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Mathematical model of irreversible cell differentiation under asynchronous division considering survival

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ABSTRACT
In this study, the non-synchronous cell division process of irreversible cell differentiation in multicellular organisms was investigated by computer simulation, taking into account the effects of survival. It was found that the selection of irreversible cell differentiation strategies decreased under different survival thresholds, and individuals would adopt other differentiation strategies. This study provides a theoretical basis for understanding the effect of survival rate on irreversible cell differentiation.

KEYWORDS
Survival rate; Asynchronous cell differentiation model; Irreversible cell differentiation

1 Introduction

Irreversible cell differentiation refers to the fact that cells cannot be reversed after differentiation in a specific direction to form specialized cell types, which is the basis of complex functions of organisms and is essential for maintaining cell diversity and life activities[1-2]. Individual survival rate is a key indicator of population health and environmental resilience, reflecting the influence of external environment and internal physiological mechanisms during the life cycle[3]. Therefore, the in-depth understanding of how survival rate affects the process of cell differentiation is of great significance for revealing the basic laws of life process.

In Yuanxiao Gao, Roman Zapien-Campos et al study on irreversible somatic cell differentiation, no external factors were taken into account and all cells were considered to be alive[4]. Subsequently, when studying the influence of state-dependent cell differentiation on the differentiation pattern, the team also did not consider any factors and applied the mathematical model of cell differentiation under synchronous cell division[5]. Cell differentiation is temporally diverse, influenced by cell type, environmental factors and cell cycle regulation, and it is important to understand the impact of survival on the growth of individuals and cell populations.

This paper simulates the process by mathematical model, shortens the research period and simplifies the research process. Changes in individual growth rates at different survival levels were studied, with emphasis on mathematical models of key survival thresholds that lead to growth rates falling to zero, and the effects of different survival thresholds on cell differentiation strategies.

2 Model construction

First, the life cycle of a multicellular body is established, assuming two cell types: germ cell g and

somatic cell *s*. After*n* cell divisions, an individual reaches maturity, and the number of cells in a mature individual is $N' = n + 1$. Survival rate $S(T,p)$ is introduced, where time *T*is the expected time of individual maturity, and *p* is the average survival rate within time *T*. At this time, the number of cells in the mature individual is $N = (n + 1)S(T,p)$.

First, $d_i = \left[g_{gg}^{(i)},g_{gs}^{(i)},g_{ss}^{(i)},s_{gg}^{(i)},s_{gs}^{(i)},s_{ss}^{(i)}\right]$ is used in this paper to represent the probability of cell differentiation when different cell types divide asynchronously for the *i* time, where $g_{gg}^{(i)}$ is the probability of one germ cell differentiating into two germ cells during the *i* time[6-7]. $g_{gg}^{(i)},g_{gs}^{(i)},g_{ss}^{(i)},s_{gg}^{(i)},s_{gs}^{(i)},s_{ss}^{(i)}$has the same definition and has the following relationships:

$$g_{gg}^{(i)} + g_{gs}^{(i)} + g_{ss}^{(i)} = 1, s_{ss}^{(i)} + s_{gs}^{(i)} + s_{gg}^{(i)} = 1 \tag{1}$$

Because cell differentiation is affected by internal and external factors, the probability of cell differentiation between continuous cell divisions will fluctuate. The cell differentiation probability space is constructed by using grid method, and the probability is limited to one decimal place and the step size is 0.1, forming a probability space containing 4356 combinations[5].Secondly, according to cell differentiation probability, the transfer probability between different cell types during subdivision can be obtained as follows:

$$\begin{aligned} &g_{g\to s}^{(i)} = g_{ss}^{(i)} + \frac{g_{gs}^{(i)}}{2}, s_{s\to g}^{(i)} = s_{gg}^{(i)} + \frac{s_{gs}^{(i)}}{2}, \\ &g_{g\to g}^{(i)} = 1 - g_{g\to s}^{(i)} = g_{gg}^{(i)} + \frac{g_{gs}^{(i)}}{2}, \\ &s_{s\to s}^{(i)} = 1 - s_{s\to g}^{(i)} = s_{ss}^{(i)} + \frac{s_{gs}^{(i)}}{2}. \end{aligned} \tag{2}$$

Table 1 Policy classification basis

Differentiation probability in the last cell division	ND	RD	Differentiation category		
			ID		
			IGD	ISD	IGSD
$g_{g\to s}^{(n)} = 1 - g_{g\to g}^{(n)}$	$\equiv 0$	$(0,1]$	0	$(0,1]$	0
$s_{s\to g}^{(n)} = 1 - s_{s\to s}^{(n)}$		$(0,1]$	$(0,1]$	0	0

According to the method of Gao Yuanxiao et al. [6], cell differentiation strategies under asynchronous cell division were classified according to cell transfer probability, which were divided into the following three categories, as shown in Table 1.

3 Construction of fitness

In order to compare the advantages and disadvantages of different strategies, the individual growth rate is selected as the fitness proxy [9]. Individual growth rate refers to the number of offspring produced by an individual per unit of time. It is assumed that the sum of all cell growth rates at the *i*division of the cell is $R^{(i)}$, so the waiting time *i* from the completion of the $(i - 1)$th division to the occurrence of the *i*th division follows an exponential distribution $f\left(t^{(i)}\right) = R^{(i)}e^{-R^{(i)}t^{(i)}}$. Thus, the expected wait time from the $(i - 1)$ th cell division to the second cell division can be expressed as $t^{(i)} = \dfrac{1}{R^{(i)}}$.

In this paper, it is assumed that the influence of cell differentiation on the growth rate of cell division can be decomposed into two aspects: benefit and cost. Combining cell differentiation probabilities to predict the growth rate of a cell at its *i*th division:

$$r^{(i)} = \frac{1 + F_b^{(i)}}{1 + F_c^{(i)}} X_{x \to xy} \tag{3}$$

Where $X_{x \to xy}$ is cell differentiation probability, *x,y* represents germ cell *g* and somatic cell *s*; $F_b^{(i)}$ is the benefit of cell differentiation in the *i* cell division:

$$\begin{cases} F_b^{(i)} = \left(bf_s^{(i-1)}\right)^a \\ b \geq 0, a = 1 \end{cases} \tag{4}$$

Where *b* is the benefit control quantity, *a* controls the shape of the function , suppose $a = 1$; $f_s^{(i)}$ is the $(i - 1)$ th somatic cell proportion. The cost of the corresponding different cell differentiation $F_c^{(i)}$ is a function of the cell differentiation fraction $f_{g \to s}$、$f_{s \to g}$ between germ cells and somatic cells at the *i*th cell division:

$$\begin{aligned} &F^{(i)}_{c_{g \to gg}} = 0, F^{(i)}_{c_{s \to ss}} = 0, \\ &F^{(i)}_{c_{g \to gs}} = c_{g \to s} f^{(i)}_{g \to s}, F^{(i)}_{c_{s \to gs}} = c_{s \to g} f^{(i)}_{s \to g}, \\ &F^{(i)}_{c_{g \to ss}} = 2c_{g \to s} f^{(i)}_{g \to s}, F^{(i)}_{c_{s \to gg}} = 2c_{s \to g} f^{(i)}_{s \to g}, \end{aligned} \tag{5}$$

Suppose that cost control quantity $c_{g \to s} = c_{s \to g}$. The fractional function of cell differentiation in the *i*th division is $f^{(i)}_{g \to s} = f_g^{(i-1)} g^{(i)}_{g \to s}, f^{(i)}_{s \to g} = f_s^{(i-1)} s^{(i)}_{s \to g}$. Where $f_g^{(i-1)}$、$f_s^{(i-1)}$ are the proportion of germ cells and somatic cells at the $(i - 1)$th cell division, respectively. To predict the ratio of different cell types after cell division by considering the probability of cell differentiation and the ratio between different cell types at present:

$$\begin{aligned} &f_g^{(i)} = g^{(i)}_{g \to g} f_g^{(i-1)} + s^{(i)}_{s \to g} f_s^{(i-1)}, \\ &f_s^{(i)} = g^{(i)}_{g \to s} f_g^{(i-1)} + s^{(i)}_{s \to s} f_s^{(i-1)}, \\ &f_g^{(i)} + f_s^{(i)} = 1, \end{aligned} \tag{7}$$

Then $f_g^{(n)}$、$f_s^{(n)}$ can be iteratively updated by the above formula:

$$\begin{aligned} \begin{pmatrix} f_g^{(n)} \\ f_s^{(n)} \end{pmatrix} &= \begin{pmatrix} g^{(n)}_{g \to g} & s^{(n)}_{s \to g} \\ g^{(n)}_{g \to s} & s^{(n)}_{s \to s} \end{pmatrix} \cdots \begin{pmatrix} g^{(i)}_{g \to g} & s^{(i)}_{s \to g} \\ g^{(i)}_{g \to s} & s^{(i)}_{s \to s} \end{pmatrix} \\ &\cdots \begin{pmatrix} g^{(1)}_{g \to g} & s^{(1)}_{s \to g} \\ g^{(1)}_{g \to s} & s^{(1)}_{s \to s} \end{pmatrix} \begin{pmatrix} f_g^{(0)} \\ f_s^{(0)} \end{pmatrix} \end{aligned} \tag{8}$$

Each organism starts from a single reproductive cell, with the initial cell ratio $f_g^{(0)} = 1, f_s^{(0)} = 0$, and subsequent ratios are iteratively calculated based on cell transition probabilities.

Thus, the cell division growth rate of different cell division results is obtained:

$$\begin{aligned} &r^{(i)}_{g \to gg} = \left(1 + \left(bf_s^{(i-1)}\right)^\alpha\right) g_{gg}, r^{(i)}_{s \to ss} = 1 + \left(bf_s^{(i-1)}\right)^\alpha s_{ss}, \\ &r^{(i)}_{g \to gs} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + F^{(i)}_{g \to gs}} g_{gs} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + c_{g \to s} f^{(i)}_{g \to s}} g_{gs}, \\ &r^{(i)}_{g \to ss} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + F^{(i)}_{g \to ss}} g_{ss} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + 2c_{g \to s} f^{(i)}_{g \to s}} g_{ss}, \\ &r^{(i)}_{s \to gs} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + F^{(i)}_{s \to gs}} s_{gs} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + c_{s \to g} f^{(i)}_{s \to g}} s_{gs}, \\ &r^{(i)}_{s \to gg} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + F^{(i)}_{s \to gg}} s_{gg} = \frac{1 + \left(bf_s^{(i-1)}\right)^\alpha}{1 + 2c_{s \to g} f^{(i)}_{s \to g}} s_{gg}, \end{aligned} \tag{9}$$

Then the total growth rate of the *i*th cell division is:

$$\begin{aligned} R^{(i)} &= N_g^{(i-1)} \left(r^{(i)}_{g \to gg} + r^{(i)}_{g \to gs} + r^{(i)}_{g \to ss}\right) \\ &+ N_s^{(i-1)} \left(r^{(i)}_{s \to ss} + r^{(i)}_{s \to gs} + r^{(i)}_{s \to gg}\right) \end{aligned} \tag{10}$$

Where $N_g^{(i-1)}$is the number of germ cells dividing at the $(i - 1)$th time and $N_s^{(i-1)}$ is the number of somatic cells:

$$\begin{aligned} &N_g^{(i-1)} = if_g^{(i-1)} S\left(T,p\right), N_s^{(i-1)} = if_s^{(i-1)} S\left(T,p\right), \\ &N^{(i-1)} = N_g^{(i-1)} + N_s^{(i-1)} = iS\left(T,p\right) \end{aligned} \tag{11}$$

Where $N^{(i-1)}$is the total number of cells at the $(i - 1)$th cell division. $S\left(T,p\right) = \ln e^{T \ln p}$ is the average survival rate of an individual at maturity, *p* is the average survival rate within *T* time, and *T* is the expected time of individual development to maturity, which can be expressed as:

$$T = \sum_{i=1}^{n} t^{(i)} = \sum_{i=1}^{n} \frac{1}{R^{(i)}} \tag{12}$$

When cell survival is further considered, the approximate growth rate of an individual is expressed as:

$$\lambda = \frac{\ln\left((n+1) f_g^{(n)} S(T,p)\right)}{\sum_{i=1}^{n} \frac{1}{R^{(i)}}} \tag{13}$$

4 Numerical experiment

In this section, the approximate individual growth rates under different survival rates were calculated by numerical simulation method. When all cells of small individuals ($n = 3$) survived, the parameters that had a greater impact on the irreversible cell differentiation strategy were determined as $\left[10^{-1}, 10^{2}\right]$.

In the absence of external factors, the proportion of irreversible cell differentiation strategies decreased compared to the average survival threshold, indicating that individuals were more inclined to adopt other differentiation strategies under specific survival conditions, as shown in Figure 1.

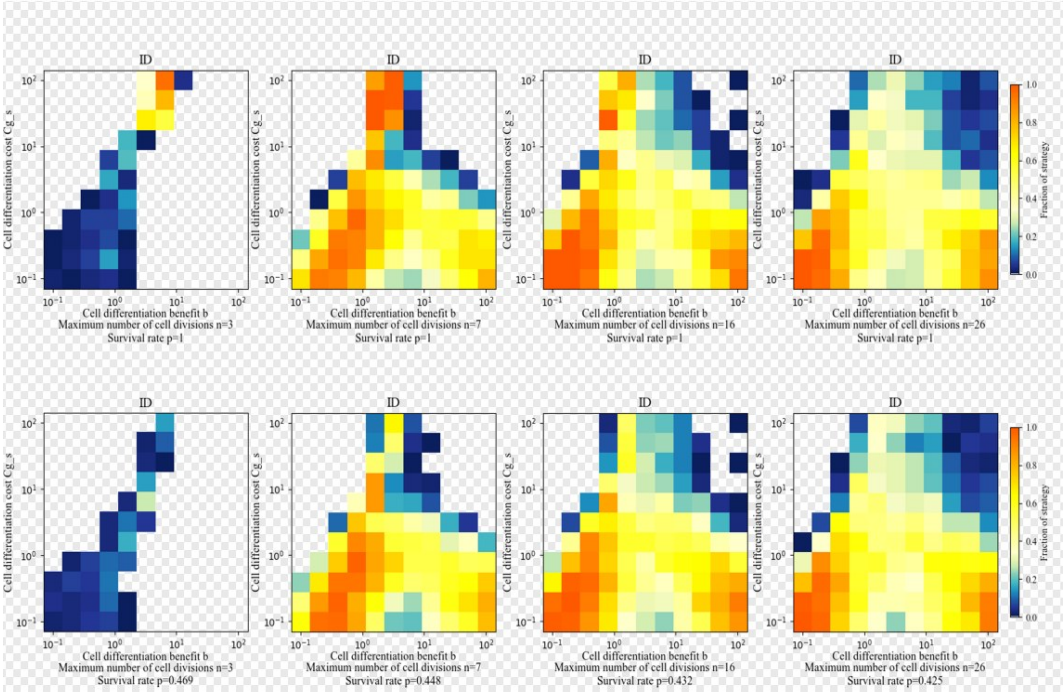

Figure 1 Map of Irreversible Cell Differentiation Strategies at Varying Survival Rates

When cell death is not considered and specific survival thresholds are set, the attractiveness of irreversible cell differentiation strategies increases with higher differentiation benefits. Larger individuals are more likely to adopt irreversible strategies at high differentiation efficiency for greater functional or survival advantages, but when differentiation income reaches a certain level, the marginal benefit of further increases diminishes, weakening the advantage of irreversible strategies and reducing their proportion.

5 Conclusion

In this paper, the growth and development model of multicellular organisms considering survival rate was constructed, and the optimal cell differentiation strategy under different average survival rate was determined by numerical simulation. The effect of survival rate on irreversible cell differentiation and evolution was discussed. Below the survival threshold, the proportion of irreversible cell differentiation decreases, suggesting that individuals are more likely to adopt other differentiation strategies. The introduction of survival factors has deepened the understanding of the relationship between cell differentiation and individual growth.

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