A Probabilistic Model for the Survivability of Cells

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September 2004

Abstract

Consider n cells, of which some are target cells, and suppose that each cell has a weight. The cells are killed in a sequential manner, with each currently alive cell being the next one killed with a probability proportional to its weight. We study the distribution of the number of cells that are alive at the moment when all the target cells have been killed.

1 Introduction

Consider n cells, with cell i having weight w_i, that are successively killed in the following manner. If S is the set of currently alive cells, then in the next stage $i \in S$ is killed with probability $w_i / \sum_{j \in S} w_j$. Let I_j be the indicator for the event that cell j $(j > r)$ is alive when the target cells $1, \ldots, r$ are all killed. We are interested in the properties of $N = \sum_{j=r+1}^{n} I_j$, the number of surviving cells when all the target cells have been killed. A possible application for this model is the case in which the target cells are cancerous while the non-target cells are healthy cells. The model can also be viewed within the framework of the coupon-collector problem [], where $n - N$ represents the number of distinct types of coupons that need be collected before all of the types $1, \ldots, r$ have been collected.

In section 2 we determine formulas for the mean and variance of N and derive simple bounds on the mean for some special cases. In section 3 we derive a lower bound for $P(N \geq k)$ and present a computational procedure as well as an efficient simulation procedure for estimating $P(N \geq k)$. In section 4 we discuss the asymptotic behavior of the mean and distribution of N for the special case in which all the target cells have the same weight and all the non-target cells have the same weight. We also obtain sharp asymptotic results in this case when we stop when all but a fixed positive fraction of target cells have been killed. In the final section, we consider the case where a stage consists of a probe, where each new probe goes into a given alive cell with probability proportional to the weight of that cell divided by the sum of the weights of all

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currently alive cells. Supposing that a probe into cell i only kills that cell with probability p_i, we compute the expected number of probes needed to kill all the cells $1, \ldots, r$, and present an efficient simulation procedure for estimating its distribution.

2 Expected Value and Variance of N

To study N, consider a model in which cell i is killed at time T_i, where $T_1, \ldots, T_n$ are independent exponential random variables with respective rates $w_1, \ldots, w_n$, and note that the order in which the cells are killed is probabilistically the same as in the original model. Consequently, letting $T = \max(T_1, T_2, \ldots, T_r)$, and for $J \subseteq \{r+1, \ldots, n\}$, letting $T_J = \min_{j \in J} T_j$ and $I_J = \bigcap_{j \in J} I_j$, we have that I_J is equivalent to the event $(T_J > T)$, which leads directly to:

Lemma 1 *With* $a(w) = \int_0^\infty w e^{-wt} \prod_{i=1}^r (1 - e^{-w_i t})\, dt$ *, and* $w(J) = \sum_{j \in J} w_j$*, we have,*

$$P(I_J) = a(w(J)) \tag{1}$$

Proof

$$P(I_J) = P(T_J > T) = \int_0^\infty w(J)\, e^{-w(J)t} \prod_{i=1}^r (1 - e^{-w_i t})\, dt \quad \blacksquare$$

Lemma 1 immediately yields

Proposition 1

(i) $E[N] = \sum_{j=r+1}^n a(w_j)$

(ii) $Var(N) = \sum_{j=r+1}^n a(w_j)(1 - a(w_j)) + 2 \sum_{j=r+1}^{n-1} \sum_{k=j+1}^n [a(w_j + w_k) - a(w_j) a(w_k)]$

For the special case in which all the target cells have identical weights we have,

Corollary 1 *Let* $w_i = w_1$ $(i = 1, 2, \ldots, r)$,

(i) *For* $J \subseteq \{r+1, \ldots, n\}$, *with* $r(J) = \frac{w(J)}{w_1}$,

$$P(I_J) = \sum_{i=0}^r (-1)^i \binom{r}{i} \frac{r(J)}{r(J) + i} = \prod_{i=1}^r \frac{i}{r(J) + i}$$

(ii) *With* $r_j = \frac{w_j}{w_1}$,

$$E[N] = \sum_{j=r+1}^n \sum_{i=0}^r (-1)^i \binom{r}{i} \frac{r_j}{r_j + i} = \sum_{j=r+1}^n \prod_{i=1}^r \frac{i}{r_j + i}$$

Proof

(i) By Lemma 1

$$\begin{aligned} P(I_J) &= \int_0^\infty w(J)e^{-w(J)t}\,(1-e^{-w_1 t})^r\,dt \\ &= \int_0^\infty w(J)e^{-w(J)t}\sum_{i=0}^{r}(-1)^i\binom{r}{i}e^{-iw_1 t}\,dt \\ &= \sum_{i=0}^{r}(-1)^i\binom{r}{i}\frac{w(J)}{w(J)+iw_1} \end{aligned}$$

On the other hand, it directly follows from the lack of memory of exponential random variables that

$$P(I_J) = \prod_{i=1}^{r}\frac{iw_1}{iw_1+w(J)}$$

Part (ii) immediately follows from (i). ■

The following yields an upper bound for $E(N)$.

Corollary 2 *Let* $\bar{w}_1 = \frac{1}{r}\sum_{i=1}^{r} w_i$*,*

(i) *For* $J \subseteq \{r+1,\ldots,n\}$ *and with* $r(J) = \frac{w(J)}{\bar{w}_1}$*,*

$$P(I_J) \le \sum_{i=0}^{r}(-1)^i\binom{r}{i}\frac{r(J)}{r(J)+i} = \prod_{i=1}^{r}\frac{i}{r(J)+i}$$

(ii) *With* $r_j = \frac{w_j}{\bar{w}_1}$*,*

$$E[N] \le \sum_{j=r+1}^{n}\sum_{i=0}^{r}(-1)^i\binom{r}{i}\frac{r_j}{r_j+i} = \sum_{j=r+1}^{n}\prod_{i=1}^{r}\frac{i}{r_j+i}$$

Proof
It is easily verified that $\prod_{i=1}^{r}(1-e^{-w_i t})$ is a Schur concave function of $w_1,\ldots,w_r$. Therefore,

$$\prod_{i=1}^{r}(1-e^{-w_i t}) \le (1-e^{-\bar{w}_1 t})^r$$

and the result follows from Lemma 1 and Corollary 1. ■

3 The distribution of N

Given (1), it is easy to construct an expression for $P(N \geq k)$. However, such an expression involves an exponential (with respect to $n-r$) number of terms, which makes it impractical for computation. We now present some bounds and computational methods.

Proposition 2 *Let* $\bar{w}_2 = \frac{1}{n-r}\sum_{j=r+1}^{n} w_j$, *then for* $k = 1, \dots, n-r$,

$$P(N \geq k) \geq \int_0^\infty \sum_{i=1}^{r} w_i e^{-w_i t} \prod_{j \neq i, j \leq r} (1 - e^{-w_j t}) \sum_{j=k}^{n-r} \binom{n-r}{j} e^{-j\bar{w}_2 t}(1 - e^{-\bar{w}_2 t})^{(n-r-j)} dt$$

Proof

$$P(N \geq k) \quad = \quad \int_0^\infty P(N \geq k | T = t) dF_T(t) \quad (\text{ where } F_T(t) = P(T \leq t))$$

However, $P(N \geq k|T = t) = P(k^{th}$ largest of $T_{r+1}, \dots, T_n$ is greater than $t)$. The result now follows because (see [2]) the order statistic of a vector of independent exponentials with rates $\mathbf{r} = (r_1, \dots, r_m)$ is stochastically smaller than the corresponding order statistic of a vector of independent exponentials with rates $\mathbf{v} = (v_1, \dots, v_m)$ when $\mathbf{v}$ majorizes $\mathbf{r}$. ■

3.1 Approximating $P(N \geq k)$

Let $\Phi(k, t) = P(N \geq k \mid T = t)$, and write

$$P(N \geq k) = \int_0^\infty \Phi(k, t)\, dF_T(t) \tag{2}$$

For a given integer m and $\epsilon > 0$, let us construct a sequence $t_0, t_1, \dots, t_{m+1}$ where $t_0 = 0$, $t_{i+1} = t_i + \epsilon$, $i = 0, \dots, m-1$ and $t_{m+1} = \infty$. Since $\Phi(k, t)$ is monotonically decreasing in t, we have,

$$\sum_{i=0}^{m} \Phi(k, t_{i+1})(F_T(t_{i+1}) - F_T(t_i)) \leq \int_0^\infty \Phi(k, t)\, dF(t) \leq \sum_{i=0}^{m} \Phi(k, t_i)(F_T(t_{i+1}) - F_T(t_i)) \tag{3}$$

Suppose that we can (as we show below) compute $\Phi(k, t)$. Then the preceding expression can be used to approximate $P(N \geq k)$ to any desirable precision, by choosing sufficiently large m and small ϵ.

We can compute $\Phi(k, t)$ by first recursively computing $\phi_t(\ell, i) \equiv P(\sum_{j=r+1}^{\ell} I(T_j > t) = i)$ (where $I(T_j > t)$ is the indicator of the event $T_j > t$, and $\ell = r + i, \dots, n$) as follows:

$$\begin{aligned}
\phi_t(\ell, 0) &= \prod_{j=r+1}^{\ell} (1 - e^{-w_j\, t}), \qquad \ell = r+1, \dots, n \\
\phi_t(\ell, 1) &= e^{-w_{r+1}\, t}, \qquad \ell = r+1 \\
\phi_t(\ell, i) &= \phi_t(\ell-1, i)P(T_\ell \leq t) + \phi_t(\ell-1, i-1)P(T_\ell > t) \\
&= \phi_t(\ell-1, i)(1 - e^{-w_\ell\, t}) + \phi_t(\ell-1, i-1)e^{-w_\ell\, t}
\end{aligned}$$

Now, $\Phi(k, t) = \sum_{i=k}^{n-r} \phi_t(n, i)$.

3.2 Using Simulation to Compute $P(N \geq k)$

We now show how to efficiently use simulation to estimate $P(N \geq k)$. To start, generate the values of $T_{r+1}, \ldots, T_n$. Then order these values, and let Y_i be the value of the i^{th} largest, $i = 1, \ldots, n-r$. Then use the conditional expectation estimator

$$P(N \geq k \mid Y_k = y_k) = \prod_{i=1}^{r} (1 - e^{-w_i y_k})$$

The preceding yields the following scheme for estimating $P(N \geq k)$, $k = 1, \ldots, n-r$.

1. Generate random numbers $U_1, \ldots, U_{n-r}$
2. Let
$$T_{r+i} = -\frac{1}{w_{i+r}} \log(U_i) \ , \qquad i = 1, \ldots, n-r$$
3. Descending order the values $T_{r+1}, \ldots, T_n$, and call the ordered values $Y_1 \geq \ldots \geq Y_{n-r}$

The preceding should be repeated many times; the average value of θ_k obtained is the estimate of $P(N \geq k)$, $k = 1, \ldots, n-r$.

Remark Note that because the preceding estimator is a monotone function of $T_{r+1}, \ldots, T_n$, antithetic variables can be used for further variance reduction (see [4]).

4 Special Case: Uniform Weights

In this section we consider the special case in which all the target weights are equal and all the non-target weights are equal. Specifically, we assume that

$$w_j = \begin{cases} 1 & \text{if } \ j = 1, \ldots, r \\ w & \text{if } \ j = r+1, \ldots, n \end{cases}$$

Letting

$$\begin{aligned} \Gamma(a) &= \int_0^\infty e^{-t} t^{a-1} dt \\ B(a,b) &= \frac{\Gamma(a)\Gamma(b)}{\Gamma(a+b)} = \int_0^1 t^{a-1}(1-t)^{b-1} dt \end{aligned}$$

we have that for $J \subseteq \{r+1, \ldots, n\}$ and $|J| = k$,

$$
\begin{aligned}
P(I_J) &= \int_0^\infty kw\, e^{-kwt}(1-e^{-t})^r\, dt \\
&= kwB(kw, r+1) \\
&= rB(kw+1, r)
\end{aligned}
$$

Thus, setting $m = n - r$,

$$
\begin{aligned}
E[N] &= mrB(w+1, r) \\
\mathrm{Var}[N] &= mrB(w+1, r) + m(m-1)rB(2w+1, r) - m^2r^2B^2(w+1, r)
\end{aligned}
$$

For the distribution of N, we get

$$
\begin{aligned}
P(N \geq k) &= \int_0^\infty P(N \geq k | T = t) dF_T(t) \\
&= \int_0^\infty re^{-t}(1-e^{-t})^{r-1} \sum_{j=k}^{n-r} \binom{n-r}{j} e^{-wtj}(1-e^{-wt})^{n-r-j}\, dt
\end{aligned}
$$

which, by using the Binomial expansion, collecting terms and evaluating the resulting integral, yields

$$
P(N \geq k) = r \sum_{j=k}^{m} \binom{m}{j} \sum_{\ell=0}^{m-j} \binom{m-j}{\ell} \sum_{i=0}^{r-1} \binom{r-1}{i} (-1)^{(\ell+i)} \frac{1}{(\ell+j)w + i + 1}
$$

Alternatively, one can recursively calculate $P(N \geq k)$ by considering the following (where $\phi(k, r', n') = P[N \geq k \mid \text{there are } r' \text{ target cells and a total of } n' \text{ cells}]$):

$$
\begin{aligned}
\phi(k, 0, n') &= 1 \quad (n' = r+k, \ldots, n) \\
\phi(k, r', r'+k) &= \prod_{i=1}^{r'} \frac{i}{kw+i} \quad (r' = 1, \ldots, r) \\
\phi(k, r', n') &= \frac{r'}{(n'-r')w + r'} \phi(k, r'-1, n'-1) + \frac{(n'-r')w}{(n'-r')w + r'} \phi(k-1, r', n'-1)
\end{aligned}
$$

where $P(N \geq k) = \phi(r, k, n)$.

Next we develop bounds for $P(N \geq k)$. Let τ denote the time at which all r target cells (which each live an exponential time with rate 1) are killed. Imagine that the $m = n - r$ non-target cells (which each live an exponential time with rate w) continue to die even after time

τ. Let $N(t)$ denote the number of non-target cells that are alive at time t. Note that $N(t)$ is a binomial random variable with parameters m and e^{-tw}, and that $N = N(\tau)$.

Fix $A < r$, and let $t = \ln(r/A)$. Note that $(1-e^{-t})^r = (1-A/r)^r$, and that $e^{-tw} = (A/r)^w$. Then,

$$
\begin{aligned}
P(N \geq k) &= P(N \geq k|\tau \leq t)P(\tau \leq t) + P(N \geq k|\tau > t)P(\tau > t) \\
&\leq P(\tau \leq t) + P(N(t) \geq k)P(\tau > t) \\
&= (1 - A/r)^r + P(N(t) \geq k)(1 - (1 - A/r)^r) \qquad (4)
\end{aligned}
$$

Letting $S = m(A/r)^w$ and $k = (1+\delta)S$, and applying to (4) the Chernoff bound that for a binomial random variable X

$$
P(X \geq (1+\delta)E[X]) \leq \left(\frac{e^\delta}{(1+\delta)^{1+\delta}}\right)^{E[X]}
$$

(see for example [3]) gives the inequality

$$
P[N \geq (1+\delta)S] \leq (1 - A/r)^r + \left(\frac{e^\delta}{(1+\delta)^{1+\delta}}\right)^S (1 - (1 - A/r)^r) < e^{-A} + \left(\frac{e^\delta}{(1+\delta)^{1+\delta}}\right)^S
$$

Finally, we comment on the asymptotic behavior of N as r and m tend to ∞.

Noting (see [5]) that

$$
B(w, r) = \Gamma(w)r^{-w}[1 - \frac{\Gamma(w)\Gamma(w-1)}{2r}[1 - O(r^{-1})]]
$$

we have that asymptotically, as $r \to \infty$, $rB(w+1, r) \sim \Gamma(w+1)r^{-w}$. Thus, for $r \to \infty$,

$$
\begin{aligned}
E[N] &\sim \Gamma(w+1)mr^{-w} \qquad (5) \\
\mathrm{Var}[N] &\sim E[N] + [\Gamma(2w+1) - \Gamma^2(w+1)]m^2 r^{-2w} \qquad (6)
\end{aligned}
$$

For asymptotic results related to the distribution of N, let $t = \ln(r/B)$, and use that

$$
\begin{aligned}
P(N \leq k) &= P(N \leq k|\tau \leq t)P(\tau \leq t) + P(N \leq k|\tau > t)P(\tau > t) \\
&\leq P(N(t) \leq k)(1 - B/r)^r + 1 - (1 - B/r)^r \qquad (7)
\end{aligned}
$$

Applying the Chernoff bound (see, for example, [3]) that for a binomial (m, p) random variable X and $a > 0$

$$
\max\left(P(X \geq mp + a),\ P(X \leq mp - a)\right) \leq e^{-2a^2/m} \qquad (8)
$$

to (4) and then to (7) gives

$$
P(N \geq m(A/r)^w + a) \leq (1 - A/r)^r + e^{-2a^2/m} \qquad (9)
$$

and

$$P(N \leq m(B/r)^w - a) \leq e^{-2a^2/m}(1-B/r)^r + 1 - (1-B/r)^r \tag{10}$$

Substituting $a = \delta m \frac{A^w}{r^w}$ in (9) and $a = \delta \frac{m}{r^w A^w}$ in (10) and letting $A < r$ be a nondecreasing unbounded function of r and $B = 1/A$, we can conclude that for a given $\delta > 0$ and as $r, m \to \infty$

(i) if $\liminf \frac{mA^w}{r^w} = \infty$ then $P[N < (1+\delta)\frac{mA^w}{r^w}] \to 1$

(ii) if $\liminf \frac{m}{(rA)^w} = \infty$ then $P[N > (1-\delta)\frac{m}{(rA)^w}] \to 1$

Remarks:
(a) If for fixed $0 < \alpha < 1$, we let $A = \alpha r$, then (i) is satisfied. Hence, letting $\epsilon = (1+\delta)\alpha^w$, we see that for any $\epsilon > 0$,

$$P(N < \epsilon m) \to 1$$

(b) It follows from (ii) that if $\frac{m}{r^{2w}} \to \infty$, then $P(N > (1-\epsilon)\frac{m}{r^{2w}}) \to 1$, for any $\epsilon > 0$.
(c) It follows that $P(N \geq k) \leq \min_{A<r}[e^{-A} + e^{-S}(\frac{eS}{k})^k]$, where $S = m(A/r)^w$.
(d) Finally we observe from (5) that if $mr^{-w} \to 0$ (a condition which is satisfied whenever the conditions of (i) and (ii) above are violated) then $P(N = 0) \to 1$.

We can obtain sharp asymptotic results if we stop the first moment when the number of surviving target cells has been reduced to a fraction $\epsilon > 0$ of its original value. Letting N_ϵ be the number of non-target cells still surviving at that time, we shall prove that N_ϵ is concentrated around the value $m\epsilon^w$.

Proposition 3 *For all δ greater than 0, as $r \to \infty$ and $m \to \infty$*

$$P\{(1-\delta)m\epsilon^w \leq N_\epsilon \leq (1+\delta)m\epsilon^w\} \to 1$$

Proof. We first show that

$$P(N_\epsilon \leq (1+\delta)m\epsilon^w) \to 1 \tag{11}$$

To show this, let τ_ϵ denote the first time at which at least $(1-\epsilon)r$ target cells have been killed, so $N_\epsilon = N(\tau_\epsilon)$. Let γ be such that $0 < \gamma < \delta$, and let $t = -\ln(\epsilon(1+\gamma)^{1/w})$. We will prove (11) by showing that as r and m approach ∞
(i) $P(\tau_\epsilon \leq t) \to 0$ and
(ii) $P(N(t) > (1+\delta)me^w) \to 0$
As the preceding implies that

$$P(N(\tau_\epsilon) \leq (1+\delta)m\epsilon^w) \geq P(\tau_\epsilon > t, N(t) \leq (1+\delta)me^w) \to 1$$

the result (11) will be proven.

The number, call it Y, of surviving target cells at time t is binomial with parameters r and $e^{-t} = \epsilon(1+\gamma)^{1/w}$. Hence, with $a = r\epsilon[(1+\gamma)^{1/w} - 1]$

$$\begin{aligned} P(\tau_\epsilon \le t) &= P(Y \le \epsilon r) \\ &= P(Y \le re^{-t} - a) \\ &\le e^{-2a^2/r} \end{aligned}$$

where the inequality follows from the Chernoff bound (8). Hence, (i) is proven because a^2/r goes to ∞ as r goes to ∞.

To prove (ii), note that $N(t)$ is binomial with parameters m and $e^{-wt} = \epsilon^w(1+\gamma)$. Hence, letting $b = m\epsilon^w(\delta - \gamma)$, and again applying the Chernoff bound (8), we obtain

$$\begin{aligned} P(N(t) > (1+\delta)m\epsilon^w) &= P(N(t) > me^{-wt} + b) \\ &\le e^{-2b^2/m} \end{aligned}$$

Hence, (ii) is proven because b^2/m goes to ∞ as m goes to ∞. Thus, we have proven (11).

The proof that

$$P(N_\epsilon \ge (1-\delta)m\epsilon^w) \to 1$$

is similar. ■

5 The Probes Model

Suppose now that whereas a probe will hit the live cell i with probability equal to w_i divided by the sum of weights of all currently alive cells, the probe only kills the cell with probability p_i. It is easy to see that the results of the previous sections are applicable, with w_k replaced with $p_k w_k$ $(k = 1, \ldots, n)$. Thus, for $j > r$

$$P(I_j = 1) = \int_0^\infty w_j p_j e^{-p_j w_j t} \prod_{i=1}^r (1 - e^{-p_i w_i t}) dt$$

and

$$E[N] = \sum_{j=r+1}^n \int_0^\infty w_j p_j e^{-p_j w_j t} \prod_{i=1}^r (1 - e^{-p_i w_i t}) dt$$

An additional random variable of interest in this model is R, the number of probes needed to kill all the target cells $1, \ldots, r$.

Proposition 4

$$E[R] = \sum_{i=1}^n \frac{1}{p_i} - \sum_{j=r+1}^n \int_0^\infty \frac{w_j}{p_j} e^{-p_j w_j t} \prod_{i=1}^r (1 - e^{-p_i w_i t}) dt$$

Proof
Imagine that the probing does not end when all the cells $1, \ldots, r$ are killed, but continues until all n cells are killed, and let Q denote the number of probes until all n cells are killed. Also, let R_j denote the number of probes of j after all of $1, \ldots, r$ have been killed. Then

$$E[R] = E[Q] - \sum_{j=r+1}^{n} E[R_j] = \sum_{i=1}^{n} \frac{1}{p_i} - \sum_{j=r+1}^{n} P(I_j = 1)\frac{1}{p_j}$$

which completes the proof ■

We now show how to efficiently use simulation to estimate $P(R < k+r)$. Suppose that probes of the cells $i, i \geq 1$, occur at times distributed according to independent Poisson processes with rates $w_i, i \geq 1$, with each probe of i being a kill probe with probability p_i or a non-kill probe with probability $1 - p_i$. Then, $T_1, \ldots, T_n$, the times to kill cells $1, \ldots, n$, are independent exponential random variables with respective rates $p_1 w_1, \ldots, p_n w_n$. Let $T = \max(T_1, \ldots, T_r)$. Because the processes of non-kill probes is independent of that of kill probes, it follows that, conditional on $\mathbf{T} = (T_1, \ldots, T_n)$, the number of non-kill probes of live cells by time T is Poisson distributed with mean $\sum_i w_i(1 - p_i)\min(T_i, T)$. Consequently, conditional on $\mathbf{T}$,

$$R =_d n - N + W$$

where W is a Poisson random variable with mean $\sum_i w_i(1 - p_i)\min(T_i, T)$ that is independent of N, and $=_d$ means "equal in distribution".

It follows from the preceding that

$$P(R < k + r|\mathbf{T}) = P\{W < k + r - (n - N)|\mathbf{T}\}$$

Therefore, we have the following approach for estimating $P(R < k + r)$, for each $k \geq 1$.

1. Generate $T_1, \ldots, T_n$, independent exponentials with rates $p_1 w_1, \ldots, p_n w_n$
2. Let $T = \max(T_1, \ldots, T_r)$
3. Let $n - N = r + \sum_{j=r+1}^{n} I(T_j < T)$
4. Let $a = \sum_i w_i(1 - p_i)\min(T_i, T)$
5. The estimate of $P(R < k + r\}$ from this run is

$$\text{est}(k) = \begin{cases} 0 & \text{if } k + r \leq n - N \\ \sum_{j=0}^{m} e^{-a}\frac{a^j}{j!} & \text{if } k + r > n - N \end{cases}$$

   where $m = k + r - (n - N) - 1$

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