FUNCTIONAL DIFFERENTIAL EQUATIONS DETERMINING STEADY SIZE DISTRIBUTIONS FOR POPULATIONS OF CELLS GROWING EXPONENTIALLY

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Abstract

A population of cells growing and dividing often goes through a phase of expo-
nential growth of numbers, during which the size distribution remains steady. In
this paper we study the function differential equation governing this *steady size
distribution* in the particular case where the individual cells themselves are growing
exponentially in size. A series solution is obtained for the case where the proba-
bility of cell division is proportional to any positive power of the cell size, and a
method for finding closed-form solutions for a more general class of cell division
functions is developed.

1 Introduction

If we consider a population of cells which are all growing and dividing, we
may define a cell number density $n(x, t)$ such that $n(x, t)\, dx$ gives the number
of cells with a size between x and $x + dx$ at time t. Biologists are interested
in the steady size distributions (SSDs) which can arise where the total num-
ber of cells in the population increases exponentially, but the proportion of
cells in any size class remains the same (Collins and Richmond [2]; Tyson
and Diekmann [8]). In our introduction to an earlier paper (Hall and Wake
[3]), we discussed the situation in which all cells of size x have the same
time-invariant growth rate $g(x)$ and division rate $b(x)$ (such that $b(x)\, dt$ is
the proportion of cells of size x which will divide in time dt), and where on
division each mother cell divides into α daughter cells each of the same size.

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We showed that if we write $n(x, t) = y(x)N(t)$, where $N(t)$ is the total pop-
ulation at time t and $y(x)$ is the probability density function describing the
SSD, then $N(t)$ is indeed an exponential function of time, and the functional
differential equation for the SSD $y(x)$ is

$$\frac{d}{dx}(g(x)y(x)) = -[b(x) + Q]y(x) + \alpha^2 b(\alpha x)y(\alpha x) \tag{1}$$

where Q is a functional on $y(x)$ defined by

$$Q = (\alpha - 1) \int_0^\infty b(x)y(x) \, dx. \tag{2}$$

Equation (1) is also given in Tyson and Diekmann [8] for the biologically
realistic case of $\alpha = 2$, which represents reproduction by binary fission with
two daughter cells of equal size. The *size* of a cell can be taken to mean
any property which is distributed evenly between the daughter cells when a
mother cell divides. For example, x could refer to the volume, mass, or
perhaps even DNA content of the cells, or in cases where cell extension and
division occur in just one dimension it may be appropriate to treat x as the
cell length.

   All cells must be of positive size, so we may set $y(x) \equiv 0$ for $x < 0$, and
as $y(x)$ is a *probability density function* it must satisfy the conditions

$$\int_0^\infty y(x) \, dx = 1, \tag{3}$$

and

$$y(x) \geq 0. \tag{4}$$

In this paper we set out to solve equations (1) and (2) for $y(x)$ subject to
conditions (3) and (4), assuming that the functions $g(x)$ and $b(x)$ are given.
The solution to an "inverse" problem of finding $g(x)$ from an observed SSD
$y(x)$ and the size distribution of *dividing* cells ($y_m(x)$ say) has been given by
Collins and Richmond [2], and Powell [7] showed how $y(x)$ can be deduced
from $y_m(x)$ if $g(x)$ is given in the form $g(x) = gx$. Tyson and Diekmann [8]
present the solution to our "forward" problem for general $g(x)$, but with $b(x)$
restricted to forms such that there exists a maximum size (x_2) and minimum
size (x_1) for cell division with $x_2 \leq 2x_1$. Here we restrict our attention to the
case $g(x) = gx$ considered by Powell [7] and Koch and Schaechter [6], and
hence solve equation (1) to (4) for forms of $b(x)$ more general than those
considered by Tyson and Diekmann. The quantity Q can be given a number
of interpretations. Hall and Wake ([3]) showed that Q as defined by (2) also
satisfies

$$dN/dt = QN(t), \tag{5}$$

where $N(t)$ is the total population at time t, so Q can be regarded as the *exponential rate of growth* of the population. Also, the rate at which the total size of all the individuals in the population increases can be found either by integrating first over all sizes to find the total size then differentiating with respect to t, or simply by integrating the growth rate over all individuals in the population. This gives

$$\frac{d}{dt}\left[\int_0^\infty xN(t)y(x)\,dx\right] = \int_0^\infty N(t)y(x)g(x)\,dx,$$

or

$$\frac{dN}{dt}\left[\int_0^\infty xy(x)\,dx\right] = N(t)\int_0^\infty y(x)g(x)\,dx, \tag{6}$$

then using (5) we obtain

$$Q = \frac{\int_0^\infty g(x)y(x)\,dx}{\int_0^\infty xy(x)\,dx}, \tag{7}$$

so Q may also be regarded as ratio of the average growth rate of the individuals in the population to their average size.

1.1 The special case $g(x) = gx$

It is difficult to see how to obtain closed-form solutions to (1) subject to (3) and (4) in the most general case, most obviously because of the presence of the unknown functional Q. However, in two simple cases we can find Q readily. The first of these is if $b(x) = b$, a constant, so that from (2) $Q = (\alpha - 1)b$. A solution for this case with $g(x)$ also constant is given in Hall and Wake [3]. A solution with $b(x)$ constant can also be obtained for $g(x) = gx^{1-k}(k > 0)$ by using the transformation $Z(x) = g(x)y(x)$ to obtain an equation of the same form as equation (21) below. However, a constant probability of division over all sizes is not plausible biologically, so this case is not discussed further in this paper.

The case where the cells themselves grow in size exponentially during their life cycle, so $g(x) = gx$ (g constant), is more plausible biologically, and has been discussed in the bacteriological literature. In this case, (7) simplifies immediately to

$$Q = g. \tag{8}$$

Equation (1) then becomes

$$gxy'(x) = -[b(x) + 2g]y(x) + \alpha^2 b(\alpha x)y(\alpha x), \tag{9}$$

as given by Powell [7] and Koch and Schaechter [6].

In this paper we seek solutions to this equation, subject to the normalising and non-negativity conditions (3) and (4).

It is trivial to show that

$$y = \delta(x), \tag{10}$$

where $\delta(x)$ is the Dirac delta function, is a generalised solution of (9) for all forms of $b(x)$, and in fact is a solution of (1) for any $g(x)$ such that $g(0) = 0$. In fact, $y(x) = \delta(x)$ is the only non-negative generalised solution satisfying (3), and therefore the only generalised solution which may be regarded as a *probability distribution*. The existence of this solution is reasonable in that it says that if we have a population all of size zero at any time, this situation will not change provided $g(0) = 0$.

We now look for classical solutions to (9) subject to conditions (3) and (4). Multiplying by x and rearranging gives

$$g[x^2 y'(x) + 2xy(x)] = -xb(x)y(x) + \alpha^2 xb(\alpha x)y(\alpha x). \tag{11}$$

This suggests the change of variable

$$Z(x) = x^2 y(x) \tag{12}$$

to give

$$gZ'(x) = -\frac{b(x)}{x} Z(x) + \frac{b(\alpha x)}{x} Z(\alpha x). \tag{13}$$

Setting

$$a(x) = \frac{b(x)}{gx} \tag{14}$$

simplifies (13) to

$$Z'(x) = -a(x)Z(x) + \alpha a(\alpha x)Z(\alpha x). \tag{15}$$

This equation needs to be solved subject to $Z(x) \geq 0$ and either of the conditions

$$\int_0^\infty \frac{Z(x)}{x^2} dx = 1, \tag{16}$$

or

$$\int_0^\infty a(x) \frac{Z(x)}{x} dx = \frac{1}{\alpha - 1}. \tag{17}$$

Here the second condition follows either from $Q = g$, or from integration by parts and substituting from (15). Equations (15) and (16) together are equivalent to (15) and (17) together.

Note that equation (15) can be written in the integral form

$$Z(x) = \int_x^{\alpha x} a(s)Z(s) \, dx, \tag{18}$$

which despite superficial similarities is very different from the classical Volterra integral equation. It follows that

$$Z(0) = 0, \tag{19}$$

then substitution into (15) and its derivatives shows that

$$Z^{(n)}(0) = 0, \ \forall n \geq 0. \tag{20}$$

Hence any solution to (15) must be non-analytic ("infinitely flat") at the origin.

In the next three sections we examine solutions of (15) subject to (16) or (17) for different forms of $b(x)$. We find solutions involving series of exponentials for the two cases $b(x) = bx^k$ and $b(x) = bx^k H(x - x_1)$, and then describe a general method of solution in cases where $b(x)$ is zero below some minimum size for division x_1, and becomes infinite at some maximum cell size x_2.

2 The case $b(x) = bx^k$

In this case, we have $a(x) = bx^k/gx = ax^{k-1}$ say (where $a = b/g$), so that (15) becomes

$$Z'(x) = x^{k-1}(-aZ(x) + a\alpha^k Z(\alpha x)). \tag{21}$$

If we make the substitutions $z = x^k/k$ and $Y(z) = Z(x)$, so $Z'(x) = Y'(z)\,dz/dx = x^{k-1}Y'(z)$ and $Z(\alpha x) = Y((\alpha x)^k/k) = Y(\alpha^k z)$, then (21) becomes (after cancellation of x^{k-1})

$$Y'(z) = -aY(z) + a\alpha^k Y(\alpha^k z) \tag{22}$$

This equation is in the same form as that dealt with in Hall and Wake [3] and Kato and McLeod [5], so we can write down the solution immediately. In terms of our variables this is

$$Y(z) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} e^{-a\alpha^{kn}z}, \tag{23}$$

where by convention the expression in the denominator is given the value 1 when $n = 0$. This solution is unique apart form the multiplicative constant C. Now reverting to our Z and x notation we obtain

$$Z(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} e^{-a\alpha^{nk}x^k/k}. \tag{24}$$

The probability density function for the SSD is then given (from 12)) by

$$y(x) = \frac{Z(x)}{x^2}, \tag{25}$$

with the constant C to be evaluated from condition (17), which can be written in this case as

$$\int_0^{\infty} x^{k-2} Z(x)\,dx = \frac{1}{a(\alpha - 1)}. \tag{26}$$

Note that for $k = 0$ the transformation, and therefore the solution, is ill-defined, and for $k < 0$ the series does not converge. The solution is therefore valid only for

$$k > 0. \tag{27}$$

Obtaining the solution (24) was straightforward because we managed to transform the original problem into one for which the solution was known. However, using the integral condition (26) to find the constant C is not so easy, as it involves carrying out the integration in

$$\int_0^\infty x^{k-2} Z(x)\, dx = C \int_0^\infty \left[\sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} x^{k-2} e^{-a^{\alpha^{nk} x^k}/k} \right] dx \tag{28}$$

for all $k > 0$.

For $0 < k \leq 1$, care must be taken over interchanging the integral and summation signs in this expression, as $\int_0^\infty x^p e^{-x}\, dx$ does not exist for $p \leq -1$. It is necessary to treat two cases separately: $k = m^{-1}$ for some integer m, and $k \neq m^{-1}$ for any such m.

2.1 The case $k \neq m^{-1}$

Firstly, consider the integral $\int_0^\infty x^p Z(x)\, dx$, where $p \neq -1$. Integrating by parts, we get

$$\int_0^\infty x^p Z(x)\, dx = \left[\frac{x^{p+1}}{p+1} Z(x) \right]_0^\infty - \frac{1}{p+1} \int_0^\infty x^{p+1} Z'(x)\, dx. \tag{29}$$

Now the square-bracket term is zero because Z is infinitely flat at the origin, and l'Hopital's rule can be used to show that $\lim_{x \to \infty} x^p Z(x) = 0$ for all real p. We can then substitute from (21) for $Z'(x)$ and use a simple change of variable to give

$$\int_0^\infty x^p Z(x)\, dx$$
$$= -\frac{1}{p+1} \left[-a \int_0^\infty x^{p+k} Z(x)\, dx + a\alpha^k \int_0^\infty x^{p+k} Z(\alpha x)\, dx \right],$$

so

$$\int_0^\infty x^p Z(x)\, dx = \frac{a(1 - \alpha^{-(p+1)})}{p+1} \int_0^\infty x^{p+k} Z(x)\, dx. \tag{30}$$

If we apply this m times, starting with $p = k - 2$, (and remembering that $km \neq 1$, $\forall m \in I^+$) we get

$$\int_0^\infty x^{k-2} Z(x)\, dx$$
$$= \frac{a^m (1 - a^{1-k})(1 - a^{1-2k}) \cdots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \cdots (mk-1)} \int_0^\infty x^{(m+1)k-2} Z(x)\, dx. \tag{31}$$

Now for all $k > 0$, it is possible to choose $m \in I^+$ such that $k > \frac{1}{m+1}$; for $k > 1$ we would choose $m = 0$. With such a choice of m, we can now substitute for $Z(x)$ and interchange the summation and integral signs. (Note that for $k < \frac{1}{m+1}$ the interchange is impossible):

$$\int_0^\infty x^{k-2} Z(x)\, dx = C \frac{a^m (1 \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \cdots (mk-1)} .$$
$$\cdot \sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \int_0^\infty x^{(m+1)k-2} e^{-a\alpha^{nk} x^k / k}\, dx. \tag{32}$$

Making the natural substitution $z = \frac{a}{k} \alpha^{nk} x^k$ we get

$$x^{mk-1} = (k/a)^{m-1/k} \alpha^{n(1-mk)} z^{m-1/k} \tag{33}$$

and

$$x^{k-1}\, dx = \frac{\alpha^{-nk}}{a}\, dz, \tag{34}$$

so

$$\int_0^\infty x^{k-2} Z(x)\, dx = C(k/a)^{m-1/k} \frac{a^{m-1}(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \cdots (mk-1)}$$
$$\cdot \sum_{n=0}^\infty \frac{(-1)^n \alpha^{n(1-mk)}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \int_0^\infty z^{m-1/k} e^{-z}\, dz. \tag{35}$$

To simplify this we define

$$K(\alpha, \beta) = \sum_{n=0}^\infty \frac{(-1)^n \beta^n}{(\alpha - 1) \cdots (\alpha^n - 1)}, \tag{36}$$

and by definition

$$\Gamma(p) = \int_0^\infty x^{p-1} e^{-x}\, dx, \tag{37}$$

so (35) can be written as

$$\int_0^\infty x^{k-2} Z(x)\, dx$$
$$= C(k/a)^{m-1/k} \frac{a^{m-1} m (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \cdots (mk-1)}$$
$$\times K(\alpha^k, \alpha^{1-mk}) \Gamma\left(m + 1 - \frac{1}{k}\right)$$
$$= C(k/a)^{-1/k} \frac{(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-mk})}{a(1 - \frac{1}{k})(2 - \frac{1}{k}) \cdots (m - \frac{1}{k})}$$
$$\times K(\alpha^k, \alpha^{1-mk}) \Gamma\left(m + 1 - \frac{1}{k}\right). \tag{38}$$

Now we have

$$\Gamma(m + 1 - 1/k) = (m - 1/k) \cdots (2 - 1/k)(1 - 1/k)\Gamma(1 - 1/k) \quad (39)$$

and, using (97) repeatedly (see appendix),

$$K(\alpha^k, \alpha) = (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-mk})K(\alpha^k, \alpha^{1-mk}), \quad (40)$$

so (38) can be simplified to

$$\int_0^\infty x^{k-2} Z(x)\, dx = C \left(\frac{k}{a}\right)^{-1/k} \frac{1}{a} K(\alpha^k, \alpha)\Gamma\left(1 - \frac{1}{k}\right). \quad (41)$$

So from the integral condition (17) we get

$$C = \left(\frac{k}{a}\right)^{1/k} \frac{1}{(\alpha - 1)K(\alpha^k \alpha)\Gamma(1 - \frac{1}{k})}. \quad (42)$$

Note that using (96) (see appendix) we could write $K(\alpha^k, \alpha)$ in a somewhat neater form as the infinite product

$$K(\alpha^k, \alpha) = \prod_{n=1}^\infty (1 - \alpha^{1-kn}). \quad (43)$$

2.2 The case km^{-1}

For $k = \frac{1}{m}$, $m \in I^+$, if we start with $p = k - 2$ we can only apply the iterative relationship (30) used in the previous section $m - 1$ times, giving

$$\int_0^\infty x^{k-2} Z(x)\, dx$$

$$= \frac{a^{m-1}(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \cdots (1 - \alpha^{1-(m-1)k})}{(k-1)(2k-1) \cdots ((m-1)k - 1)} \int_0^\infty x^{-1} Z(x)\, dx. \quad (44)$$

The integral on the right can be integrated by parts once more, giving

$$\int_0^\infty x^{-1} Z(x)\, dx = -\int_0^\infty (\log x) Z'(x)\, dx$$

$$= a\left[\int_0^\infty (\log x) x^{k-1} Z(x)\, dx - \alpha^k \int_0^\infty (\log x) x^{k-1} Z(\alpha x)\, dx\right]$$

$$= a\left[\int_0^\infty (\log x) x^{k-1} Z(x)\, dx - \int_0^\infty (\log s - \log \alpha) s^{k-1} Z(s)\, ds\right],$$

so

$$\int_0^\infty x^{-1} Z(x)\, dx = a \log \alpha \int_0^\infty x^{k-1} Z(x)\, dx, \quad (45)$$

where once again we have used (15) to replace $Z'(x)$. Now substitute for $Z(x)$ from (24) and interchange the integral and summation signs (which is now permitted) to give

$$\int_0^\infty x^{-1} Z(x)\,dx = Ca\log\alpha \sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1)\cdots(\alpha^{kn}-1)} \int_0^\infty x^{k-1} e^{-a\alpha^{kn} x^k / k}\,dx$$

$$= C\log\alpha \sum_{n=0}^\infty \frac{(-1)^n}{(\alpha^k - 1)\cdots(\alpha^{kn}-1)} \int_0^\infty s e^{-s}\,ds,$$

so

$$\int_0^\infty x^{-1} Z(x)\,dx = CK(\alpha^k, 1)\log\alpha. \tag{46}$$

Thus (44) becomes

$$\int_0^\infty x^{k-2} Z(x)\,dx$$

$$= CK(\alpha^k, 1)\log\alpha\, \frac{a^{m-1}(1 - \alpha^{1-k})(1 - \alpha^{1-2k})\cdots(1 - \alpha^{1-(m-1)k})}{(k-1)(2k-1)\cdots((m-1)k-1)}. \tag{47}$$

Applying the integral condition (26) leads to

$$C = \frac{(k-1)(2k-1)\cdots((m-1)k-1)}{(1 - \alpha^{1-k})(1 - \alpha^{1-2k})\cdots(1 - \alpha^{1-(m-1)k})} \cdot \frac{1}{a^m(\alpha - 1)K(\alpha^k, 1)\log\alpha}. \tag{48}$$

This can be written a little more tidily by (taking m factors of k out of the numerator and using $m = 1/k$. Then

$$C(k/a)^{1/k} \frac{m!}{(\alpha^k - 1)(\alpha^{2k} - 1)\cdots(\alpha^{mk} - 1)} \cdot \frac{1}{K(\alpha^k, 1)\log\alpha}, \tag{49}$$

where of course $mk = 1$.

2.3 Discussion and examples

We have shown that the SSD in the case $g(x) = gx$ and $b(x) = bx^k$ is

$$y(x) = \frac{C}{x^2} \sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn} e^{-a\alpha^{nk} x^k / k}}{(\alpha^k - 1)\cdots(\alpha^{kn}-1)}. \tag{50}$$

where $a = b/g$ and

$$C = \begin{cases} (k/a)^{1/k} \frac{m!}{(\alpha^k-1)(\alpha^{2k}-1)\cdots(\alpha^{mk}-1)} \frac{1}{K(\alpha^k,1)\log\alpha}, & k = \frac{1}{m}, m \in I^+ \\ (k/a)^{1/k} \frac{1}{(\alpha-1)K(\alpha^k,\alpha)\Gamma(1-\frac{1}{k})}, & k \neq \frac{1}{m}, m \in I^+. \end{cases} \tag{51}$$

The form of C for $k = 1/m$ can be shown to be equal to the limit of the form for $k \neq 1/m$ as $k \to 1/m$ by expanding the gamma function, expressing

$K(\alpha^k, \alpha)$ in terms of $K(\alpha^k, 1)$, then using the L'Hopital limit

$$\lim_{mk \to 1} (1 - \alpha^{1-mk})/(mk - 1) = \log \alpha.$$

Hence C is a continuous function of k.

When k is an integer, we can obtain the kth moment of the SSD about the origin, $\mu_k = \int_0^\infty x^k y(x) \, dx$, directly from the integral condition (26) as

$$\mu_k = \frac{1}{a(\alpha - 1)} \tag{52}$$

An iterative expression for moments beyond the kth is obtainable by applying a *Mellin Transform* to (21): multiplying through by x^{m-1} and integrating over all x), remembering that $y(x) = x^{-2} Z(x)$ gives

$$\int_0^\infty x^{m-1} Z'(x) \, dx = -a\mu_{m+k} + a \int_0^\infty \alpha^k x^{m+k} [x^{-2} Z(\alpha x)] \, dx. \tag{53}$$

Integration by parts on the left and the substitution $z = \alpha x$ on the right then leads to

$$-(m-1)\mu_m = -a\mu_{m+k} + a\alpha^{-(m-1)}\mu_{m+k}, \tag{54}$$

so we have the iterative equation

$$\mu_{m+k} = \frac{(m-1)}{a(1 - \alpha^{-(m-1)})}\mu_m \tag{55}$$

provided $m > 1$. This enables us to deduce all the moments of the SSD once we have found the kth moment by using (52) and all other moments up to the $k + 1$th by integration of (50). For example, in the particular case $k = 1$, the mean is

$$\mu = \frac{1}{a(\alpha - 1)} \tag{56}$$

and the second moment about the origin ($\mu_2 \int_0^\infty x^2 y(x) \, dx = \int_0^\infty Z(x) \, dx$) can be obtained by integrating (24) term by term to give

$$\mu_2 = \frac{1}{a^2(\alpha - 1) \log \alpha}. \tag{57}$$

We can then apply (55) repeatedly to obtain

$$\mu_n = \frac{(n-2)!}{a^n(\alpha - 1) \log \alpha \prod_{k=1}^{n-2}(1 - \alpha^{-k})}, \quad n > 2. \tag{58}$$

Figure 1 shows the shape of the SSD function $y(x)$ with $a = 1$ and $\alpha = 2$ for a range of values of k. Consideration of the differential equation formed in the extreme cases shows that as $k \to 0$, the SSD $y(x)$ approaches the Dirac
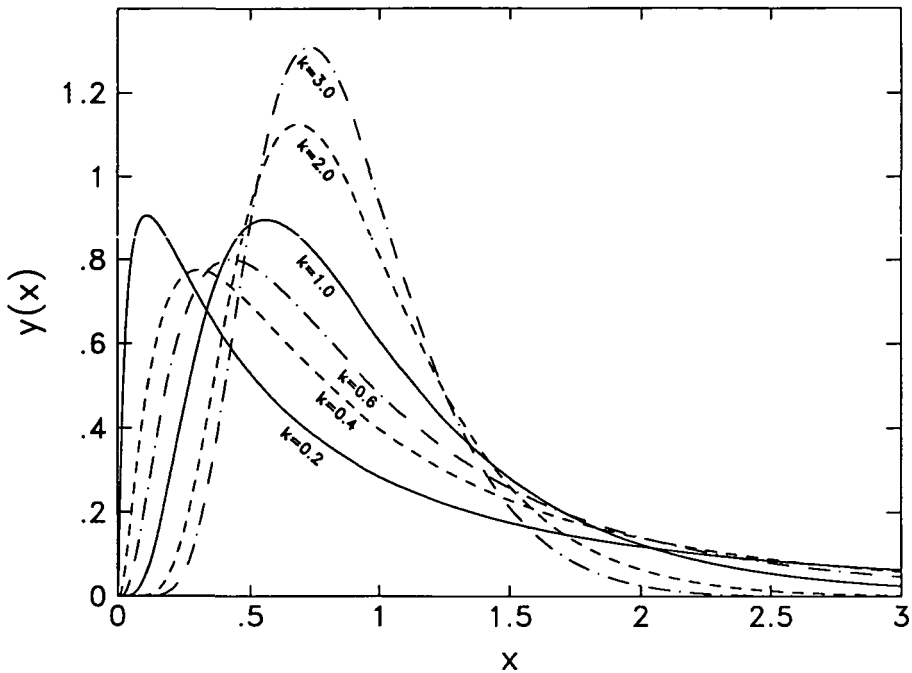
FIGURE 1. SSD probability density functions $y(x)$ for $g(x) = gx$ and $b(x) = bx^k$ for a range of values of k. The variables a and α have been fixed at 1 and 2 respectively.

delta function $\delta(x)$, and as $k \to \infty$ it approaches (Koch and Schaechter [6]) the function

$$y(x) = \begin{cases} a/(\alpha - 1)x^2, & a/\alpha < x < a \\ 0, & \text{otherwise} \end{cases} \tag{59}$$

3 A minimum size for Division: The case $b(x) = bx^k H(x - x_1)$

This case is the same as that discussed in the previous section, except that there is a minimum size $x_1 > 0$ below which cells do not divide. Substituting $b(x) = bx^k H(x - x_1)$, $k > 0$, (b, x_1 constant) into equation (15) we get

$$Z'(x) = x^{k-1}(-aH(x - x_1)Z(x) + a\alpha^k H(\alpha x - x_1)Z(\alpha x)). \tag{60}$$

In this case we choose to couple (60) with the integral condition (17) as this simplifies to a condition dependent only on $Z(x)$ for $x \geq x_1$, namely

$$\int_{x_1}^{\infty} x^{k-2} Z(x)\,dx = \frac{1}{a(\alpha - 1)}. \tag{61}$$

It is convenient to solve the equation in three regions starting with the region $x > x_1$. We let

$$Z(x) = \begin{cases} Z_1(x), & x \geq x_1 & \text{(region 1)} \\ Z_2(x), & x_1/\alpha \leq x \leq x_1 & \text{(region 2)} \\ Z_3(x), & x \leq x_1/\alpha & \text{(region 3)} \end{cases} \tag{62}$$

where continuity considerations require $Z_1(x_1) = Z_2(x_1)$ and $Z_3(x_1/\alpha) = Z_2(x_1/\alpha)$.

3.1 Region 1, $x \geq x_1$

In this region, (60) becomes (21), so the solution is

$$Z_1(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} e^{-a(\alpha^n x)^k/k}. \tag{63}$$

To find the constant C we substitute $Z(x) = Z_1(x)$ into (61) above, giving

$$C \int_{x_1}^{\infty} \left[\sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} x^{k-2} e^{-a\alpha^{nk}/x^k/k} \right] dx = \frac{1}{a(\alpha - 1)}. \tag{64}$$

This time there is no difficulty in immediately interchanging the integral and summation operations as the integration starts at $x_1 > 0$ and therefore avoids the singularity at $x = 0$ when $k \leq 1$. Making the change of variable $z = a \frac{\alpha^{nk} x^k}{k}$ in each integral leads to

$$\frac{C}{a} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \left(\frac{a}{k} \right)^{1/k} \int_{a\alpha^{nk} x_1^k/k}^{\infty} z^{-1/k} e^{-z} dz = \frac{1}{a(\alpha - 1)}. \tag{65}$$

Hence we can write

$$C = \left(\frac{k}{a} \right)^{1/k} \frac{1}{(\alpha - 1)S} \tag{66}$$

where

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \Gamma \left(1 - \frac{1}{k}, \frac{a}{k} \alpha^{kn} x_1^k \right) \tag{67}$$

and $\Gamma(c, x) = \int_x^{\infty} s^{c-1} e^{-s} ds$ is an *incomplete gamma function*.

In the particular case $k = 1$, (66) reduces to

$$C = \frac{1}{a(\alpha - 1)S} \tag{68}$$

where

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha - 1) \cdots (\alpha^n - 1)} E_1(a\alpha^n x_1) \tag{69}$$

and E_1 is the exponential integral.

3.2 Region, $x_1/\alpha \leq x \leq x_1$

In this region we have $H(x - x_1) = 0$ and $H(\alpha x - x_1) = 1$ so we may immediately integrate (60) to obtain

$$Z_2(x) = a \int_{x_1}^{\alpha x} x^{k-1} Z_1(s)\, ds. \tag{70}$$

This integration can be carried out term by term, again using the substitution $z = a\alpha^{nk} x^k / k$, to give

$$Z_2(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \left[e^{-a\alpha^{nk} x_1^k / k} - e^{-a\alpha^{(n+1)k} x^k / k} \right], \tag{71}$$

where the constant C is the same as that in the expression for $Z_1(x)$ in (63).

3.3 Region 3, $x \leq x_1/a$

In this region (60) becomes

$$Z_3'(x) = 0 \tag{72}$$

so as we have $Z_3(x_1/\alpha) = Z_2(x_1/\alpha) = 0$ from (71) the solution is simply

$$Z_3(x) = 0 \tag{73}$$

as expected.

3.4 Discussion and examples

Combining the results above and noting $Z(x) = x^2 y(x)$ the SSD in the case $g(x) = gx$ and $b(x) = bx^k H(x - x_1)$ is given by

$$y(x) = \begin{cases} C/x^2 \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} e^{-a(\alpha^n x)^k / k}, & x \geq x_1 \\[2ex] C/x^2 \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} [e^{-a\alpha^{nk} x_1^k / k} - e^{-a\alpha(n+1)k_x k / k}], \\ & x_1/\alpha \leq x \leq x_1 \\[2ex] 0, & x \leq x_1/\alpha \end{cases} \tag{74}$$

where

$$C = (ka)^{1/k} \frac{1}{(\alpha - 1)S} \tag{75}$$

and

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} \Gamma\left(1 - \frac{1}{k}, \frac{a}{k} \alpha^{kn} x_1^k\right). \tag{76}$$

Figure 2 shows this piecewise function for $y(x)$ for a range of minimum sizes for cell division x_1, with $k = 2$, $a = b/g = 1$, and $\alpha = 2$. The discontinuity in the slope of $y(x)$ at $x = x_1$ is a natural consequence of the step change in
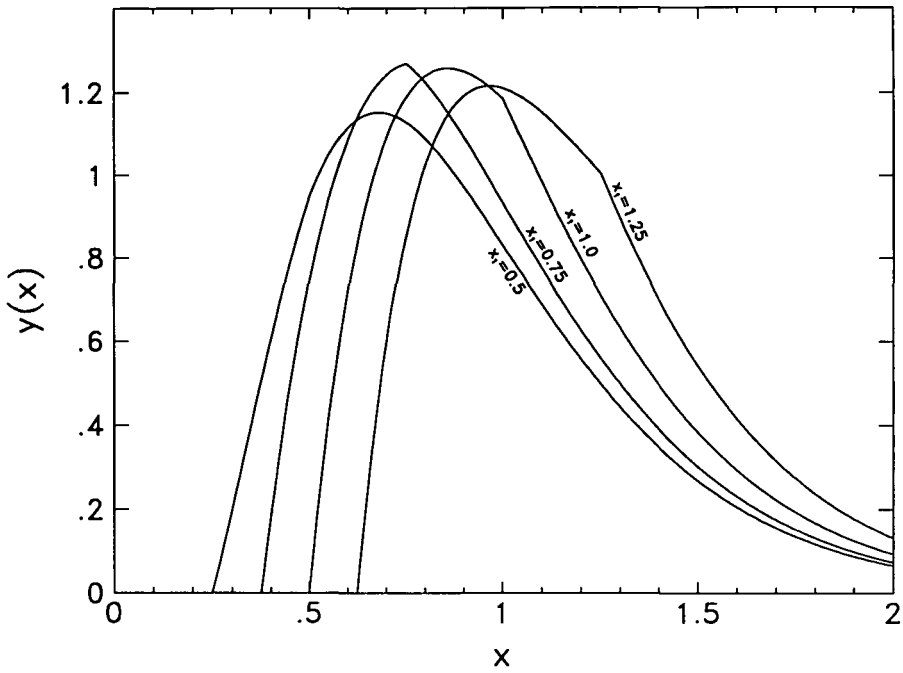
FIGURE 2. SSD probability density functions $y(x)$ for $g(x) = gx$ and $b(x) = bx^k H(x_2 - x)$, with $k = 2$, $a = 1$, $\alpha = 2$, and a range of values of x_1.

the probability of cell division $b(x)$ (from 0 to bx_1^k) at this size. The form of $y(x)$ for small values of x_1 approaches the form given in figure 1 for $k = 2$.

4 A minimum and maximum size for cell division

Consider the case where $g(x) = gx$ and there exists a minimum size for cell division x_1 as in the previous section, and there is also a maximum cell size $x_2(0 < x_1 < x_2)$ such that all cells divide before they reach size x_2. This means we are considering non-negative forms of $a(x) = b(x)/gx$ such that

$$a(x) = 0, \qquad x \leq x_1,$$
$$a(x) \to \infty, \qquad x \to x_2^-, \qquad (77)$$

and we will assume $y(x) \equiv 0$ for $x > x_2$. For reasons that will become apparent later we will in fact restrict our attention to forms of $a(x)$ which are integrable over all closed regions $[c, d]$ such that $c, d < x_2$, but with a

non-integrable singularity at x_2, so

$$\int_c^{x_2} a(x)\,dx = \infty \tag{78}$$

for any $c < x_2$.

4.1 The solution method

The solution, $Z(x)$, to (15) can be constructed as follows. Firstly, let m be the largest integer such that $x_1 < x_2\alpha^{-m}$. In typical cell populations, m is usually quite small—less than 3. Tyson and Diekman [8] give the solution for the special case $m = 0$ and $\alpha = 2$, and show how in this case solutions may be obtained for forms of $g(x)$ other than $g(x) = gx$ by treating Q (see section 1) as an unknown constant to be found numerically. The method outlined here could be similarly extended to more general forms of $g(x)$.

We split $Z(x)$ into regions so that

$$Z(x) = \begin{cases} Z_0(x), & x \geq x_2 \\ Z_k(x), & x_2\alpha^{-k} \leq x < x_2\alpha^{-k+1}, \ 1 < k \leq m+1. \end{cases} \tag{79}$$
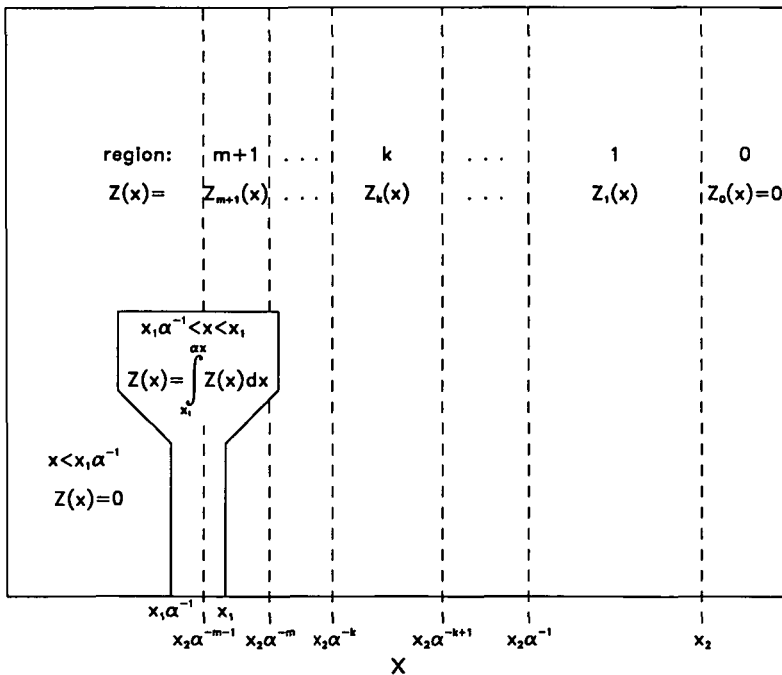

FIGURE 3. Regions used in solving for the SSD. $Z_1(x)$ is found first using (81), $Z_2(x)$ to $Z_{m+1}(x)$ are found iteratively using (82), then finally $Z(x)$ for $x < x_1$ is found using (83).

This scheme is shown in Fig. 3. Note that as no cell division occurs below size x_1, no new cells can appear of size less than $x_1\alpha^{-1}$, so we must have $z(x) = 0$ for $x < x_1\alpha^{-1}$. We now write (15) in the form

$$Z'_{k+1}(x) = -a(x)Z_{k+1}(x) + \alpha a(\alpha x)Z_k(\alpha x), \qquad k \geq 0. \tag{80}$$

This equation can then be used iteratively to find $Z(x)$ over the whole range of sizes of interest. We know $Z_0 \equiv 0$ (because $y(x) = 0$ for $x > x_2$), so it follows from (80) that

$$Z_1(x) = Ce^{-A(x)} \tag{81}$$

where C is a constant to be evaluated, and $A'(x) = a(x)$. If we now assume that the solution in region k is known, then (80) becomes a simple first-order ODE in $Z_{k+1}(x)$, and the solution is

$$Z_{k+1}(x) = \exp\left(\int_x^{x_2\alpha^{-k}} a(s)\,ds\right) Z_k(x_2\alpha^{-k})$$
$$- \int_{\alpha x}^{x_2\alpha^{1-k}} \exp\left(\int_x^{s\alpha^{-1}} a(s')\,ds'\right) a(s)Z_k(s)\,ds, \tag{82}$$

where the limits of the integration have been fixed by the continuity requirement $Z_{k+1}(x_2\alpha^{-k}) = Z_k(x_2\alpha^{-k})$. Hence we can deduce the solution $Z_k(x)$ for all $k \geq 1$, then calculate the constant C from the either of the integral conditions (16) or (17). The desired SSD can then be simply calculated from $y(x) = x^{-2}Z(x)$.

Two points are worth noting in this solution process. Firstly, from (81), continuity of Z_1 with Z_0 at $x = x_2$ for non-zero C requires that $A(x_2) = \infty$, so x_2 must be a non-integrable singularity of $a(x)$ as pointed out earlier. The alternative would be to allow a discontinuity in $Z(x)$ at x_2, in which case $y(x)$ would be discontinuous at $x = x_2\alpha^{-k}$ for $0 \leq k \leq m+1$, so the argument involving continuity used above would be invalid. Equation (81) must clearly be used in place of (82) for $k = 0$ because the first term in (82) becomes a product of infinity and zero. Secondly, once the solution has been found in the size region between x_1 and x_2 using the above process, the solution in the region $x < x_1$ is most simply found by noting that $a(x) \equiv 0$, so the integral form of the equation (18) can be used in the form

$$Z(x) = \int_{x_1}^{\alpha x} a(s)Z(s)\,ds, \qquad x < x_1. \tag{83}$$

It is clear from this formulation that we will have $Z(x) = 0$ for $x < x_1$ as expected, with continuity of $Z(x)$ at $x = x_1$.

4.2 An example

As an analytical example of this process, consider the simplest form of $a(x)$ which satisfies the conditions (77), namely

$$a(x) = \begin{cases} 1/(x_2 - x), & x_1 < x < x_2 \\ 0, & x < x_1, \end{cases} \tag{84}$$

which corresponds to a birth rate $b(x)$ of

$$b(x) = \begin{cases} gx/(x_2 - x), & x_1 < x < x_2 \\ 0, x < x_1 \end{cases} \tag{85}$$

where g is the constant in $g(x) = gx$. We will choose $x_1 = \alpha^{-2}x_2$ exactly, as this is the simplest choice which involves use of all of the equations (81), (82), and (83). In region 1 we then find, using (81),

$$\begin{aligned} Z_1(x) &= Ce^{-\int 1/(x_2-x)\,dx} \\ &= Cx_2(1 - x/x_2). \end{aligned} \tag{86}$$

In region 2, using (82) we obtain

$$Z_2(x) = Cx_2(1 - x/x_2)[1 - \alpha\log(1 - x/x_2) + \alpha\log(1 - \alpha^{-1})]. \tag{87}$$

Applying integral condition (17) we get

$$\int_{x_2\alpha^{-2}}^{x_2\alpha^{-1}} \frac{Z_2(x)}{x(x_2 - x)}\,dx + \int_{x_2\alpha^{-1}}^{x_2} \frac{Z_1(x)}{x(x_2 - x)}\,dx = \frac{1}{\alpha - 1} \tag{88}$$

which leads to

$$C = [(\alpha - 1)[(2 + \alpha\log(1 - \alpha^{-1}))\log\alpha + \alpha(S(\alpha^{-1}) - S(\alpha^{-2}))]]^{-1}, \tag{89}$$

where $S(u) = \sum_{n=1}^{\infty} u^n/n^2$.

We now use (82) to find the solution in the region $x < x_1$ as

$$\begin{aligned} Z_3(x) = Cx_2\alpha & \left[(1 + \alpha\log(1 - \alpha^{-1})) \left[\frac{x}{x_2} - \alpha^{-3} \right] \right. \\ & + \left(1 - \alpha\frac{x}{x_2} \right) \left[\log\left(1 - \alpha\frac{x}{x_2} \right) - 1 \right] \\ & \left. - (1 - \alpha^{-2})[\log(1 - \alpha^{-2}) - 1] \right]. \end{aligned} \tag{90}$$
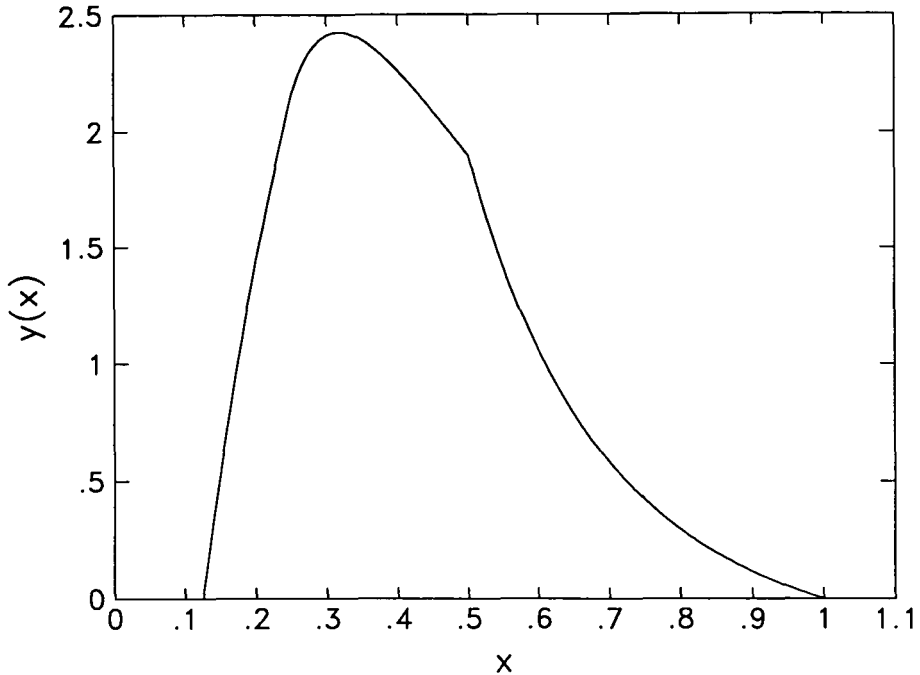
FIGURE 4. The SSD probability density functions $y(x)$ for $a(x) = b(x)/gx = (1-x)^{-1} \cdot H(x-0.25)$ and $\alpha = 2$.

Now using $u(x) = x^{-2}Z(x)$ we can write the SSD $y(x)$ as

$$y(x) = \begin{cases} 0, & x \le x_2\alpha^{-3} \\ \frac{Cx_2}{x^2} \cdot \alpha[(1 + \alpha\log(1-\alpha^{-1}))[\frac{x}{x_2} - \alpha^{-3}] \\ \quad + (1 - \alpha\frac{x}{x_2})[\log(1-\alpha\frac{x}{x_2}) - 1], & x_2\alpha^{-3} < x \le x_2\alpha^{-2} \\ \quad - (1 - \alpha^{-2}[\log(1-\alpha^{-2}) - 1]], \\ \frac{Cx_2}{x^2}(1 - \frac{x}{x_2})[1 - \alpha\log(1-\frac{x}{x_2}) + \alpha\log(1-\alpha^{-1})], \\ & x_2\alpha^{-2} < x \le x_2\alpha^{-1} \\ \frac{Cx_2}{x^2}(1 - \frac{x}{x_2}), & x_2\alpha^{-1} < x \le x_2 \\ 0, & x > x_2. \end{cases} \qquad (91)$$

where C is given by (89).

Fig. 4 shows this function with binary fission ($\alpha = 2$) and with x_2 equal to one size unit. Substitution is straightforward apart from the calculation of $S(0.5)$ and $S(0.25)$ required to find C. Jolley [4] gives

$$S(0.5) = \frac{\pi^2}{12} - \frac{(\log 2)^2}{2}, \qquad (92)$$

but the only way to find $S(0.25)$ seems to be to substitute into the series, which actually converges very rapidly in this case. From the form of (91) it is clear that x_2 is just a scaling factor, so the solution for other values of x_2 is simply obtained by relabelling the horizontal and vertical axes in Fig. (4) as x/x_2 and $x_2 y(x)$ respectively.

Acknowledgement

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Appendix: Identities involving $K(\alpha^k, \beta)$

If we take the well-known identity (for example, see [1])

$$\sum_{n=0}^{\infty} \frac{q^{n(n-1)/2} z^n}{(1-q)(1-q^2)\cdots(1-q^n)} = \prod_{n=0}^{\infty}(1 + zq^n), \qquad (93)$$

and substitute $q = \alpha^{-k}$ we get

$$\sum_{n=0}^{\infty} \frac{\alpha^{kn} z^n}{(\alpha^k - 1)(\alpha^{2k} - 1)\cdots(\alpha^{nk} - 1)} = \prod_{n=0}^{\infty}(1 + z\alpha^{-kn}). \qquad (94)$$

Substituting $\beta = -\alpha^k z$ gives

$$\sum_{n=0}^{\infty} \frac{(-1)^n \beta^n}{(\alpha^k - 1) \cdots (\alpha^{kn} - 1)} = \prod_{n=1}^{\infty}(1 - \beta\alpha^{-kn}) \tag{95}$$

so that using the definition of K given in (36) we obtain

$$K(\alpha^k, \beta) = \prod_{n=1}^{\infty}(1 - \beta\alpha^{-kn}). \tag{96}$$

Substituting $\beta = \alpha^m$ into (96) then gives

$$K(\alpha^k, \alpha^m) = \prod_{n=1}^{\infty}(1 - \alpha^{-k(n-1)+m-k}),$$

so

$$K(\alpha^k, \alpha^m) = (1 - \alpha^{m-k})K(\alpha^k, \alpha^{m-k}). \tag{97}$$