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Stage-dependent density effect in the cell cycle of budding yeast

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Abstract

Yeasts in culture media grow exponentially in early period but eventually stop growing. The saturation of population growth is due to "density effect". The budding yeast, *Saccharomyces cerevisiae*, is known to exhibit a stage-dependent cell division. Daughter cell, which gives no birth, has longer generation time than mother, because daughter needs maturity time. So far, investigations have been restricted in exponential or non-crowding state; very little is known for the stage dependence of density effect. Here we present a lattice gas model to explore the population dynamics of crowding period. We compare theoretical results with experimental data, and find a stage-dependent density effect. Although small daughter cells can develop to a critical size, the reproduction of large daughter cells suddenly stops when the total density exceeds some critical level. Our results imply the existence of an inhibitor that specifically halts the reproduction of matured daughter cell.

Keywords: Budding yeast; Stage-dependent density effect; Lattice gas model; Population dynamics

1. Introduction

The reproduction is one of the most important events for organisms. In some animals and birds, the experience of giving birth becomes a key factor of reproductive decision during environmental deterioration (Clutton-Brock, 1988). When environmental condition becomes worse than ordinary condition, naïve daughters who have no experience of birth fail reproduction more easily than experienced mothers who have given birth at least once in the previous reproductive attempts. As an adaptive response, naïve daughters often halt reproduction when environments become deteriorate. The budding yeast, *Saccharomyces cerevisiae*, exhibits such a reproductive response for environmental deteriorations. It is known that the reproduction of daughter cells is disturbed, when nutrition condition becomes worse compared to the complete medium (Carter and Jagadish, 1978; Wheals and Lord, 1980; Hartwell and Unger, 1977). Namely, the growth of small daughter cells is disturbed in exponential period. In contrast, the aim of the present paper is to report another disturbance of daughter reproduction. We study the density effect to demonstrate the following result: although the growth of small daughter cells is not disturbed, the matured daughter cells suddenly stop reproduction by the density effect.

The dynamics of yeast growth in a shaking culture is represented by logistic curve. The total population size of yeast initially grows exponentially but eventually reaches a certain population size (carrying capacity). The saturation of population growth is due to the density effect. In the budding yeast, mothers receive a bud scar after budding, while the daughter has no scar. The stage dependence of cell cycle in exponential period or non-crowding state has been extensively studied by many authors (Carter and Jagadish, 1978; Wheals and Lord, 1980). Hartwell and Unger (1977) well explained the generation times of both daughter and mother by unequal division model as illustrated in Fig. 1. This model has several assumptions (collectively call HU assumption): (i) all mothers (daughters) have the same generation time G_m (G_d), (ii) the generation time G_d is longer than G_m, because daughter needs maturity (growth) time, and (iii) the reproduction

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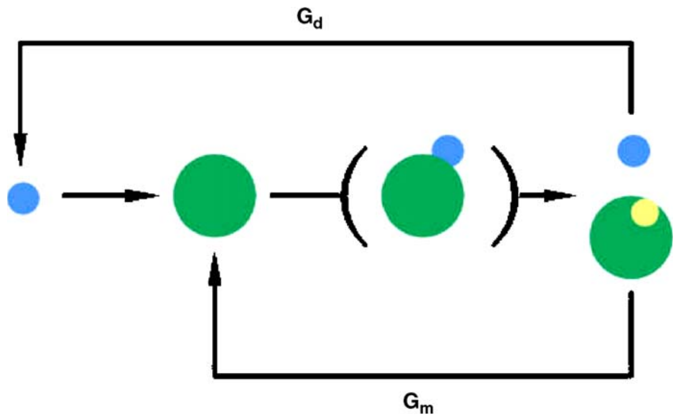

Fig. 1. Schematically illustrations of cell cycle by Hartwell and Unger (HU) model. The generation time of daughter (G_d) is longer than that of mother (G_m). The yellow spot indicates the bud scar.

rates between daughter and mother are different, whereas those between matured daughter and mother are identical.

Hamada et al. (1982) presented the stage-structured dynamic model (Hamada model) of daughter and mothers, depending on the number of scars (see Appendix A). They compared theoretical results with experimental data of the frequencies of cell that had n scars ($n = 1, 2, \ldots$). The agreement between the theoretical prediction and experimental data in exponential period is fairly good, provided that the HU assumption is applied. This means that the Hamada model with HU assumption works well in exponential period. In contrast, Hamada et al. (1985) suggested the invalidity of the HU assumption in the saturation period. Despite such suggestion, they never sufficiently discussed the stage dependence of density effect, because they did not distinguish the growth stage (to a critical size) from the reproductive (pre-budding and budding) stage of daughters.

2. Models

2.1. Overview

In the present paper, we apply lattice gas model which is convenient for the density effect. For example, we consider one-dimensional lattice. The number of total lattice sites is set to be equal to the carrying capacity K. Each lattice site takes one of the two states: empty (O) or occupied (X) site. The lattice gas model is unique to have an empty site (O) that takes into account the density effect automatically. We carry out computer simulation as follows: we randomly and independently choose a pair of lattice sites. If the pair is X and O, then the latter site is changed into X with a rate r. Note that such a growth can be represented by the following chemical reaction: $X + O \rightarrow 2X$. Let the density of X be x, then the empty density becomes $1 - x$. The densities are equal to the population sizes divided by carrying capacity K. If the carrying capacity is infinitely large, then the population dynamics approximately becomes $\dot{x} = rx(1 - x)$, where the dot means the time derivative. This is called the logistic equation which is valid for one-stage model.

Here we develop the lattice gas model to multi-stage case. The cell cycle of budding yeast is assumed to be composed of three stages (Fig. 2): immature daughter (D_i), matured daughter (D_m) and mother (M). A distinct point of the current model is to divide the daughter into two stages D_i and D_m. The present model includes both the separation of growth and reproduction as in the HU model and the separation of daughters and mothers. We apply it to investigate the effects of density on daughters and mothers during the saturation period, where the density effects are in effect.

The interactions of the lattice gas model occur as follows:

$$D_i \rightarrow D_m \quad (\text{rate} : g), \tag{1a}$$

$$D_m + O \rightarrow M + D_i \ (\text{rate} : r_{md}), \tag{1b}$$

$$M + O \rightarrow M + D_i \ (\text{rate} : r_m). \tag{1c}$$

Reactions (1a)–(1c), respectively, represent growth of daughter, reproduction of daughter and reproduction of mother, where g, r_{md} and r_m are reaction rates for respective processes. Note that r_{md} is the reproduction rate of matured daughter that differs from the rate r_d of overall daughter contained in two-stage (daughter–mother) model [see (A.5) in Appendix A]. Each lattice site is either empty (O) or occupied by one of three stages (D_i, D_m or M). The total number of lattice sites is assumed to be equal to the carrying capacity K.

2.2. Simulation method

The simulation procedure is described as follows:

(1) Initially, we distribute three kinds of cells on a one-dimensional lattice, where almost all sites are empty. Initial conditions are not so important both in late exponential and saturation periods.

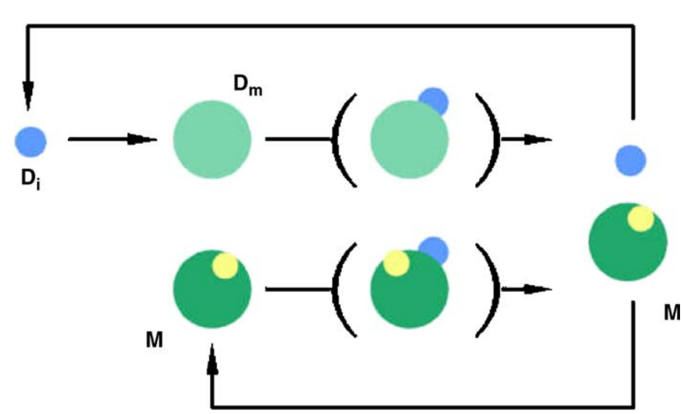

Fig. 2. Our cell cycle model. There are three stages in cell cycle: immature daughter (D_i), matured daughter (D_m) and mother (M).