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Woldringh, C.L.; Grover, N.B.

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Relationship between the Fraction of Cells of Different Genealogical Ages and their Cycle Times in Saccharomyces cerevisiae: A Theoretical Analysis

N. B. Grover†§ and C. L. Woldringh‡

† Hubert H. Humphrey Center for Experimental Medicine and Cancer Research, Hebrew University, Faculty of Medicine, Box 12272, Jerusalem 91120, Israel, and
‡ Section of Molecular Cytology, Institute for Molecular Cell Biology, University of Amsterdam, BioCentrum, Plantage Muidergracht 14, 1018TV Amsterdam, The Netherlands

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In Saccharomyces cerevisiae, two separate subpopulations can be distinguished visually: parents and daughters, the former receiving the major portion of the septal material as a bud scar. These scars persist as stable structures, and so can serve as indicators of the number of times a cell has undergone division—its genealogical age. Daughters can be similarly classified according to the generation of the parent cell from which they separated. The actual fraction of each class of cells depends on their lifetime. Previous attempts to derive a relationship between these two entities were restricted to the special case in which all parent cells possess a common cycle time, regardless of their genealogical age, and so do all daughters. Experimental evidence suggests that such extreme assumptions are unwarranted; they are also unnecessary. The relationship between the number of parent cells in any particular genealogical age class is shown here to depend solely on their lifetime and on those of younger parent cells. The expressions obtained consist exclusively of closed elementary algebraic forms, and the calculation of age at division from cell fraction is easy and straightforward. The analysis is then extended to cover the case of heterogeneous daughter cells. The results there turn out to be simpler still: the fraction of daughter cells of a particular genealogical age is dependent on its own doubling time only, and not on those of younger cells.

Introduction

Cells of the budding yeast Saccharomyces cerevisiae form a chitin-containing ring around the site of their emerging bud. The septum that is synthesized at this location prior to separation splits asymmetrically at cell division. Because of this, two separate subpopulations can be distinguished visually: parents and daughters, the former receiving the major portion of the septal material as a bud scar. These scars persist as stable structures, and so can serve as indicators of the number of times a cell has undergone division, its genealogical age. The parent population can thus be subdivided into first-generation parents, second-generation parents, and so on.

Daughters can be similarly classified according to the generation of the parent cell from which they separated (Beran et al., 1969; Egilmez & Jazwinski, 1989), although current staining procedures are not able to provide persistent markers and the faint ring structure formed by the so-called birth scar disappears within a cycle or two.

The actual fraction of each class of cells depends on their lifetime. Previous attempts (Hartwell & Unger, 1977; Lord & Wheals, 1980) to derive a relationship between these two entities were restricted to the special case in which all parent cells possess a common cycle time, regardless of their genealogical age, and so do all daughters. Experimental evidence suggests that such extreme assumptions are unwarranted (Hartwell & Unger, 1977; Egilmez & Jazwinski, 1989); fortunately, they are also unnecessary. We show below that the relationship between the number of parent cells in any

§ Author to whom correspondence should be addressed. e-mail: norman@md2.huji.ac.il
particular genealogical age class depends only on their lifetime and on those of younger parent cells. The relationship in the case of daughter cells turns out to be even simpler.

The reason that cell cycle time varies with genealogical age, increasing slowly at first and then ever more rapidly, is not at all clear, although there are indications that an accumulating deficiency in energy metabolism may be involved (Jazwinski, 1993). But whatever the mechanism, empirically the cycle time of an individual cell has been found to be an accurate predictor of when it is destined to die and, as such, constitutes a valuable biomarker for the aging process since it reflects physiological or functional age rather than nominal age, unlike the genealogy of the cell or its size (Jazwinski, 1990). The purpose of the present communication is to make this property readily accessible to the experimental mycologist.

Theory

Consider a population of *S. cerevisiae* in balanced exponential growth. Let \( n_g(a) \) be the number of cells at age \( a \) with \( g \) scars (that is, of genealogical age \( g \)), and let \( \tau_g \) be the age at which these cells divide. In principle, in order for a steady state to exist, there must be a relationship in the case of daughter cells turns out to be even simpler.

From eqn (1), since all summations are over \( g \) from 0 to \( G \), the intermediate terms in this last expression cancel, leaving just \( x^{-1} n_0(0) - x^{-1} n_{g+1}(0) \). But cells of genealogy \( G \) do not divide, so that \( n_{G+1}(0) \) is zero and the total number of cells is simply \( x^{-1} n_0(0) \). In order to interpret the \( F_g \) as frequencies rather than numbers, one merely sets the total number of cells to unity, so that finally

\[
F_g = \frac{x^{-1} n_0(0)}{\sum F_g}. \tag{2}
\]

By substituting for \( n_g(\tau_g) \) in eqn (2), it is easy to show that, not surprisingly, the total frequency of newborn cells is equal to \( 2x \), the same as in symmetrical binary fission (Powell, 1956).

**Heterogeneous Daughter Cells**

Up to this point we have treated daughter cells (those with \( g = 0 \)) as a homogeneous group. It would appear, however, that this may not be justified (Beran et al., 1969; Egilmez & Jazwinski, 1989). We therefore generalize our analysis to cover this situation also. The only effect a heterogeneous daughter population has on the expressions derived above for the parent cells, is to require a reinterpretation of \( \tau_0 \). For the moment, it is sufficient to define it formally as the solution to the equation \( n_g(0) = x^{-1} e^{-\tau_g} \). A more biological interpretation is presented below.

Let \( n_g(a) \) be the frequency of daughter cells of age \( a \) separated from parents with \( g \) scars, and let \( \theta_g \) be their
doubling time. Since a parent cell with \( g \) scars gives rise on division to one newborn parent cell with \( g + 1 \) scars and one daughter cell of genealogical age \( g \), and since that is the only source of these newborn cells, then

\[ m_g(0) = n_g(0) = n_g(\tau_g). \quad (7) \]

Whenever a daughter cell divides, it gives rise to one newborn parent cell with a single scar and one daughter cell of genealogical age 0. Since this obtains for all dividing daughter cells, regardless of genealogical age,

\[ m_0(0) = n_1(0) = S m_g(0). \quad (8) \]

But \( n_1(0) = n_0(\tau_0) = n_0(0) 2^{-\theta_0} \), and so it follows from eqn (8) that

\[ n_0(0) 2^{-\theta_0} = \sum m_g(\theta_g) = m_g(0) 2^{-\theta_0}, \]

or

\[ 2^{-\theta_0} = \sum m_g(0) 2^{-\theta_g} = \sum m_g(0) 2^{-\theta_g}, \quad (9) \]

where we have used the identity

\[ \sum m_g(0) = n_0(0), \quad (10) \]

the total frequency of newborn daughter cells.

Equation (9) provides us with the biological interpretation for \( \tau_0 \): as expected, it is the average doubling time of the daughter cells, suitably weighted according to the size of the fraction. This can be recast as

\[ 2^{-\theta_0} = \langle 2^{-\theta_g} \rangle, \quad (11) \]

where the angle brackets denote averaging according to eqn (9).

Let \( G_g \) represent the fraction of daughter cells of genealogical age \( g \). Then

\[ G_g = \int m_g(0) 2^{-\theta_g} \, da \\
= z^{-1} m_g(0) [1 - 2^{-\theta_g}] \\
= z^{-1} n_{g+1}(0) [1 - 2^{-\theta_g}] \quad (12) \]

from eqn (7). This allows us to obtain \( \theta_g \) from experimental values of \( G_g \) since the \( n_{g+1}(0) \) are known from the parent distribution derived above. Note that, unlike in the case of the parents, \( G_g \) depends only on \( \theta_g \) itself and not on the doubling times of daughters of lesser genealogical age.

REFERENCES


