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 a patient responds 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 significance level of 0.1. If fewer than seven respond then the null 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 with one patient's outcome realized before the next one enters the trial. 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 between seven and 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 15^{th} 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 seven through 10 since p is small and it is unlikely the treatment will succeed quickly. Fig. 2

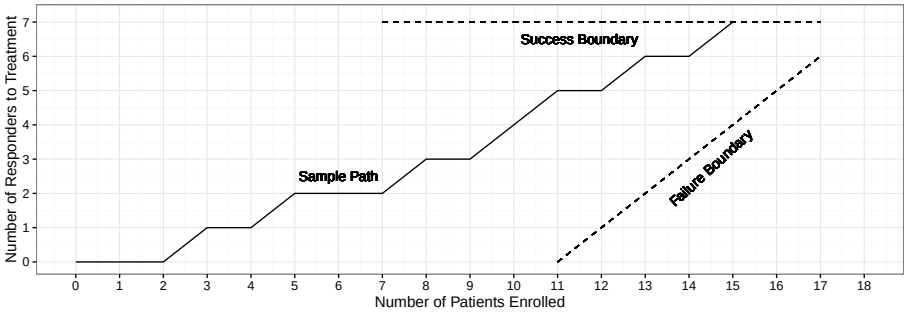
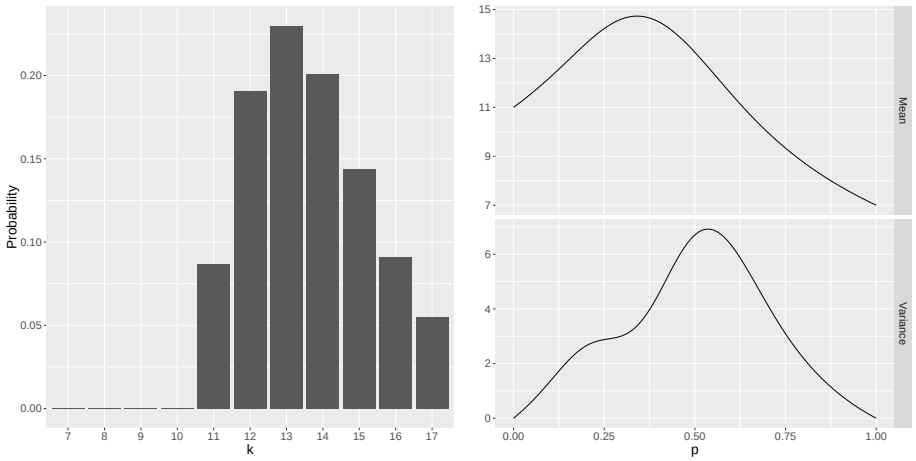


Figure 1: A hypothetical realization of the trial.

(b) shows the expected value and variance for the number of trial enrollments varying p between zero and one. When p is small the probability of an individual response is small and the treatment is more likely to fail shortly after the 11^{th} enrollment. When p is large the treatment is more likely to succeed and the number of enrollees approaches seven from above.

Since $p = 1$ and $p = 0$ represent the deterministic case the corresponding variances are zero. The variance is determined by the size of the support of the two endpoints and p, which weights the contribution of an endpoint based on how likely it is reached. When p is small it is more likely the trial will reach the failure endpoint which has a support size of seven. As p increases it becomes more likely the trial reaches the success endpoint with a support size of 11. The "bump" 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



(a) enrollment distribution

(b) mean and variance varying p

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).

Table 1: Characteristics of the Stopped Negative Binomial Distribution

Parameters	p the success probability ($0 \leq p \leq 1$; $q = 1 - p$) s the number of successes before stopping ($s = 1, 2, ...$) t the number of failures before stopping ($t = 1, 2, ...$)
Support	$\min(s, t) \leq k \leq s + t - 1$
$\mathbb{P}[Y = k]$	$\binom{k-1}{s-1} p^s (1-p)^{k-s} I_{\{s \leq k \leq s+t-1\}} + \binom{k-1}{t-1} (1-p)^s p^{k-t} I_{\{t \leq k \leq s+t-1\}}$
$\mathbb{P}[Y \leq k]$	$2 - \mathcal{I}_q(k+1, s) - \mathcal{I}_p(k+1, t)$ where $\mathcal{I}$ is the regularized incomplete beta function.
Mean	$\frac{s}{p}\mathcal{I}_p(s,t) + \frac{p^{s-1}q^{t-1}}{B(s,t)} + \frac{t}{q}\mathcal{I}_q(t,s) + \frac{p^{t-1}q^{s-1}}{B(s,t)}$ where B is the beta function
MGF	$\left(\frac{pe^x}{1-qe^x}\right)^s \mathcal{I}_{1-qe^x}(s,t) + \left(\frac{qe^x}{1-pe^x}\right)^t \mathcal{I}_{1-pe^x}(t,s)$
Predictive Distribution	$\binom{k-1}{s-1} \frac{B(\alpha+s, k-s+\beta)}{B(\alpha,\beta)} + \binom{k-1}{t-1} \frac{B(\alpha+k-t, t+\beta)}{B(\alpha,\beta)}$ for p distributed as Beta(α, β).

as the Stopped Negative Binomial (SNB). Some of its characteristics are summarized in Tab. 1. This paper derives these results and explores properties of the distribution. 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 generating function. Section 5 derives the predictive distribution when p has a beta distribution.

2. Probability Mass Function

Let $b_1, b_2, \ldots$ 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 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 $\{b_1, \ldots, b_Y\}$ 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

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

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

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

is the negative binomial probability mass.

To prove (1), consider the process $\mathbf{X} = \{X(k) : k = 0, 1, ...\}$ 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 kth patient responds to treatment then the process advances diagonally in the positive horizontal and vertical direction. If the kth patient does not respond then the sample path advances in the positive horizontal direction only. The process continues until either $X_k = s$ or $X_k = k - t$.

Proposition 1. *The distribution of the stopping time*

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

is given at (1).

Proof. The probability a given realization of $\mathbf{X}$ reaches s at the kth outcome is 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 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:

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

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. □

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

Corollary 1. *The number of subsequent enrollments needed to reach either endpoint 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.

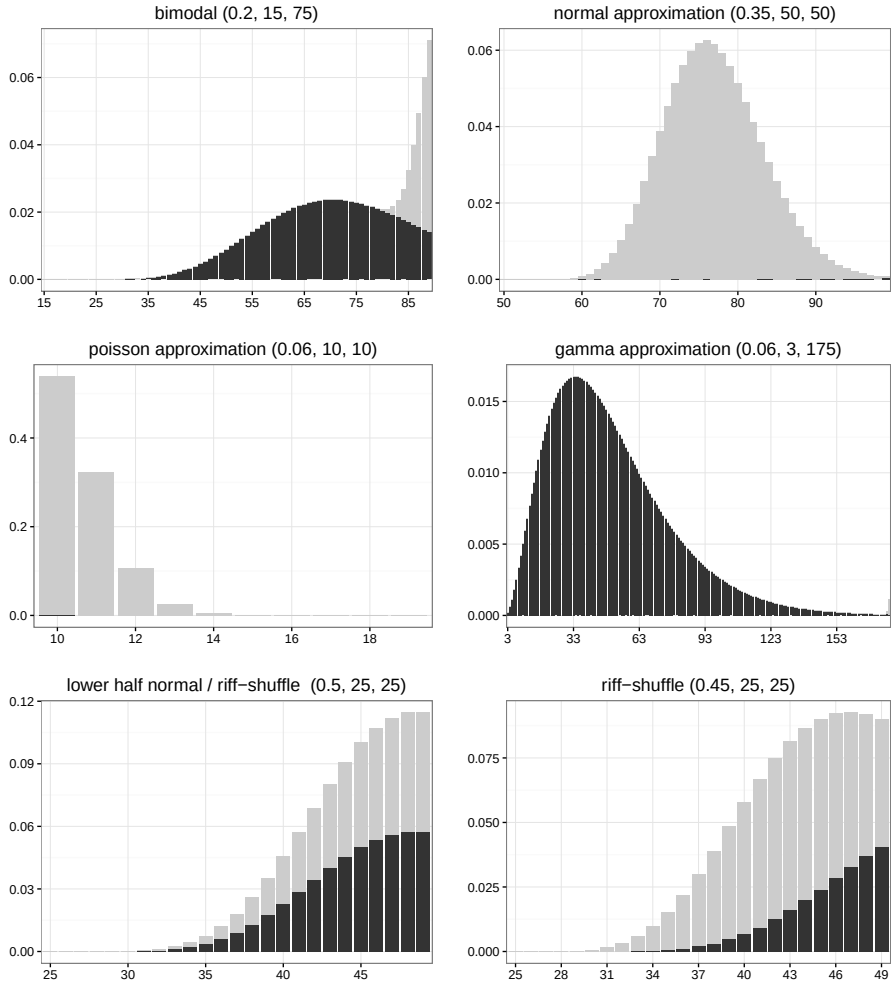


Figure 3: Different shapes of the SNB distribution with parameters (p, s, t), as given. Black indicates mass contributed by reaching s responders before t non-responders. Grey indicates mass contributed by reaching t non-responders first.

3. Connections and Approximations to Other Distributions

The SNB is a generalization of the negative binomial distribution. When t is large $Y - s$ 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 $j = 0, 1, \ldots$. A similar statement can be made when s is large and t is small. 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.

The SNB is the number of enrollment outcomes to observe *either* s responders *or* t non-responders. 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]. The maximum negative binomial [5, 6] 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.

Proposition 2. *Let Y be distributed as SNB(p, s, t) and recall that X_Y corresponds to the number of responders in a trial. Let B be distributed binomial with size $n = s + t - 1$ and response probability p. Then*

$$\mathbb{P}[B \geq s] = \mathbb{P}[X_Y = s]. \tag{4}$$

Proof. The binomial tail probability is

$$\mathbb{P}[B \geq s] = 1 - \mathcal{I}_{1-p}.$$

The corresponding success probability is

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

Let $i = k - s$. Since

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

the last summation can be rewritten as

$$\mathbb{P}[X_Y = s] = \sum_{i=0}^{t-1} \binom{i+s-1}{i} p^s (1-p)^i \tag{5}$$

$$= 1 - \mathcal{I}_{1-p}(t, s) \tag{6}$$

completing the proof. □

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.

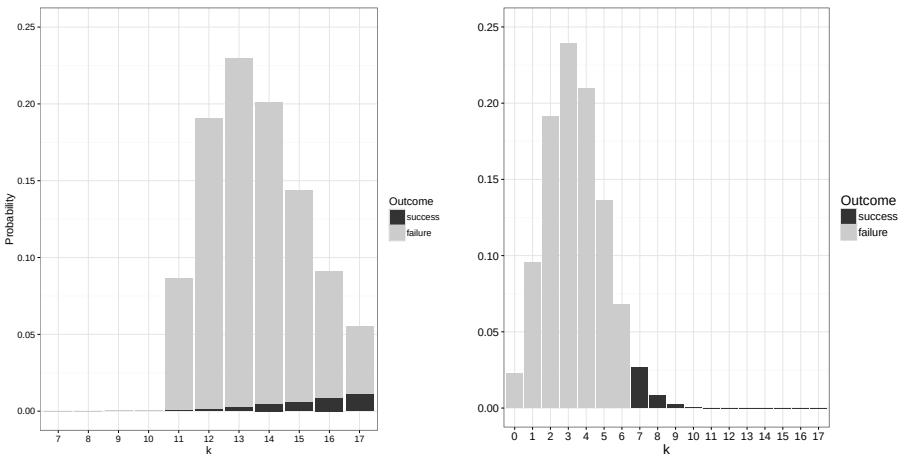
4. The Moment Generating Function

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*

$$\mathbb{E}\ e^{xY} = \left(\frac{pe^x}{1-qe^x}\right)^s \mathcal{I}_{1-qe^x}(s, t) + \left(\frac{qe^x}{1-pe^x}\right)^t \mathcal{I}_{1-pe^x}(t, s) \tag{7}$$

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



(a) SNB distribution (b) binomial distribution

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:

$$\mathbb{E}\ e^{xY} = \sum_{k=s}^{s+t-1} \binom{k-1}{s-1} (pe^x)^s (qe^x)^{k-s} + \sum_{k=t}^{s+t-1} \binom{k-1}{t-1} (qe^x)^t (pe^x)^{k-t}. \quad (8)$$

The first summation in (8) satisfies

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

115 Since the incomplete beta function's subscript parameter has support on zero to one, we have $qe^x \leq 1$. This also shows we must restrict $x \leq -\log(q)$. A similar expression can be derived for the second summation in (8) and results in the constraint $x \leq -\log(p)$. □

The SNB's ability to approximate the geometric, normal, gamma, and poisson distributions follow from it generalizing the negative binomial distribution. To recover the MGF of the negative binomial consider the case where $t \to \infty$ in (7). The regularized incomplete beta function in the first term goes to one and zero in the second term. We are left with the MGF of the negative binomial distribution.

When $s = 1$ (and t is still large) the SNB's MGF is 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.

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 [7, 8, 4] for examples). A connection to the poisson appears in [9] where it is shown that if the mean of a poisson is proportional to a χ^2_{2k} distribution then the negative binomial is obtained. Both of these approximations work by equating cumulants and then showing that differences between betwen 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 as identical, negative binomials approximating a normal and truncated at the median.

5. The Predictive Probability Distribution

Let us consider the SNB distribution where p has a beta distribution.

Proposition 4. *The predictive distribution of the SNB distribution when p is distributed Beta(α, β) is*

$$\mathbb{P}[Y = k|s,t,\alpha,\beta] = \binom{k-1}{s-1}\frac{B\left(\alpha+s, k-s+\beta\right)}{B(\alpha,\beta)}\, I_{\{s\leq k\leq s+k-1\}} + \binom{k-1}{t-1}\frac{B\left(\alpha+k-t, t+\beta\right)}{B(\alpha,\beta)}\, I_{\{t\leq k\leq s+k-1\}}. \tag{9}$$

Proof. For notational simplicity, assume that k is in the range $\min(s,t) \leq k \leq s+t-1$. When this is not the case appropriate terms should be removed as dictated by the indicator functions.

$$\begin{aligned} f(k|s,t,\alpha,\beta) &= \frac{1}{B(\alpha,\beta)} \int_0^1 \binom{k-1}{s-1} p^{\alpha+s-1} (1-p)^{k-s+\beta-1} + \\ &\qquad \binom{k-1}{t-1} p^{k-t+\alpha-1} (1-p)^{t+\beta-1} \, dp \\ &= \frac{1}{B(\alpha,\beta)} \binom{k-1}{s-1} \int_0^1 p^{\alpha+s-1} (1-p)^{k-s+\beta-1} \, dp + \\ &\qquad \frac{1}{B(\alpha,\beta)} \binom{k-1}{t-1} \int_0^1 p^{k-t+\alpha-1} (1-p)^{t+\beta-1} \, dp. \end{aligned}$$

The result in (9) follows by the definition of the beta function. □

To better understand the predictive distribution, let us once again return to our example where $s = 7$, $t = 11$. However, we assume p is a beta distribution with shape parameters $\alpha = 0.2c$ and $\beta = 0.8c$ for any $c > 0$. This parameterization allows us to examine the relationship between uncertainty in p and the SNB.

Fig. 5 shows how the mean and variance of the predictive distribution is related to the SNB's mean and variance. As c increases the predictive distribution sample statistics converge to corresponding statistics for the SNB with $p = 0.2$. When the distribution of p is centered close to zero or one the mean estimate approach the deterministic limit relatively slowly in the uncertainty parameter c. Because of this, we note that for estimation it may be preferable to select shape parameters based on the median or mode of the beta distribution since they are less sensitive to distributional uncertainty.

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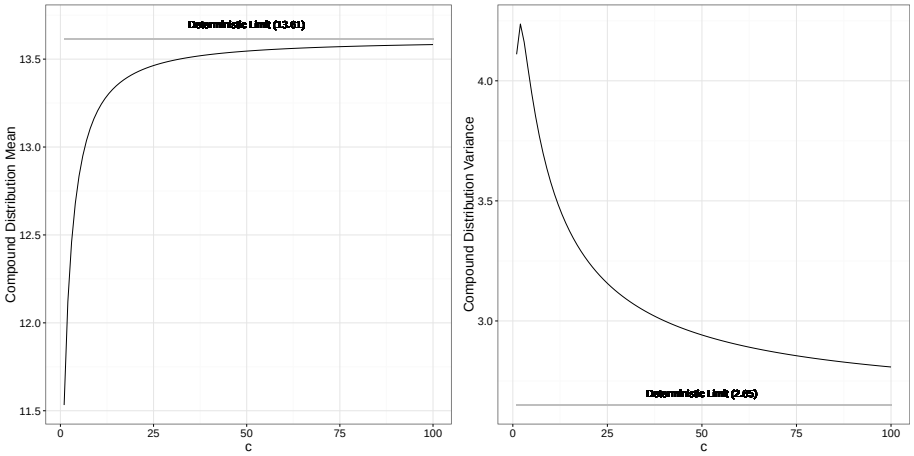

(a) mean (b) variance

Figure 5: The mean and variance of the predictive SNB with $s = 7$, $t = 11$ with $\mathbb{E}\ p = 0.2$ varying the uncertainty in the distribution of p. A larger value of c corresponds to a beta with smaller variance.

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