

*J. Appl. Prob.* **29**, 255–267 (1992)
*Printed in Israel*


# ANALYSIS OF THE LURIA–DELBRÜCK DISTRIBUTION USING DISCRETE CONVOLUTION POWERS

W. T. MA,
G. vH. SANDRI AND
S. SARKAR,* *Boston University*

**Abstract**

The Luria–Delbrück distribution arises in birth-and-mutation processes in population genetics that have been systematically studied for the last fifty years. The central result reported in this paper is a new recursion relation for computing this distribution which supersedes all past results in simplicity and computational efficiency: $p_0 = e^{-m}$; $p_n = (m/n)\sum_{i=0}^{n-1} p_i/(n-i+1)$ where $m$ is the expected number of mutations. A new relation for the asymptotic behavior of $p_n$ ($\approx c/n^2$) is also derived. This corresponds to the probability of finding a very large number of mutants. A formula for the $z$-transform of the distribution is also reported.

BACTERIAL MUTAGENESIS; DIRECTED MUTATIONS

AMS 1991 SUBJECT CLASSIFICATION: PRIMARY 60E05
SECONDARY 92D10

## 1. Introduction

Unicellular organisms such as bacteria usually reproduce by binary fission. Sometimes they are also transformed so that new strains arise. For bacteria, one transformation that was the subject of much discussion in the 1920s and 1930s was that from being sensitive to a lethal virus to being resistant to that virus (see Sarkar (1991a) for details). One school held that the bacteria were transformed due to interaction with virus in their environment (the 'directed mutation' hypothesis). Another school held that transformed bacteria (called 'mutants') arose by random changes or 'mutations' during the growth of the bacteria (the 'random mutation hypothesis').

In order to distinguish between these two hypotheses, Luria and Delbrück (1943) devised an ingenious experiment. A single bacterium would be allowed to reproduce to form several (presumably) identical bacteria. Each of these would then be allowed to reproduce for many generations in separate test-tubes. If the rate of cell division is roughly constant, and the bacteria are allowed to grow for a time allowing $n$ cell divisions, on average each test-tube would contain about $2^n$ cells. The contents of each of

Received 6 December 1990; revision received 22 April 1991.
* Postal address: Boston Theoretical Biology Group, Center for the Philosophy and History of Science, Boston University, 745 Commonwealth Avenue, Boston, MA 02215, USA.

these test-tubes would then be separately plated on to plates containing the virus. All sensitive cells would die. Resistant cells, however, would prosper and soon form visible colonies. The number of such colonies would, therefore, be equal to the number of resistant (mutant) cells present in the test-tube at the time of plating.

Under the hypothesis of directed mutation, cells became mutants only due to interaction with the virus after plating. This is basically a probabilistic process. The number of mutants (represented by visible colonies) on a plate would therefore follow the usual Poisson distribution. If $p_k$ is the probability of finding $k$ mutants, $p_k = e^{-m}m^k/k!$ where the Poisson parameter , $m$, is equal to the product of the probability of a single cell becoming mutant and the number of cells being plated (that is, roughly $2^n$). The variance of this distribution is equal to the mean.

Under the hypothesis of random mutation, mutations would have been occurring with some small probability during the growth of the cells in the test-tubes prior to plating. Moreover, once a mutation has taken place, the mutant cell produces more mutants through exponential growth. Each of these mutants would form colonies after plating. The distribution of the number of mutants in this case is known as the Luria–Delbrück distribution (Sarkar (1990)).

Luria and Delbrück (1943) were unable to provide any procedures for calculating this distribution, though they provided a formula for its variance. However, the problem of the determination of the distribution itself has attracted considerable attention among statisticians over the years. Haldane was probably the first to provide a partial solution in an unpublished paper from 1946 (summarized by Sarkar (1991b)). Lea and Coulson (1949) were the first to describe a procedure for calculating the distribution. More importantly, they derived the generating function

$$F(x) = (1 - x)^{m(1-x)/x} \tag{1}$$

for the distribution where $m$ is the expected number of mutations. Koch (1982) and Stewart et al. (1990) have produced alternative procedures for calculating the distribution. Armitage (1952), (1953), Bartlett (1978), Fu et al. (1982) and Li et al. (1985) have studied other aspects of the distribution, while Mandelbrot (1974) provided a formula for its Laplace transform.

The central result reported in this paper is a new recursion relation to compute the Luria–Delbrück distribution (Equation (22), using the Lea–Coulson generating function (Equation (1)) as the starting point. In simplicity and computational efficiency this new recursion relation supersedes previous results. The asymptotic behavior of the probability $p_k$, of finding $k$ mutants, for large $k$ is obtained (Equation (23)). A formula for the $z$-transform of the distribution is also presented (Equation (24)).

Section 2 gives a sketch of the derivation of Equation (1). It is not particularly original, essentially following Lea and Coulson (1949). However, it is included for the sake of completeness and because it helps make precise the nature of the biological model being discussed here. Section 3 then reviews the use of convolution products and powers of discrete sequences. These are necessary for the derivation of the asymptotic behavior of the $p_k$ which is taken up in Section 4 along with the derivation of the recursion relation

itself. Section 5 gives a derivation of the formula for the $z$-transform and Section 6 briefly discusses the relevance of these results to recent experimental work in bacterial mutagenesis. Laborious proofs that would otherwise interrupt the flow of the derivations have been relegated to appendices.

## 2. The generating function

The generating function (Equation (1)) for the Luria–Delbrück distribution is obtained from a model of bacterial growth and mutation where mutation and growth of the mutant cells are assumed to be stochastic while growth of normal cells is assumed to be deterministic. Assume, with Lea and Coulson (1949), that each culture in a test-tube is grown from a single bacterium and that growth is exponential. What is wanted is the probability, $p_r$, of finding $r$ mutants in the culture at time $t$, when the size of the culture is $n_t$. Let mutagenesis be strictly proportional to the growth rate of the culture. Then $\mu$, the mutation rate per cell division, is constant and the expected number of mutations, $m$, is given by $m = \mu n_t$.

In order to obtain an equation for the $p_r$, consider a very large (in principle infinite) population of cultures. Then $p_r$ is the proportion of culture in which $r$ mutants are present at time $t$, or culture size $n_t$. For notational convenience, $n_t$ will henceforth be written as $n$. Assume that in the interval $(t, t + dt)$, the culture grows from size $n$ to $n + dn$. If $p_r + (dp_r/dn)dn$ is the proportion of cultures that have $r$ mutants at time $t + dt$, or culture size $n + dn$, assuming $dn$ to be small enough,

$$p_r + \frac{dp_r}{dn}dn = p_{r-1}\left(\mu dn + (r-1)\frac{dn}{n}\right) + p_r\left(1 - \mu dn - r\frac{dn}{n}\right). \tag{2}$$

The first term on the right-hand side comes from cultures which had $r - 1$ mutants at time $t$, and either (i) a mutation occurred during $(t, t + dt)$, giving the $\mu dn$ part or (ii) a mutant cell underwent division, giving the $(r - 1)dn/n$ part. The second term is simply the proportion of cultures with $r$ mutants at $t$ but no further mutations were produced by new mutation or mutant cell division; the two such possibilities are subtracted from $p_r$. Reorganizing terms and changing variables to $m = \mu n$,

$$\frac{dp_r}{dm} + p_r + \frac{r}{m}p_r = p_{r-1}\left(1 + \frac{r-1}{m}\right). \tag{3}$$

This equation was first obtained by Lea and Coulson ((1949), pp. 266–267).

Now consider the generating function $F(x, m)$ of the distribution. Then

$$F(x, m) = p_0 + p_1 x + p_2 x^2 + \cdots = \sum_{r=0}^{\infty} p_r x^r. \tag{4}$$

The dependence on $m$ is captured in the $p_r$ which are functions of $m$ because the probability of finding a certain number of mutants changes with time and $m = \mu n_t$. In fact, $p_0$ would decrease and all other $p_r$ would increase with time,

assuming that mutations are not reversible (i.e. back mutations are negligible). From Equation (4),

$$\frac{\partial F}{\partial x} = \sum_{r=0}^{\infty} r x^{r-1} p_r \tag{5}$$

and

$$\frac{\partial F}{\partial m} = \sum_{r=0}^{\infty} x^r \frac{dp_r}{dm}. \tag{6}$$

Multiplying Equation (3) by $x^r$ and summing from $r = 0$ to $\infty$,

$$\sum_{r=0}^{\infty} x^r \frac{dp_r}{dm} + \sum_{r=0}^{\infty} x^r p_r + \frac{x}{m} \sum_{r=0}^{\infty} x^{r-1} r p_r$$

$$= x \sum_{r=0}^{\infty} x^{r-1} p_{r-1} + \frac{x^2}{m} \sum_{r=0}^{\infty} (r-1) x^{r-2} p_{r-1}. \tag{7}$$

Using Equations (5) and (6) and using $p_r = 0$ for all $r < 0$, Equation (7) becomes

$$\frac{\partial F}{\partial m} + F + \frac{x}{m} \frac{\partial F}{\partial x} = xF + \frac{x^2}{m} \frac{\partial F}{\partial x}$$

or

$$m \frac{\partial F}{\partial m} = m(x-1)F + \frac{\partial F}{\partial x}(x^2 - x). \tag{8}$$

Equation (8) was known to Bartlett (1978), p. 135, who obtained it in an entirely different manner. The general solution of Equation (8) can be obtained by Monge theory (see, e.g. Hildebrand (1976), pp. 387–392). However, if $F(0, m) = p_0 = e^{-m}$ (as shown by Luria and Delbrück (1943) and Lea and Coulson (1949)), $F(x, m) = (1-x)^{m(1-x)/x}$. In fact, this solution can easily be checked by substitution. More detail can be obtained from Lea and Coulson (1949). Now, since what is of interest is the generating function at a particular time, that is, the time of plating, $m$ can be treated as fixed. Therefore, the function that is of interest is $F(x) = (1-x)^{m(1-x)/x}$ (Equation (1)).

### 3. Discrete convolution powers

Let the power series representation for an analytic function $w$ of the complex argument $z$ be $w(z) = \Sigma_{k=0}^{\infty} \alpha_k z^k$. If $z$ is a function of the real variable $x$, its power series can be represented as $z(x) = \Sigma_{k=0}^{\infty} a_k x^k$. Ultimately, what is needed is the power series representation in powers of $x$ for $w$ with argument $z(x)$.

In order to compute this representation, discrete convolution powers are particularly helpful. They are defined using discrete convolution products which are treated in detail by Feller (1968), pp. 266–270. If $a = (a_0, a_1, \cdots, a_n, \cdots)$ and similarly $b$ and $c$ are infinite sequences, the discrete convolution product $c$ of $a$ and $b$, denoted by $a * b$, is

defined by $c_n = \Sigma_{k=0}^{n} a_{n-k}b_k$. The discrete convolution product is commutative, associative, and distributive over term-by-term addition of sequences.

Discrete convolution powers of an infinite sequence are now recursively defined by

$$a^{*1} := a; \quad a^{*n} := a^{*n-1} * a, \qquad \text{for } n > 1.$$

Using this definition, if $z(x)$ is the monomial in $x$ defined by Equation (2), raising $z(x)$ to the $n$th power gives

$$z^n(x) = \sum_{k=0}^{\infty} (a^{*n})_k x^k \tag{9}$$

where the $(a^{*n})_k$ are recursively given by

$$(a^{*n})_0 = a_0^n, \quad (a^{*n})_k = \frac{1}{ka_0} \sum_{i=1}^{k} (in - k + i)a_i(a^{*n})_{k-i} \qquad \text{for } k > 0.$$

This relation is easily proved by induction. Note that the sum is a linear combination of powers of $a_0$. Hence it is defined when $a_0 \to 0$. Now, $(a^{*n})_k$ is the coefficient of $x^k$ in $(a_0 + a_1x + a_2x^2 + \cdots)^n$. Therefore, if $a_0 = 0$, then $(a^{*n})_k = 0$ for all $k < n$. This case ($a_0 = 0$) is particularly important because it holds for the Luria–Delbrück distribution. Moreover, $(a^{*0})_k = 0$ for $k > 0$ and $(a^{*0})_0 = 1$. Now, consider the power series representation of the analytic function $w$:

$$w = (w(z))(x) = \sum_{k=0}^{\infty} b_k x^k. \tag{10}$$

In order to compute this representation, as was noted above, the $b_k$ have to be calculated. Now,

$$\sum_{k=0}^{\infty} b_k x^k = \sum_{j=0}^{\infty} \alpha_j z^j$$

$$= \sum_{j=1}^{\infty} \alpha_j \left( \sum_{k=0}^{\infty} (a^{*j})_k x^k \right)$$

by Equation (9), and then, interchanging sums:

$$\sum_{k=0}^{\infty} b_k x^k = \sum_{k=0}^{\infty} \sum_{j=1}^{\infty} \alpha_j (a^{*j})_k x^k. \tag{11}$$

If $a_0 = 0$, then because $(a^{*j})_k = 0$ for all $j > k$,

$$(w(z))(x) = \sum_{k=0}^{\infty} \sum_{j=0}^{k} \alpha_j (a^{*j})_k x^k.$$

Therefore, from Equation (10),

$$b_k = \sum_{j=0}^{k} \alpha_j (a^{*j})_k. \tag{12}$$

It is important to note that the sum is finite, a fact which is the key to the explicit results given below. It is sometimes instructive to rewrite Equation (12) in a simple mnemonic form where the index $k$ is suppressed and a convention to sum over repeated indices assumed:

$$b = \alpha_k a^{*k}. \tag{13}$$

In the general case, when $a_0 \neq 0$ the formula for $b_k$ is slightly more complicated because $a_0$ appears with all the powers of $x$. Denote the sequence $\tilde{a} = (0, a_1, a_2, \cdots)$. Then

$$b_k = \sum_{j=1}^{k} (\tilde{a}^{*j})_k \left( \alpha_j + \sum_{i=j+1}^{\infty} C_j^i \alpha_i a_0^{i-j} \right) \tag{14}$$

where $C_j^i$ is the binomial coefficient ($C_j^i = i!/j!(i-j)!$). Equation (14) is proved in Appendix A. Note that when $a_0 = 0$, the second term in Equation (14) disappears and Equation (12) is obtained as expected.

Finally, as an example, consider the exponential of a power series which will turn out to be relevant below. Here $w = e^z = \Sigma_{k=0}^{\infty} b_k x^k$ with $z = \Sigma_{k=0}^{\infty} a_k x^k$. The usual result (see e.g. Mayer and Mayer (1940), p. 460) is

$$b_k = e^{a_0} \sum_{n_j=0}^{k} \prod_{j=1}^{k} (a_j)^{n_j}/n_j!$$

with $n_j$ defined by the constrained sum, $\Sigma_{j=1}^{k} j n_j = k$. In the convolution powers representation, simply $\alpha_k = 1/k!$ and

$$b_k = e^{a_0} \sum_{j=1}^{k} (a^{*j})_k / j!$$

thus avoiding the complexities of the constrained sums.

## 4. The recursion relation and the asymptotic behavior of the Luria–Delbrück distribution

The generating function for the Luria–Delbrück distribution (Equation (1)) can be written as

$$F(x) = (1-x)^{m(1-x)/x} = \exp((m(1-x)/x)\ln(1-x)) \tag{15}$$

where $m$ is the expected number of mutations. This function can now be interpreted as

$$w(z) = e^{z-m} = \sum_{i=0}^{\infty} p_i x^i \tag{16}$$

with

$$z = m \frac{1-x}{x} \ln(1-x) + m = \sum_{i=0}^{\infty} a_i x^i$$

where

$$a_0 = 0, \quad a_i = \frac{m}{i(i+1)}, \qquad (i \geqq 1). \tag{17}$$

Equation (14) was first obtained by Lea and Coulson (1949). $z$ can be shown to be analytic in the complex plane as long as $x$ is in the unit disc. It follows from Equation (17) that $\Sigma_0^\infty a_k = m$ and

$$\sum_{i=0}^{\infty} p_i = 1. \tag{18}$$

Note that the $p_i$ here are the same as the $b_i$ of the last section. The change of notation merely reflects the fact that these quantities are now to be interpreted as probabilities (of finding mutants) and Equation (18) merely verifies the usual sum rule of probabilities.

It is now possible to derive a recursion relation for the $p_n$. Differentiating Equation (16) with respect to $x$

$$w' = z'w. \tag{19}$$

Differentiating Equation (19) a further $n-1$ times,

$$w^{(n)} = \sum_{i=0}^{n-1} z^{(n-i)} w^{(i)} C_i^{n-1} \tag{20}$$

where the superscripts in parentheses denote the corresponding higher-order derivatives. Evaluating Equation (20) at $x = 0$ gives

$$np_n = \sum_{i=0}^{n-1} (n-i) a_{n-i} p_i.$$

Now, using Equation (17),

$$np_n = m \sum_{i=0}^{n-1} p_i/(n+1-i). \tag{21}$$

Since the sum in Equation (21) stops at $n-1$, it can be used as a recursion relation once $p_0$ is directly evaluated. This gives

$$p_0 = e^{-m}; \quad p_n = \frac{m}{n} \sum_{i=0}^{n-1} p_i/(n-i+1). \tag{22}$$

This recursion relation is new and is the simplest and computationally most efficient procedure for calculating the Luria–Delbrück distribution obtained so far (for an extended discussion of past results, see Stewart et al. (1990)). For some detail about the increase in efficiency, see Section 6 (the discussion).

It is also easy to obtain the asymptotic behavior of $p_n$ for large $n$. This requires the systematic use of convolution powers. First, the asymptotic behavior of $(a^{*m})_n$ for large $n$ must be computed. It turns out that

$$(a^{*2})_n = \sum_{i=1}^{n-1} \frac{m^2}{(n-i)(n+1-i)i(i+1)} \sim 2c_2 m^2/n^2$$

where $c_2$ is a constant to be evaluated. The proof of this equation is simple and elegant and is given in Appendix B. The asymptotic behavior of $(a^{*k})_n$ can now be calculated by induction over $k$. It turns out that $(a^{*k})_n \sim c_k 2^{k-1} m^k/n^2$ where the $c_k$ have to be evaluated. The proof is given in Appendix C. Numerical evaluation of $(a^{*2})_n$ and $(a^{*3})_n$ for large $n$ gives

$$c_2 \approx 1, \qquad c_3 \approx 0.75, \qquad c_4 \approx 0.50.$$

The asymptotic behavior of $p_n$ can now be easily obtained. Using Equation (11),

$$p_n = e^{-m} \sum_{i=1}^{n} (a^{*i})_n/i! \approx c/n^2 \qquad \text{for large } n \tag{23}$$

where

$$c = e^{-m} \sum_{i=1}^{n} c_i 2^{i-1} \mu^i/i!.$$

This result is new. It is remarkable that both $a_k$ (Equation (17)) and $p_k$ (Equation (23)) behave as $k^{-2}$ for large $k$. Mandelbrot (1974) reports the first result, but not the second, which is more interesting because the asymptotic form of $p_n$ is interpreted as the probability of finding a very large number of mutants in a culture, usually called a 'jackpot' in the experimental literature (following Luria and Delbrück (1943)). When $m = 1$, numerical evaluation of $p_n$ using Equation (22) suggests $c = 1$. As a consequence of the asymptotic behavior of the $p_n$, the moments of the Luria–Delbrück distribution are all infinite. The nature of the divergence is logarithmic for the first moment, linear for the second, and quadratic for the third. The divergence of the moments has been noted before (e.g. by Luria and Delbrück (1943), Mandelbrot (1974), Sarkar (1991b)) though the explicit specification of the divergence is new.

## 5. The $z$-transform

Since the exponential of any analytic function is itself analytic, and $\mu((1-z)/z)\ln(1-z)$ is analytic when $|z| < 1$, a formula for the $z$-transform of the Luria–Delbrück distribution can be easily written down. If the generating function of the distribution is written with a complex argument, $z$,

$$F(z) = (1-z)^{m(1-z)/z} = \sum_{k=0}^{\infty} p_k z^k$$

then

$$\sum_{k=0}^{\infty} p_k z^k/z^{n+1} = (1-z)^{m(1-z)/z}/z^{n+1}$$

and by analyticity of $F(z)$ for $|z| < 1$,

$$p_k = \frac{1}{2\pi i} \oint (1 - z)^{m(1-z)/z} / z^{n+1} dz \tag{24}$$

where the contour of integration is around the origin. This result is not particularly useful. It is presented mainly for the sake of completeness and because Mandelbrot (1974) derived similar results in a much more complicated fashion.

## 6. Discussion

The renewed interest in the Luria–Delbrück distribution which led to the derivation of Equations (22) and (23) has been motivated by some recent experimental results in biology that have generated considerable controversy. In their original experiments, Luria and Delbrück (1943) observed that the distribution of mutants had a variance much higher than the mean. This observation was obviously inconsistent with the Poisson distribution and consistent with the expression for the variance they had derived for the Luria–Delbrück distribution. They concluded, on this basis, that the random mutation hypothesis was true in the case of virus resistance. In the subsequent decade the same conclusion was extended to a wide variety of bacterial mutations using the same statistical argument and Lea and Coulson's numerical procedure for actually calculating the Luria–Delbrück $p_k$'s (see Sarkar (1991a) for details of this history).

However, in 1988, Cairns et al. (1988) reported deviations from the Luria–Delbrück distribution for a mutation in a strain of bacteria from inability to ability to digest lactose. On the basis of this observation, and from the fact that the deviation was in the direction of decreased variance and seemed to be under genetic control, they concluded that some mutations were directed.

Since evolutionary biology conventionally assumes that all mutagenesis is random (in the so-called 'neo-Darwinian synthesis'), these results generated considerable controversy. Many biologists argued that the observed deviations from the Luria–Delbrück distribution could be accounted for by the operation of secondary factors such as differential growth rate of mutant and non-mutant cells in the test-tubes, delayed appearance of mutants, and so on (see Sarkar (1990) for a review).

In order to evaluate these conflicting claims it became imperative to compute the Luria–Delbrück distribution *systematically* in the absence or presence of various secondary factors. This was first systematically accomplished by Stewart et al. (1990). The central result of the present paper (Equation (22)) is a new recursion relation to compute the Luria–Delbrück distribution in the absence of secondary factors which is much simpler and computationally more efficient than the procedure of Stewart et al. (1990) and earlier work.

Computational tests have been carried out on both ordinary single CPU machines (including a VAX 780) and on a CM-2 Connection Machine which allows massive parallel computation (up to 16000 processors). As far as the first possibility is concerned, Stewart (personal communication) has indicated that the use of Equation (22) speeds up computation by a factor of 6 over the older procedure of Stewart et al. (1990). The

new procedure for computing the basic Luria–Delbrück distribution has been incorporated into the general environment for computing this distribution that can be obtained following the procedure given by Stewart et al. (1990), p. 180. Alternatively, programs in C and FORTRAN implementing Equation (22) are available from the Boston Theoretical Biology Group. When a CM-2 Connection Machine with only 16 000 processors is used and advantage is taken of its 'dot product', the computations are speeded up, in general, by another factor of 10. Such a remarkable increase in efficiency is possible because the convolution product is formally similar to a dot product. The older procedure of Stewart et al. (1990) has not been implemented on a Connection Machine since it is superseded by Equation (22), so its possibilities under massively parallel computation are not known. A program implementing Equation (22) on the Connection Machine is also available from the Boston Theoretical Biology Group.

Finally, it should be noted that the potential utility of discrete convolution powers and products is quite general. They can be used for the computation of many other statistical distributions. For instance, Feller (1968), pp. 268–270, has shown how the binomial, negative binomial, Poisson and geometric distributions can be computed using them. Moreover, Ma et al. (1991) have shown how the use of convolution powers greatly simplifies the computation of the configuration and cluster integrals in statistical mechanics. These examples and the possibilities they raise suggest that further investigation of the mathematical properties of discrete convolution products and powers might well deserve serious consideration.

**Acknowledgements**

Thanks are due to D. Deutsch, D. Konstontopoulos, B. Rhodes and T. Wu for helpful discussions. Thanks are especially due to Frank Stewart for a careful, critical reading of an earlier draft of this paper that led not only to the removal of some errors but to a much better exposition. This is Contribution No. BTBG 90–5 from the Boston Theoretical Biology Group.

## Appendix A: Proof of Equation (17)

Consider the power series

$$w(z) = \sum_{k=0}^{\infty} \alpha_k z^k, \tag{25}$$

and

$$z(x) = \sum_{k=0}^{\infty} a_k x^k. \tag{26}$$

What are needed are coefficients $b_k$ in the sum $w(z) = \Sigma_{k=0}^{\infty} b_k x^k$. Observe that $w(z) = w(z - a_0 + a_0)$. Substituting Equation (26) into Equation (25),

$$w(z) = \sum_{k=0}^{\infty} \alpha_k \sum_{j=0}^{k} C_j^k a_0^{k-j} (z - a_0)^j \tag{27}$$

and

$$w(z-a_0)=\sum_{k=0}^{\infty}\alpha_k(z-a_0)^k. \tag{28}$$

Subtracting Equation (27) from Equation (28)

$$w(z)-w(z-a_0)=\sum_{k=1}^{\infty}\alpha_k\sum_{j=0}^{k-1}C_j^k a_0^{k-j}(z-a_0)^j.$$

From Equation (9) $(z-a_0)^j=\Sigma_{k=1}^{\infty}(\tilde{a}^{*j})_k x^k$, and from Equation (28), interchanging sums,

$$w(z-a_0)=\sum_{n=1}^{\infty}\sum_{k=1}^{n}\alpha_k(\tilde{a}^{*k})_n x^n+\alpha_0.$$

Hence:

$$\sum_{0}^{\infty}b_k x^k=\sum_{k=1}^{\infty}\alpha_k\left(a_0^k+\sum_{j=1}^{k-1}C_j^k a_0^{k-j}\sum_{i=1}^{\infty}(\tilde{a}^{*j})_i x^i\right)$$

$$+\sum_{n=1}^{\infty}\sum_{k=1}^{n}\alpha_k(\tilde{a}^{*k})_n x^n+\alpha_0.$$

Interchanging sums and comparing coefficients of $x^n$ for $n\geqq 1$,

$$b_n=\sum_{j=1}^{k}\alpha_j(\tilde{a}^{*j})_k+\sum_{j=1}^{k}(\tilde{a}^{*j})_k\sum_{k=j+1}^{\infty}C_j^k\alpha_k a_0^{k-j}$$

$$=\sum_{j=1}^{k}(\tilde{a}^{*j})_k\left(\alpha_j+\sum_{k=j+1}^{\infty}C_j^k\alpha_k a_0^{k-j}\right).$$

## Appendix B: Proof of $(a^{*2})\sim 2c_2/n^2$

For the Luria–Delbrück distribution,

$$(a^{*2})_n=\sum_{k=1}^{n-1}\frac{1}{(n-k)(n+1-k)k(k+1)}.$$

Using partial fractions, after reindexing,

$$(a^{*2})_n=\frac{2}{n(n+1)}\sum_{k=1}^{n-1}\frac{1}{k}-\frac{1}{(1+2/n)(k+1)}.$$

Define

$$T^2(n)=\sum_{k=1}^{n-1}\left(\frac{1}{k}-\frac{1}{(1+2/n)(k+1)}\right).$$

Simply rearranging terms,

$$T^2(n)=\sum_{k=1}^{n-1}\frac{1}{k(k+1)}+\frac{2}{n+2}\sum_{k=1}^{n-1}\frac{1}{k+1}.$$

When $n$ gets big the first sum tends to 1 while the second sum tends to 0. Hence $\lim_{n\to\infty} T^2(n) = 1$. Since $(a^{*2})_n = (2/n(n+1))T^2(n)$, the asymptotic behavior of $(a^{*2})_n$ is $2/n^2$.

**Appendix C: Proof of $(a^{*k})_n \sim 2^{k-1}c_k(n)/n^2$**

Using partial fractions, $(a^{*k})_n$ can be rewritten as

$$(a^{*k})_n = \frac{2^{k-1}}{n(n+1)} T^{k-1}(n)$$

where the $T^k(n)$ are defined by

$$T^k(n) = \sum_{l=k-1}^{n-1} \left(\frac{1}{l} - \frac{1}{(1+2/n)(l+1)}\right) T^{k-1}(l).$$

By induction over $k$, $T^k(n)$ will now be shown to be eventually decreasing for sufficiently large $n$. For $k = 3$,

$$T^3(n) = \sum_{l=2}^{n-1} T^2(l)\left(\frac{1}{l} - \frac{1}{(1+2/n)(l+1)}\right)$$

where $T^2(l)$ is defined as in Appendix B. Note that $T^2(l)$ is bounded. Let $T^2_{\min}$ denote the minimum value of $T^2(l)$ for $l \leqq n-1$. Also note that $T^2_{\min}$ is greater than 0 even when $n \to \infty$.

$$\begin{aligned} T^3(n+1) - T^3(n) &= T^2(n)\frac{3}{n(n+3)} - \frac{2}{(n+2)(n+3)} \sum_{l=2}^{n-1} \frac{T^2(n)}{l+1} \\ &< T^2(n)\frac{3}{n(n+3)} - \frac{2T^2_{\min}}{(n+2)(n+3)} \sum_{l=2}^{n-1} \frac{1}{l+1}. \end{aligned}$$

For a sufficiently large $n$ the difference in the $T^3$'s will become negative since the sum in the second term grows logarithmically as $n$ while other terms are of the same order $n^{-2}$ (recall that $T^2(n)$ is bounded and $T^2_{\min} > 0$). Hence $T^3(n)$ is eventually decreasing.

Now consider the inductive hypothesis on $k$ that $T^{k-1}(n)$ is eventually decreasing. Note that this implies $T^{k-1}(n)$ is bounded since it is always greater than 0. Further

$$T^k(n+1) - T^k(n) = \frac{3}{n(n+3)} T^{k-1}(n) - \frac{2}{(n+2)(n+3)} \sum_{l=k-1}^{n-1} \frac{T^{k-1}(l)}{(1+l)}.$$

Following the same argument, the inductive hypothesis implies that $T^{k-1}(n)$ is eventually decreasing so that for a sufficiently large $n$ the difference in $T^k$'s will become negative. Hence $T^k(n)$ is eventually decreasing for all $k$. Since it is also bounded below by 0, a limit exists. Let $\lim_{n\to\infty} T^k(n) = c_k$. This confirms the asymptotic behavior of $(a^{*k})_n$.

## References

ARMITAGE, P. (1952) The statistical theory of bacterial populations subject to mutation. *J.R. Statist. Soc.* **B14**, 1–40.

ARMITAGE, P. (1953) Statistical concepts in the theory of bacterial mutation. *J. Hygiene* **51**, 162–184.

BARTLETT, M. S. (1978) *An Introduction to Stochastic Processes*, 3rd edn. Cambridge University Press.

CAIRNS, J., OVERBAUGH, J. AND MILLER, S. (1988) The origin of mutants. *Nature* **335**, 142–145.

FELLER, W. (1968) *An Introduction to Probability Theory and Its Applications*, Vol. 1. 3rd edn. Wiley, New York.

FU, J., LI, I.C. AND CHU, E. H. Y. (1982) The parameters for quantitative analysis of mutation rates with cultured mammalian somatic cells. *Mutat. Res.* **105**, 363–370.

HILDERBRAND, F. B. (1976) *Advanced Calculus for Applications*, 2nd edn. Prentice-Hall, Englewood Cliffs, NJ.

KOCH, A. L. (1982) Mutation and growth rates from Luria–Delbrück fluctuation tests. *Mutat. Res.* **95**, 129–143.

LEA, D. E. AND COULSON, C. A. (1949) The distribution of the number of mutants in bacterial populations. *J. Genetics* **49**, 264–285.

LI, I.-C., WU, S.-C. H., FU, J. AND CHU, E. H. Y. (1985) A determinist approach for the estimation of mutation rates in cultured mammalian cells. *Mutation Res.* **149**, 127–132.

LURIA, S. E. AND DELBRÜCK, M. (1943) Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* **28**, 491–511.

MA, W. T., SANDRI, G. VH. AND SARKAR, S. (1991) Novel representation of power series that arise in statistical mechanics and population genetics. *Phys. Lett.*

MANDELBROT, B. (1974) A population birth-and-mutation process, I: explicit distributions for the number of mutants in an old culture of bacteria. *J. Appl. Prob.* **11**, 437–444.

MAYER, J. E. AND MAYER, M. G. (1940) *Statistical Mechanics*, Wiley, New York.

SARKAR, S. (1990) On the possibility of directed mutations in bacteria: statistical analysis and reductionist strategies. In *PSA 1990*, ed. A. Fine et al., Vol. I. Philosophy of Science Association, East Lansing, 111–124.

SARKAR, S. (1991a) Lamarck contre Darwin, reduction versus statistics: conceptual issues in the controversy over directed mutagenesis in bacteria. In *Organism and the Origin of Self*, ed. A. I. Tauber, pp. 235–271. Kluwer, Dordrecht.

SARKAR, S. (1991b) Haldane's solution of the Luria–Delbrück distribution. *Genetics* **127**, 257–261.

STEWART, F. M., GORDON, D. M. AND LEVIN. B. R. (1990) Fluctuation analysis: the probability distribution of the number of mutants under different conditions. *Genetics* **124**, 175–185.