

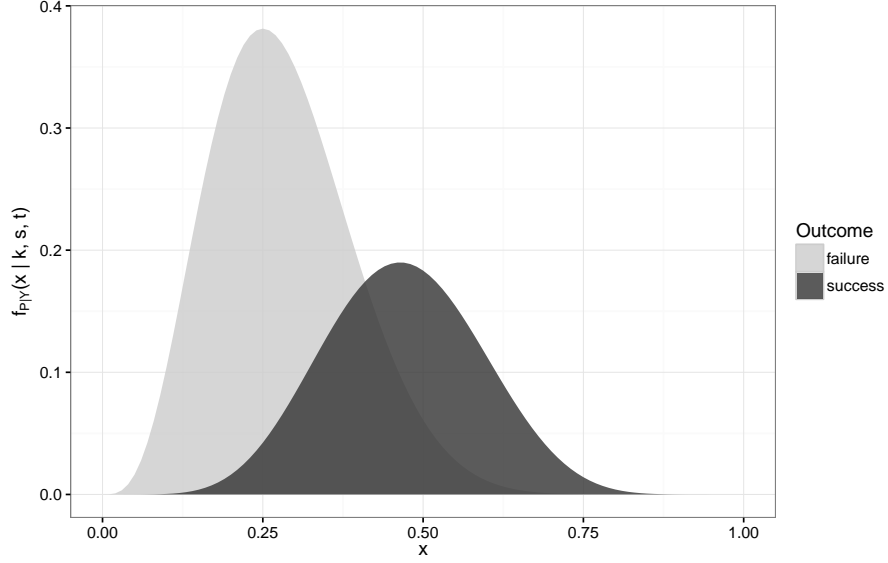


Figure 5: The posterior distribution of the response probability with the Jeffreys prior ($\alpha = \beta = 1/2$) for the trial where $s = 7$, $t = 11$, $k = 15$.

140 number of non-responders ($k - s$). Terms in the second summand are interpreted similarly for non-responders.

The ratio of (9) divided by (10) gives the posterior distribution of P . It is a mixture of beta distributions. The mixing parameter depend on the endpoints (s and t), the number of enrollees needed to reach an endpoint (k), and the
 145 prior parameters (α and β).

The posterior result above is for the case where the parameters are known and the endpoint is not. That is, we do not which boundary was reached. Fig. 5 shows this distribution based on the parameters in the hypothetical trial assuming the Jeffreys prior [11]. If we include the fact that the trajectory
 150 reaches the endpoint then the second terms in (9) and (10) are both zero and the posterior distribution is $\text{Beta}(7.5, 8.5)$. This is proportional to the area labeled “success” in Fig. 5.

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