J. Appl. Prob. **46,** 1221–1224 (2009)
Printed in England

LETTER TO THE EDITOR

Dear Editor,

Remarks on the asymptotics of the Luria–Delbrück and related distributions

The Luria–Delbrück distribution models the number of mutant cells in a cell population initiated with one or more wild-type cells. The distribution is defined by the generating function

$$G_0(z) \equiv \sum_{j\geqslant 0} p_j z^j = \exp\left\{m\left(\frac{1}{z}-1\right)\log(1-z)\right\}, \tag{1}$$

where m is a positive real number. In the 1990s several authors investigated the asymptotics of this distribution, including Ma *et al.* [5], Pakes [6], Kemp [4], Goldie [2], and Prodinger [7]. Thus, there exist several proofs of the asymptotic relations

$$p_n \sim \frac{m}{n^2} \quad \text{and} \quad \tilde{p}_n \equiv \sum_{j>n} p_j \sim \frac{m}{n} \quad (n\to\infty). \tag{2}$$

The approach taken by Prodinger [7] to derive (2), which is based on the singularity analysis technique perfected by Flajolet and Odlyzko [1], seems the most suitable for studying asymptotics of so-called mutant distributions that include the Luria–Delbrück distribution and several related distributions.

One important mutant distribution sprang from the assumption that, at the end of the experiment, each mutant has a probability $\varepsilon \in (0,1)$ of being observed (see [8] and [10]). The generating function for the number of observed mutants is thus $G_0(1-\varepsilon-\varepsilon z)$, which takes the form

$$G_1(z) = \exp\left\{m\xi\,\frac{(1-z)\log[\varepsilon(1-z)]}{1+\xi z}\right\}$$

with $\xi = \varepsilon/(1-\varepsilon)$. Asymptotics of this distribution are currently unknown.

Following Flajolet and Odlyzko [1], we let $[z^n]f(z)$ be the nth Maclaurin coefficient of $f(z)$, that is, the coefficient a_n in a power series expansion $f(z)=\sum_{n=0}^{\infty} a_n z^n$. Furthermore, for $\eta>0$ and $\psi\in(0,\pi/2)$, we define $\Delta(\psi,\eta)$ to be the region

$$\{z\colon |z|\leqslant 1+\eta,\ |\arg(z-1)|\geqslant\psi\}$$

in the complex plane. Asymptotic information about mutant distributions can often be obtained by applying results similar to Corollary 2 of [1], which we quote as follows.

Proposition 1. ([1].) *Let $f(z)$ be analytic in $\Delta(\psi,\eta)\setminus\{1\}$ for some $\eta>0$ and $\psi\in(0,\pi/2)$. Assume that, as $z\to 1$ in $\Delta(\psi,\eta)$,*

$$f(z)\sim K(1-z)^{\alpha}$$

for some real constants α and K. If α is a nonnegative integer then

$$[z^n]f(z) = o(n^{-\alpha-1}).$$

Received 20 July 2009; revision received 28 September 2009.

https://doi.org/10.1239/jap/1261670701 Published online by Cambridge University Press

Otherwise,

$$[z^n]f(z) \sim \frac{K}{\Gamma(-\alpha)} n^{-\alpha-1}.$$

We now apply Proposition 1 to the generating function $G_1(z)$ to establish an analogue of (2). Note that the point $z = -1/\xi$ is a removable singularity of $G_1(z)$. Since we use the principal branch of the logarithm, $G_1(z)$ has only one singularity at $z = 1$ in $\Delta(\psi, \eta)$ for arbitrarily fixed $\eta > 0$ and $\psi \in (0, \pi/2)$. After a little calculation we find that

$$\frac{(1-z)\log[\varepsilon(1-z)]}{1+\xi z} = (1-\varepsilon)(1-z)\log(1-z) + R_0$$

with

$$R_0 = (\log\varepsilon)(1-\varepsilon)(1-z) + \varepsilon\frac{\log(1-z)+\log\varepsilon}{1+\xi z}(1-z)^2.$$

Clearly,

$$R_0 \sim (\log\varepsilon)(1-\varepsilon)(1-z) \quad \text{as } z \to 1 \text{ in } \Delta(\psi, \eta).$$

Consequently,

$$G_1(z) = 1 + m\varepsilon(1-z)\log(1-z) + R_1 \tag{3}$$

with

$$R_1 \sim K(1-z) \quad \text{as } z \to 1 \text{ in } \Delta(\psi, \eta)$$

for some real constant K. Because $G_1(z)$ is analytic in $\Delta(\psi, \eta) \setminus \{1\}$, so is R_1 in view of (3). If follows at once from Proposition 1 that

$$[z^n]R_1 = o(n^{-2}).$$

Furthermore, $[z^n](1-z)\log(1-z) = n^{-2} + o(n^{-2})$. Combining these two results, we infer from (3) that

$$p_n \sim \frac{\varepsilon m}{n^2}.$$

(We henceforth use p_n and $\tilde{p}_n$ as generic symbols for the probability and tail probability, respectively.) Because $\sum_{j>n} 1/j^2 \sim 1/n$ as $n \to \infty$, we further obtain

$$\tilde{p}_n \sim \frac{\varepsilon m}{n}.$$

Another mutant distribution of practical interest is defined by the generating function

$$G_2(z) = \exp\left\{\frac{m}{\phi}\left(\frac{1}{z} - 1\right)\log(1-\phi z)\right\},$$

where $\phi \in (0, 1)$. Pakes [6] was the first to give an asymptotic expression equivalent to

$$\frac{p_n}{\phi^n} \sim \frac{1}{\Gamma(m(1-\phi)/\phi)} n^{m(1-\phi)/\phi - 1}. \tag{4}$$

It is easy to see that, as $z \to 1-$ on the real axis,

$$G_2(\phi^{-1}z) \sim (1-z)^{-m(1-\phi)/\phi}. \tag{5}$$

https://doi.org/10.1239/jap/1261670701 Published online by Cambridge University Press

Citing a Tauberian theorem, Jaeger and Sarkar [3] used (5) to conclude (4). However, as Flajolet and Odlyzko [1] noted, application of Tauberian theorems requires so-called Tauberian side conditions. In this case positivity of $\phi^{-n} p_n$ is easy to verify, and, hence, the asymptotic relation holds at least in the following Cesàro sense:

$$\frac{1}{n}\sum_{j=0}^{n-1}\frac{p_j}{\phi^j} \sim \frac{1}{\Gamma(m(1-\phi)/\phi+1)} n^{m(1-\phi)/\phi-1}.$$

To prove (4) itself, we need to verify the monotonicity condition that $p_{n+1} < \phi p_n$ for sufficiently large n, which seems a cumbersome task. On the other hand, it is simple to verify that

$$G_2(\phi^{-1}z) = \exp\left\{m\left(\frac{1}{z}-\frac{1}{\phi}\right)\log(1-z)\right\}$$

has just one (logarithmic) singularity at $z = 1$ in the whole region of $\Delta(\psi, \eta)$, the point $z = 0$ being a removable singularity. Moreover, (5) holds for $z \to 1$ in $\Delta(\psi, \eta)$. The validity of (4) therefore follows readily from Proposition 1 (see [11]).

Our third mutant distribution is defined by the generating function

$$G_3(z) = \left[\frac{(1-\phi)z}{1-\phi z-(1-z)(1-\phi z)^{\alpha}}\right]^k, \tag{6}$$

where $\alpha, \phi \in (0, 1)$ and k is a positive integer. A detailed derivation of $G_3(z)$ as a valid probability generating function for $k = 1$ is given in [9]. It was shown in [11] that, as $z \to 1$ in $\Delta(\psi, \eta)$,

$$G_3(\phi^{-1}z) \sim (1-z)^{-k\alpha}.$$

This expression implies that

$$p_n \sim \frac{\phi^n}{\Gamma(k\alpha)} n^{k\alpha-1},$$

provided that $G_3(\phi^{-1}z)$ is analytic in $\Delta(\psi, \eta) \setminus \{1\}$ for some $\eta > 0$ and $\psi \in (0, \pi/2)$. But a proof of the analyticity of $G_3(\phi^{-1}z)$ in $\Delta(\psi, \eta) \setminus \{1\}$ was missing in [11]. For completeness, we give one here. It is readily seen from (6) that

$$G_3(\phi^{-1}z) = \left[\frac{1-\phi}{\phi}a(z)(1-z)^{-\alpha}\right]^k$$

with

$$a(z) = \frac{z}{(1-z)^{1-\alpha}-(1-\phi^{-1}z)}.$$

Since we use the principal branch of the logarithm, both $(1-z)^{-\alpha}$ and $(1-z)^{1-\alpha}$ are analytic in $\Delta(\psi, \eta) \setminus \{1\}$. Furthermore, because $a(z) \to \phi^{-1}[1-(1-\alpha)\phi]$ as $z \to 0$, zero is not a singularity of $a(z)$. Therefore, it suffices to ascertain that the denominator of $a(z)$ does not vanish in $\Delta(\psi, \eta) \setminus \{0, 1\}$. This can be accomplished by considering three cases. First, if $z \in (0, 1)$ then

$$(1-z)^{1-\alpha} > 1-z > 1-\frac{z}{\phi}.$$

Second, if $z \in (-\infty, 0)$ then

$$(1-z)^{1-\alpha} < 1-z < 1-\frac{z}{\phi}.$$

https://doi.org/10.1239/jap/1261670701 Published online by Cambridge University Press

Third, consider the case $\mathrm{Im}(z) \neq 0$. Let $\arg z$ denote the principal branch satisfying $-\pi < \arg z \leq \pi$. Because $0 < \phi < 1$, we have

$$|\arg(1 - z)| < |\arg(1 - \phi^{-1}z)|.$$

Using the above inequality and the fact that $0 < 1 - \alpha < 1$, we arrive at

$$|\arg(1 - z)^{1-\alpha}| = |(1 - \alpha) \arg(1 - z)| = (1 - \alpha)|\arg(1 - z)| < |\arg(1 - \phi^{-1}z)|.$$

Combining the above three cases we conclude that the denominator of $a(z)$ has no zeros in $\Delta(\psi, \eta) \setminus \{0, 1\}$.

In summary, singularity analysis is a powerful tool for tackling asymptotics of mutant distributions. To reinforce this message, we conclude by outlining a proof of the first expression in (2). We note that (1) implies that

$$G_0(z) = 1 + m\left(\frac{1}{z} - 1\right) \log(1 - z) + R, \tag{7}$$

where $R = O((1 - z)^2 \log^2(1 - z))$ as $z \to 1$ in $\Delta(\psi, \eta)$. According to another result (Theorem 2) of [1], we have

$$[z^n]R = O(n^{-3} \log^2(n)).$$

Thus, $p_n \sim m/n^2$ is evident from (7).

Acknowledgement

The author is grateful to an anonymous referee for helpful comments.

References

[1] Flajolet, P. and Odlyzko, A. (1990). Singularity analysis of generating functions. *SIAM J. Discrete Math.* **3,** 216–240.
[2] Goldie, C. M. (1995). Asymptotics of the Luria-Delbrück distribution. *J. Appl. Prob.* **32,** 840–841.
[3] Jaeger, D. and Sarkar, S. (1995). On the distribution of bacterial mutants: the effects of differential fitness of mutants and non-mutants. *Genetica* **96,** 217–223.
[4] Kemp, A. W. (1994). Comments on the Luria-Delbrück distribution. *J. Appl. Prob.* **31,** 822–828.
[5] Ma, W. T., Sandri, G. vH. and Sarkar. S. (1992). Analysis of the Luria-Delbrück distribution using discrete convolution powers. *J. Appl. Prob.* **29,** 255–267.
[6] Pakes, A. G. (1993). Remarks on the Luria-Delbrück distribution. *J. Appl. Prob.* **30,** 991–994.
[7] Prodinger, H. (1996). Asymptotics of the Luria-Delbrück distribution via singularity analysis. *J. Appl. Prob.* **33,** 282–283.
[8] Stewart, F. M. (1991). Fluctuation analysis: the effect of plating efficiency. *Genetica* **54,** 51–55.
[9] Zheng, Q. (1999). Progress of a half century in the study of the Luria-Delbrück distribution. *Math. Biosci.* **162,** 1–32.
[10] Zheng, Q. (2008). A note on plating efficiency in fluctuation experiments. *Math. Biosci.* **216,** 150–153.
[11] Zheng, Q. (2008). On Bartlett's formulation of the Luria-Delbrück mutation model. *Math. Biosci.* **215,** 48–54.

Yours sincerely,

Qi Zheng

Department of Epidemiology and Biostatistics,
School of Rural Public Health,
Texas A&M Health Science Center,
College Station,
Texas 77843,
USA.
Email address: qzheng@srph.tamhsc.edu