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Population fitness growth rate model based on cell death

Xueyan Zhao, Yuanxiao Gao, Xiaolin Lin, Caixia Li

Shaanxi University of Science and Technology, Xi'an, 710016, China

ABSTRACT
Irreversible somatic differentiation is crucial for the growth and development of multicellular organisms. However, current research on irreversible somatic cell differentiation and evolution has overlooked the impact of cell death. We constructed a population fitness growth rate model for multicellular organisms that includes cell death based on the death of two cell types, germ-like cells and soma-like cells. The results indicate that the death of two types of cells has varying degrees of impact on the formation conditions and individual size of irreversible cell differentiation, which also demonstrates the rationality of the model.

KEYWORDS
Population Fitness Growth Rate; Cell Death; Irreversible Somatic Cell Differentiation

1 Introduction

Cell death exists throughout the growth and development of multicellular organisms. Generally speaking, by regulating the balance between cell proliferation and death, it can affect the development and growth of cell clusters and even multicellular organisms to varying degrees. For example, in order to maintain the ability of hematopoietic stem cells to perform a series of complex tasks, these cell populations must coordinate the functions between proliferation, differentiation, and death [1-3]. Irreversible cell differentiation plays an important role in the evolutionary process of advanced animals, often preventing cancer of cells or tissues. Therefore, this article focuses on irreversible somatic cell differentiation (ID) of cells. The issue of cell differentiation in multicellular organisms has always been a concern. Researchers in the field of evolutionary biology focus on three aspects of research: the construction of population growth rates [4-7], the mechanism of cell death[8-10], and whether cell differentiation is state dependent [11-12]. Among them, Gao et al. [11-12] studied the reasons for cell differentiation evolution and the impact of the cost and benefits of cell differentiation on irreversible differentiation without cell death. However, they overlooked cell death caused by limitations in living space or interactions between cells, whereas previous studies have indicated that cell death is a necessary form of existence in the growth process of multicellular organisms. Based on the above analysis, in this paper, cell death is introduced into the population fitness growth rate model of multicellular organisms, and the development trajectory of the population is described by random probability, and the effect of cell death on the evolution of irreversible cell differentiation is studied.

2 The proposed approach

(1) The life cycle of multicellular organisms

In this section, we will introduce the lifecycle of multicellular organisms with cell death rates. Cells in multicellular organisms are mainly divided into two types: germ-like cells and soma-like cells. The mortality rate per unit time of germ-like cells (somatic cells) is $d_g^{(i)}(d_s^{(i)})$, and the product of its and cell division times is the probability of death under that division. Afterwards, the cell undergoes its final binary division to reach the mature stage, and the soma-like cells do not have the function of reproducing offspring. Eventually, all of them die and disappear, and the germ-like cells, as individual entities, begin the evolution of the next life cycle [12] (see Fig. 1).

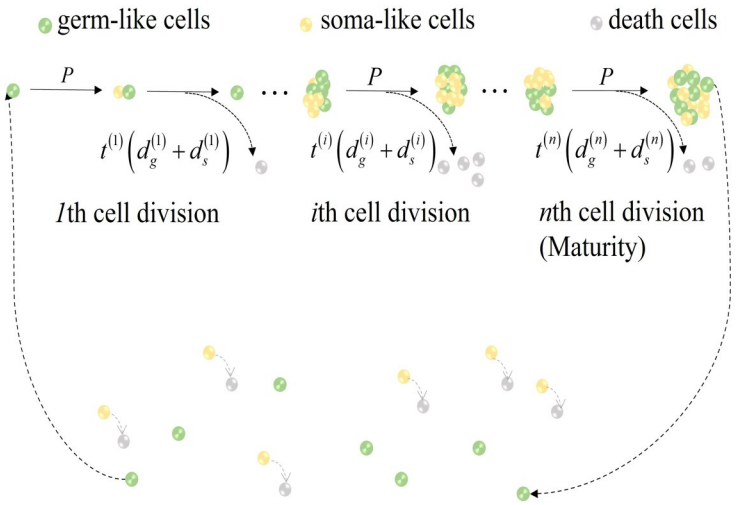

Figure 1 Life cyclel of multicellular organisms.

(2) Population fitness growth rate model

In this section, we mainly introduce the population fitness growth rate model. Each cell division produces six division probabilities, g_{gg}, g_{gs}, g_{ss}, s_{gg}, s_{gs} and s_{ss}. So the probability of transformation between these two cell types is

$$g_{g\to s}=g_{ss}+0.5g_{gs}$$
$$s_{s\to g}=s_{ss}+0.5s_{gs}$$

At the same time, there are,

$$g_{g\to s}+g_{g\to g}=1$$
$$s_{s\to g}+s_{s\to s}=1$$

Different differentiation probabilities represent different differentiation strategies, and the three types of differentiation strategies discussed in this article include irreversible somatic cell differentiation (ID), reversible differentiation (RD), and undifferentiation (ND) [11]. Among them, ID indicates that the differentiation of soma-like cells is irreversible, RD indicates that both germ-like cells and soma-like cells exist and can transform into each other, ND indicates that cells do not differentiate during proliferation.

Cell death affects the total number and proportion of cells during each division. When the mortality rates of germ-like cells and soma-like cells are the same, the total number of cells after the (i+1)-th division is

$$N^{(i+1)}=2N^{(i)}-2d^{(i)}N^{(i)}t^{(i+1)}$$
$$=2(1-d^{(i)}t^{(i+1)})N^{(i)}$$

So, the total number of cells that reach maturity after n divisions is

$$N^{(n)} = 2^{(n)} N^{(0)} \prod_{i=1}^{n} (1 - d^{(i)} t^{(i)})$$
$$= 2^{(n)} \prod_{i=1}^{n} (1 - d^{(i)} t^{(i)})$$

Where $N^{(0)}$ represents the total number of cells before cell division. Since there is only one germ-like cell, hence $N^{(0)} = 1$.

When the mortality rates of germ-like cells and soma-like cells are different, the total number of cells after the (*i+1*)-th division is

$$N^{(i+1)} = 2N^{(i)} - 2(d_g^{(i)} N_g^{(i)} + d_s^{(i)} N_s^{(i)}) t^{(i+1)}$$
$$= 2N^{(i)} - 2d_g^{(i)} N_g^{(i)} t^{(i+1)} - 2d_s^{(i)} (N^{(i)} - N_g^{(i)}) t^{(i+1)} \text{ Because of } N_g^{(i)} = N^{(i)} f_g^{(i)}, \text{ then}$$
$$= N^{(i)} [2(1 - d_s^{(i)} t^{(i+1)})] + N_g^{(i)} [2t^{(i+1)} (d_s^{(i)} - d_g^{(i)})]$$
$$N^{(i+1)} = 2N^{(i)} [1 + f_g^{(i)} (d_s^{(i)} - d_g^{(i)}) t^{(i+1)} - d_s^{(i)} t^{(i+1)}]$$

The total number of mature cells obtained was

$$N^{(n)} = 2^{(n)} \prod_{i=1}^{n} [1 + f_g^{(i)} (d_s^{(i)} - d_g^{(i)}) t^{(i)} - d_s^{(i)} t^{(i)}]$$

Where $N_g^{(i)}$ represents the total number of germ-like cells after the *i*-th division.

The proportion of two types of cells after each division will vary with the degree of cell death. The change in cell proportion can be divided into two stages. Firstly, the proportion of cells produced before death is $f_{gx}^{(i)}(f_{sx}^{(i)})$, and when some cells die, the proportion of remaining surviving cells is $f_g^{(i)}(f_s^{(i)})$. The proportion of germ-like cells $f_{gx}^{(i)}$ and soma-like cells $f_{sx}^{(i)}$ before cell death are

$$f_{gx}^{(i)} = f_g^{(i-1)} g_{g \to g} + f_s^{(i-1)} s_{s \to g}$$
$$f_{sx}^{(i)} = f_g^{(i-1)} g_{g \to s} + f_s^{(i-1)} s_{s \to s}$$

Furthermore, considering the impact of cell death, the proportion of surviving germ-like cells $f_g^{(i)}$ and the proportion of soma-like cells $f_s^{(i)}$, *i* represent the number of cell divisions.

$$f_g^{(i)} = \frac{f_{gx}^{(i)} (1 - d_g^{(i)} t^{(i)})}{f_{gx}^{(i)} (1 - d_g^{(i)} t^{(i)}) + f_{sx}^{(i)} (1 - d_s^{(i)} t^{(i)})}$$
$$f_s^{(i)} = \frac{f_{sx}^{(i)} (1 - d_s^{(i)} t^{(i)})}{f_{gx}^{(i)} (1 - d_g^{(i)} t^{(i)}) + f_{sx}^{(i)} (1 - d_s^{(i)} t^{(i)})}$$

The approximate growth rate model of population fitness based on cell death is obtained from the above,

$$\lambda = \frac{\ln(N^{(n)} f_g^{(n)})}{t} = \frac{\ln(N^{(n)} f_g^{(n)})}{\sum_{i=1}^{n} \frac{1 + F_c}{1 + F_b}}$$

$$N^{(n)} = 2^{(n)} \prod_{i=1}^{n} (1 - d^{(i)} t^{(i)}), \boxtimes d_s^{(i)} = d_g^{(i)} = d^{(i)}$$

$$N^{(n)} = 2^{(n)} \prod_{i=1}^{n} [1 + f_g^{(i)} (d_s^{(i)} - d_g^{(i)}) t^{(i)} - d_s^{(i)} t^{(i)}], \boxtimes d_s^{(i)} \neq d_g^{(i)}$$

Where $f_g^{(n)}$ represents the proportion of germ-like cells

$$F_c^{(i-1)} = c_1 (f_g^{(i-1)} g_{g \to s} + c_2 f_s^{(i-1)} s_{s \to g})$$

$$F_b^{(i-1)} = b f_s^{(i-1)}$$

after the *n*-th division, and *t* represents the expected growth time of the organism after the *n*-th division.

3 Smulation results

(1) The problem of existence conditions of ID

In this section, we analyze the conditions for the existence of ID strategies. ID satisfies and at each division. However, when the mortality rate of germ-like cells is high, they are restricted from differentiating into soma-like cells at the beginning of their life cycle, and approaches 0. Therefore, ID only has the advantage of promoting population growth when the mortality rate of germ-like cells is low, and is therefore selected.

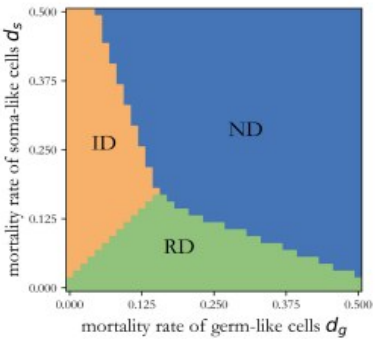

Figure 2 Optimal strategy based on mortality interval

Our numerical results show that in multicellular organisms containing 32 cells and undergoing 5 divisions, the existence condition of the ID is when the death rate of germ-like cells is less than 0.17, as shown in Figure 2. Among them, each pixel represents the optimal strategy of cells at each mortality rate, and the growth benefits b and differentiation costs c_1 and c_2 of cells are both 1. In addition, an excessive cell death rate can lead to the extinction of the entire multicellular organism population.

To eliminate the influence of different parameters on the conclusions of this section and further verify the generality of the conclusions, the range of values for parameters b and c_1 is expanded to $[10^{-1},10^{2}]$. The distribution of optimal strategies under three representative mortality rates is discussed, as shown in Figure 3.

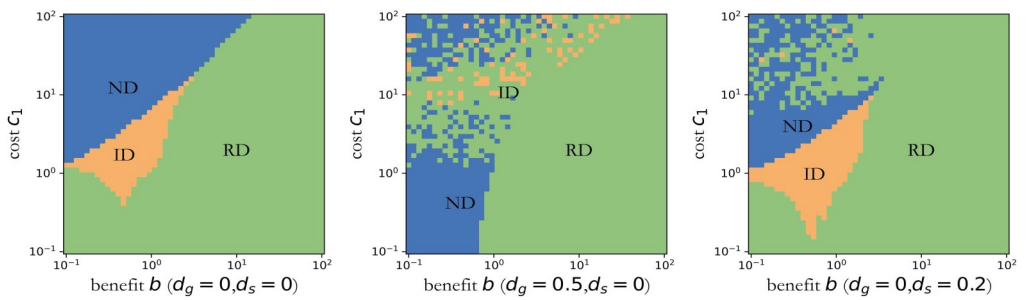

Figure 3 Optimal strategy based on parameter interval

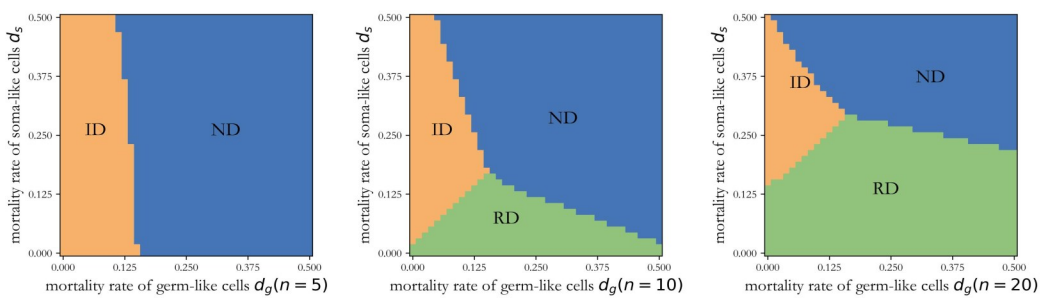

Figure 4 Optimal strategy under different splitting times

When germ-like cells have a very high mortality rate, due to the fact that ID does not produce germ-like cells, germ-like cells are close to extinction within an individual, which will greatly hinder the development of ID strategies. At the same time, the higher the cost c_1 generated by differentiation, the more cells tend not to differentiate, and the likelihood of ID occurrence is smaller, as shown in Figure 3. In addition, subgraphs 1 and 3 in Figure 3 show the distribution of strategies without considering cell death and when soma-like cells have lethality. The ID in both cases have a significant proportion which is consistent with expectations. In summary, it further confirms that the low mortality rate of germ-like cells is a necessary condition for the existence of the ID.

Furthermore, this study investigates whether the death of soma-like cells also affects the emergence of ID. A large number of numerical experiments have shown that as the number of divisions increases, the distribution of ID only becomes more pronounced when the cell death rate is high. So, three representative splitting numbers were selected, with n = 5, 10, and 20, respectively. Figure 4 shows that as the number of divisions n increases, the existence of the ID becomes more dependent on the high death of soma-like cells. At higher mortality rates of soma-like cells, more cells tend to undergo irreversible somatic differentiation, thereby differentiating into more soma-like cells to reduce the significant loss of soma-like cells caused by high mortality rates. When an individual divides more frequently, the number of cell divisions increases, and the individual tends to differentiate into more germ-like and soma-like cells at the end of their life cycle to produce more offspring, making the ID be selected.

(2) The impact of cell death on an organism's final size

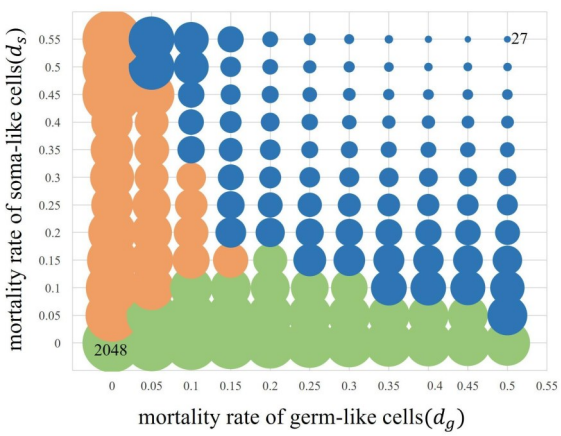

Figure 5 Evolution of individual size

We analyze an organism's final cell number under the effects of cell death for the optimal ID. When the mortality rates of germ-like cells and soma-like cells increase synchronously, it leads to the death of most cells. Therefore, the number of surviving cells decreases with the increase of cell mortality rate, thereby inhibiting the occurrence of larger individuals (see Fig. 5). Among them, the orange area represents the ID, the bubble size represents the individual size corresponding to the optimal strategy under the mortality rate of the group, and the bubble sizes are all scaled by 50%.

However, in the irreversible strategy of somatic differentiation (ID), as the mortality rate of soma-like cells increases, individual size shows a trend of first decreasing and then increasing. When soma-like cells have a moderate mortality rate, the ID tends to grow smaller individuals (see Fig. 5). Furthermore, to explore the special changes in individual size affected by cell death in the ID, Figure 6 extracted the proportion of germ-like cells f_g from each optimal strategy. The proportion of germ-like cells was reflected by the degree of color intensity, with darker colors indicating a larger proportion of germ-like cells.

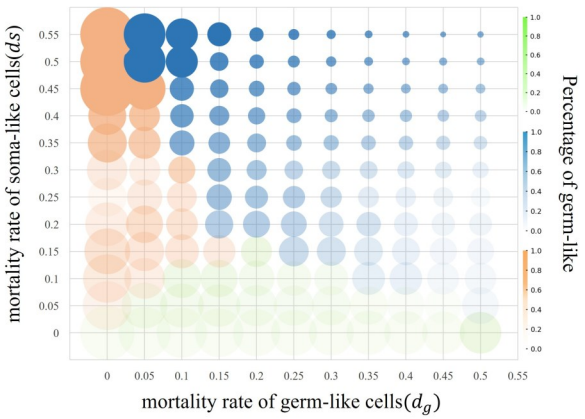

Figure 6 Proportion of germ cells in individuals

When the mortality rates of both germ-like cells and soma-like cells are low, individuals tend to divide more soma-like cells to accelerate their growth. At this time, the ID is prioritized, and soma-like cells within the individual dominate. When soma-like cells have a moderate mortality rate, although there is a slight decrease in the number of soma-like cells within the individual, their infinite proliferation and fast proliferation rate are still the dominant factors promoting individual growth. Therefore, at this time, soma-like cells within the individual still dominate. At the same time, the mortality rate of germ-like cells remains unchanged, maintaining the original growth rate. Therefore, germ-like cells and soma-like cells are the smallest at any stage, resulting in the smallest individual. Finally, when the mortality rate of germ-like cells is high, individuals tend to produce more germ-like cells to reduce the shrinkage of their morphology caused by the massive death of germ-like cells. At this time, the mortality rate of germ-like cells is low, which meets the conditions for producing germ-like cells. Therefore, cells differentiate into a large number of germ-like cells. Until the mortality rate of soma-like cells reaches its maximum, the individual is completely occupied by germ-like cells, as shown in Figure 6. In summary, when soma-like cells have a moderate mortality rate, individuals under the ID have the smallest mortality rate.

4 Conclusion

This article proposes a population fitness growth rate model for multicellular organisms that includes two types of cell death, based on the phenomenon of cell death in individuals. This model not only simulates the complete life process of cell proliferation, differentiation, and death in multicellular organisms, but also uses probability sequences to describe various forms of cell division. The research results indicate that the population fitness growth rate model proposed in this paper can effectively explain the conditions for the existence of ID strategies and changes in individual size.

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