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A mathematical model of cell population dynamics with autophagy response to starvation ☆

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ABSTRACT

In this paper, we study the role of autophagy in yeast cell population dynamics in response to starvation by a mathematical model based on the logistic growth model. We analytically study the boundedness of solutions, and the existence and stability of equilibrium states under general biologically acceptable assumptions. Finally, we perform numerical studies for *Saccharomyces cerevisiae* response to starvation with autophagy. The results show that autophagy is valuable in maintaining cell population in starvation, and attenuating population fluctuations in response to perturbations in environmental nutrients. Furthermore, we show that proper level autophagy promotes cell survival through the inhibition of cell death by autophagy as well as the secretion of nutrients from autophagic cells, however excessive autophagy can decrease cell population due to autophagic cell death.

1. Introduction

The word *autophagy* was first introduced by de Duve in 1963 which means "self-eating" in Greek [1]. Biologically, autophagy is a highly conserved catabolic process in which cells *eat* their own cytoplasmic components to promote survival. During autophagy, cytoplasmic components including long lived proteins, cytoplasm and organelles are delivered to lysosome (vacuole in plants or yeasts) for degradation, and monomeric units (such as amino acids) from the degraded macromolecules are transported back to cytosol for reuse [1–3]. Autophagy is classified into three types according to the way of how cargo is transported to lysosome (or vacuole): macroautophagy, microautophagy and chaperone-mediated autophagy [2,4]. Among which macroautophagy that is characterized by double-membrane vesicular structures (autophagosomes) is the major type of autophagy [3]. Hereafter we always refer macroautophagy as autophagy [5,2,6]. Autophagy is maintained at a basal level in normal niche, and can be highly induced by starvation or other stresses in order to support metabolism and cell survival [2,3,6]. Autophagy is not only an important way of degradation for removing stable proteins, but also a powerful mechanism for stress response. Nevertheless, excessive autophagy can promote cell death that is called type II programmed cell death [7,8]. Autophagic dysfunctions associate with many diseases including neurodegradation, liver disease, heart disease, myopathies and various types of cancers [4,9,10]. Autophagy has been getting more and more attentions in recent years.

Autophagy is a way of cytoprotection during nutrient depletion by generating endogenous metabolites that are necessary to maintain cell viability [11], and thus plays important roles in maintaining cell population in many situations from mammalian tissue growth to cell culture. Autophagy is crucial for tumor growth. In the central part of a tumor, autophagy can result in adaptive response for cancer cells survival and tumor growth when energy limitation and insufficient blood-supply that fail to provide necessary metabolic resources for maintaining cell cycles [3]. Autophagy inhibition is known to be able to induce tumor cells death in mouse models [12]. In experiments, starvations of amino acids or nitrogen are often used to induce autophagy in mammalian or yeast cells [3]. Cells with normal autophagy show robust population maintenance during starvation, while impaired autophagy sensitizes cells to starvation-induced cell death and thus results in a population loss in culture cells [13,14].

It has been a long history for the study of cell population dynamics. Many models have been established and well studied to explain various cell growth curves under different conditions. Among these models, the logistic type models, first established by Verhulst in 1838 [15], is a basic paradigm in population ecology [16,17]. The logistic model is a reasonable approximation of growth behavior in many sit-

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uations and is qualitatively correct in that it captures the phenomenon of exponential growth at low population levels and saturation in the case of high population levels. Many biological systems, such as yeast growth, herding behavior of African elephants and population growth for Peruvian anchovies, can be well described by the logistic curve [18–20]. The classical logistic model has been widely developed and various form models were proposed, including the new model with low growth rate during a lag phase [21], the bi-logistic growth model for two phases growth cells [22], and diffusive model for species transportation [23], *etc*. However, to the best of our knowledge, the logistic type models are not developed to include cell autophagy response to nutrient limitation. In the starvation, cells undergoing autophagy can produce nutrient resources to supply the survival of other cells. Hence autophagy introduces a feedback to the nutrients supplement, and can add novel features to the logistic model.

In this paper, we consider a logistic type model including dynamic nutrients supplement and cell autophagy to study cell population dynamics in response to starvation. We analytically study the mathematical aspects of the model, including the boundedness of solutions, existence and stability of equilibrium states under biologically acceptable assumptions. Finally, we perform numerical simulations to examine the roles of autophagy and compare our results with experiments of *Saccharomyces cerevisiae* in starvation.

2. Model and assumptions

Fig. 1 illustrates the model of cell growth with nutrient delivery control and cell autophagy studied in this paper. Consider cells cultured in a container with fixed volume V (unit l). The cells are classified into normal phase (population x, cells/l) or autophagy phase (population y, cells/l). Normal phase cells can renew with a rate λ_1 (h^{-1}), and enter the autophagy phase with a rate k_1 (h^{-1}) in low nutrient level. The cells undergoing autophagy can get back to normal phase with a rate of k_2 (h^{-1}). Normal and autophagic cells are lost randomly (for example, through apoptosis or autophagic cell death) at a rate δ_1 and δ_2 (h^{-1}), respectively. Here we omit the proliferation of autophagic cells since growth arrest is often seen in cells undergoing autophagy [24,25]. Each cell consumes an amount k_3 (mM/(h × cell)) of nutrients per unit time. Meanwhile, each autophagic cell supplies nutrients (a_3, mM/(h × cell)) for cell consumption through the monomeric units generated by autophagy. The rates $\lambda_1, k_1, k_2, k_3, a_3$ are dependent on the average nutrients concentration per cell. Autophagy is known to affect cell death in a complicated way. Low level autophagy can promote cell survival, while excessive autophagy can induce type II programmed cell death [7]. For the simplicity, we assume that δ_2 depends on the ratio of autophagic cells. The nutrient solutions are pumped in and out with the same flux V_0 (l/h) so that the solution volume remains unchanged in our model.

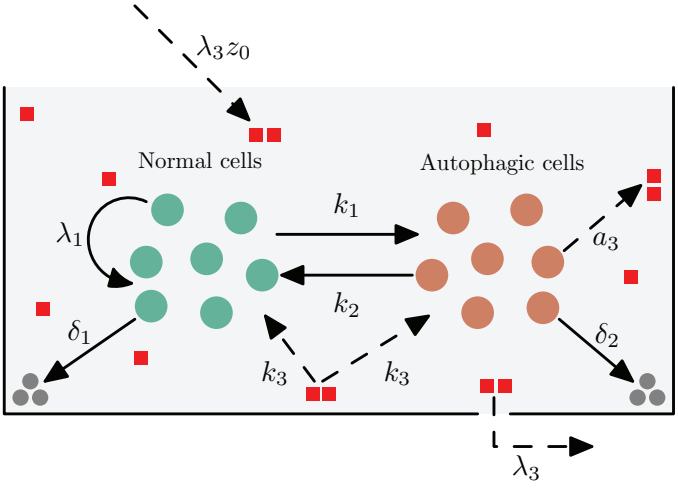

Fig. 1. Illustration of the cell culture model. Red squares represent nutrients, cyanic and brown circles represent normal and autophagic cells respectively. When the nutrient is sufficient, normal cells proliferate with intrinsic rate λ_1. Normal cells can turn into autophagic cells with a rate k_1 when nutrient is deficient. Autophagy is a reversible process so that autophagic cells can get back to their normal phase with a rate k_2 when the nutrient level restores. Normal and autophagic cells are removed randomly with rates δ_1 and δ_2, respectively. Dashed lines show nutrient fluxes. Nutrients are added and discharged respectively with rates $\lambda_3 z_0$ and λ_3. Each cell consumes nutrient in a rate k_3, and each autophagic cell produces nutrient in a net production rate of a_3 per unit time. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Letting z (mM/l) be the concentration of nutrients in the container, $z_0(t)$ (mM/l) the nutrient concentration in the input flux, $\lambda_3(t) = V_0(t)/V$ (h^{-1}) the rate of nutrient loss by the output flux (dilution rate), $r = y/(x+y)$ the ratio of autophagic cells in the whole population, and $w = z/(x+y)$ (mM/cell) the average nutrients per cell, the dynamics of cell populations and nutrient concentration can be modeled by the following modified logistic model equations

$$\begin{cases} \dfrac{dx}{dt} = \lambda_1(w)\left(1 - \dfrac{x+y}{M}\right)x - k_1(w)x + k_2(w)y - \delta_1 x \\ \dfrac{dy}{dt} = k_1(w)x - k_2(w)y - \delta_2(r)y \\ \dfrac{dz}{dt} = \lambda_3(t)(z_0(t) - z) - k_3(w)(x+y) + a_3(w)y \\ w = \dfrac{z}{x+y}, \quad r = \dfrac{y}{x+y}. \end{cases} \tag{1}$$

Here M gives the saturation level of the cell population and is assumed to be a constant (depending on the volume V). In Eq. (1), the time dependent concentration z_0 and flux λ_3 are used to represent the controls in nutrient delivery.

Biologically, all parameters are positive, and the rate functions $\lambda_1(w), k_1(w), k_2(w), k_3(w), a_3(w), \delta_2(r)$ are nonnegative and bounded for all $w \in \mathbb{R}^+$, $r \in [0, 1]$. We assume further that these functions are of first order derivable for the convenience of analysis below. Thus, we have the basic assumptions below:

(A0): **Basic assumptions**: The rate constants/functions satisfy

$$\delta_1, M > 0, \quad \lambda_3(t), z_0(t) \geq 0, \quad \forall t \tag{2}$$

and there exits $C < +\infty$ so that

$$\lambda_1(w), k_1(w), k_2(w), k_3(w), a_3(w) \in C^1(\mathbb{R}^+, [0, C]) \tag{3}$$

and

$$\delta_2(r) \in C^1([0, 1], (0, C]) \tag{4}$$

Additional we assume the following properties for the rate functions:

(A1): The renewal rate of normal cells increases with the average nutrient level. Moreover, the renewal rate is smaller than the apoptosis rate δ_1 in the absence of nutrient, and larger than δ_1 when the nutrient is sufficient. Mathematically we have

$$\lambda_1'(w) \geq 0 \tag{5}$$

and

$$\lambda_1(0) < \delta_1 < \lim_{w \to +\infty} \lambda_1(w). \tag{6}$$

(A2): The transition rate of cells from normal to autophagy phase decreases with the increasing of average nutrient level, and no cell will undergo autophagy when the nutrient is sufficient. Hence,

$$k_1'(w) \leq 0, \quad \lim_{w \to +\infty} k_1(w) = 0. \tag{7}$$

(A3): The transition rate of cells from autophagy to normal phase increases with the average nutrient level, *i.e.*,

$$k_2'(w) \geq 0. \tag{8}$$