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Short communication

Optimal design of cell culture chip on the basis of oxygen and glucose supply to cultivated cells in the chip

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Abstract

In this study, we discuss diffusion based oxygen and glucose supplies in cell culture chips of three different setups, where cells are regularly arranged and cultivated, using oxygen and glucose transport models on the basis of the previous work. In the first setup, oxygen is continuously supplied through a gas-permeable wall equipped with the chip, but glucose is supplied only at the start. In this case, the life span of the cultivated cells is governed by the balance between the initial amount and the consumption rate of glucose. Secondly, a setup, where oxygen and glucose are continuously supplied through a semi-permeable membrane, is discussed. In this case, oxygen supply is so critical that the membrane must be well designed. Finally, a setup with reserves for glucose supply, where oxygen is supplied through a gas-permeable wall, is discussed. In this case, we can find an optimal thickness of the medium filled in the cell culture chamber because an increase in the thickness is advantageous to glucose supply but is contrary disadvantageous to oxygen supply. In all cases, cautious design of a cell chip is needed, if the consumption rates of the cultivated cells for oxygen and glucose are higher than $10\,g\,m^{-3}\,s^{-1}$, which are very likely for hepatocytes.

Keywords: Transport model; Cell chip; Numerical simulation; Semi-permeable membrane; Hepatocytes; Hemispheroids

1. Introduction

Devices utilizing biological cells such as hybrid artificial organ and cell culture microchip have received much attention in the biomedical field. We need to optimally design such a device to cultivate the specific cells and maintain their function in it. We have assumed that the dominant factor to cultivate cells is oxygen supply to the cells and have presented a mathematical model to simulate the cell growth on a scaffold [1]. In the model, we have also assumed that oxygen transport occurs solely by diffusion in the organoids, which is a micro tissue formed by cells, and then have presented that the size of an organoid is limited by oxygen supply to the cultivated cells. This situation imposes severe restrictions on the system; necrosis due to oxygen deficiency occurs in the regions where the partial oxygen pressure is lower than a certain critical value. The maximum size of cylindroids (cylindrical organoids) estimated by the model coincides well with the experimental data presented in the previous literatures, showing the validity of the model.

Recently, cell microarray, where cells are regularly arranged and cultivated, is noticed as a novel tool for high-throughput diagnoses and pharmacological evaluation [2–7]. In these studies, cells were cultivated by immersing the cell microarray into the culture medium. On the other hand, the minute control of the cell culture microenvironment has been feasible in miniaturized devices using microfabrication technologies [8–10]. A closed cell culture microchip with a diffusion-based nutrition supply has been noticed because it enables the well-controlled culture microenvironment, such as gradient generation [11–13] and the cell culture at a low shear stress. The closed cell culture chip is also advantageous to prevent contamination and to be easily designed as to be disposable. However, Yu et al. have reported that the cell growth in a micro channel is worse than that in a flask [14], indicating the lacks in oxygen and/or nutrition supplies. In this study, we discuss an optimal design of a closed and independent cell culture chip with nutrition supply by diffusion. We discuss glucose transfer besides oxygen transfer in cell culture chips of three different setups, where cells are regularly

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Nomenclature

$C(0)$	the initial concentration of glucose in the medium ($g\,m^{-3}$)
C_c	the concentrations of the substance at the interface between the medium and apparent cell layer ($g\,m^{-3}$)
C_c^*	the critical value for C_c to maintain cell growth ($g\,m^{-3}$)
C_o	the concentrations of the substance at the outer surface of the wall or the membrane ($g\,m^{-3}$)
C_s	the concentration in the reservoirs ($g\,m^{-3}$)
C_w	the concentrations of the substance at the inner surface of the wall or the membrane ($g\,m^{-3}$)
D_m	the diffusion coefficient of the substance in the medium ($m^2\,s^{-1}$)
D_w	the diffusion coefficient of the substance in the wall or the membrane ($m^2\,s^{-1}$)
f	the ratio of the total volume of the cells in the cell culture chamber to the volume of the medium filled in the chamber
J	the flux of the substance (oxygen or glucose) ($g\,m^{-2}\,s^{-1}$)
k_w	the permeability of the wall or the membrane for the substance ($m\,s^{-1}$)
l	the lattice constant (the interval) of hemispheroids (hemispheric organoids) (m)
L	the length of the cell culture chamber (m)
m_c	the consumption rate of the substance coming from the metabolism of the cultivated cells per unit volume of the cultivated cells ($g\,m^{-3}\,s^{-1}$)
p_c	the partial pressure of the gas in the medium (mmHg)
p_c^*	the minimum for p_c to maintain cell growth (mmHg)
p_o	the partial pressure of the gas at the outer surface of the wall or the membrane (mmHg)
p_w	the partial pressure of the gas at the inner surface of the wall or the membrane (mmHg)
r	the radius of hemispheroids (hemispheric organoids) (m)
t_E	the life span of the cultivated cells (s)
x	the position along L (m)

Greek letters

α_m	the solubility of the gas in the medium ($g\,m^{-3}\,mmHg^{-1}$)
α_w	the solubility of the gas into the wall or the membrane ($g\,m^{-3}\,mmHg^{-1}$)
δ_c	the thickness of the apparent cell layer (m)
δ_m	the thickness of the medium filled in the cell culture chamber (m)
δ_w	the thickness of the wall or the membrane (m)

arranged and cultivated, and make some concrete proposals to optimally design the chip.

2. Formulation of models

The basic design of the cell culture chips discussed in this study is as follows: cells are cultivated on the bottom surface of the cell culture chamber equipped in the chip; the cell culture chamber is filled with a cell culture medium; the cell culture medium is stagnant to prevent the detachment of the cultivated cells.

If oxygen and nutrition are supplied to the chamber through a gas-permeable wall or a semi-permeable membrane equipped on the cell culture chamber, the flux of a substance transferred from the surface of the wall or the membrane to the chamber, J [$g\,m^{-2}\,s^{-1}$], in a steady state, is equal to the consumption rate of the substance caused by the metabolism of the cultivated cells as

$$J = \delta_c m_c \tag{1}$$

where m_c [$g\,m^{-3}\,s^{-1}$] denotes the consumption rate of the cultivated cells per unit volume of the cultivated cells and δ_c [m] is the thickness of the apparent cell layer, which can be defined as a uniform and even layer consisting of the cells cultivated in the cell culture chamber.

Here, the permeability of the wall or the membrane for the substance is k_w [m/s], and the thickness of the medium filled in the cell culture chamber and the diffusion coefficient of the substance in the medium are δ_m [m] and D_m [$m^2\,s^{-1}$], respectively. In a steady state, the following equations can be formulated as

$$J = k_w(C_o - C_w) = \frac{D_m}{\delta_m}(C_w - C_c) \tag{2}$$

where C_o [$g\,m^{-3}$], C_w [$g\,m^{-3}$] and C_c [$g\,m^{-3}$] denote the concentrations of the substance at the outer surface of the wall or the membrane, at the inner surface of the wall or the membrane and at the interface between the medium and the apparent cell layer, respectively. Eq. (2) gives the following equation,

$$J = \frac{(C_o - C_c)}{((\delta_m/D_m) + (1/k_w))}. \tag{3}$$

Combining Eq. (1) with Eq. (3), the following equation is obtainable:

$$C_c = C_o - \delta_c m_c \left(\frac{\delta_m}{D_m} + \frac{1}{k_w}\right). \tag{4}$$

For a gas dissolving in the medium and permeating through the membrane, Eq. (2) is transformed as

$$J = \frac{D_w \alpha_w}{\delta_w}(p_o - p_w) = \frac{D_m}{\delta_m}(C_w - C_c) \tag{5}$$

where p_o [mmHg] is the partial pressure of the gas at the outer surface of the wall or the membrane, p_w [mmHg] the partial pressure of the gas at the inner surface of the wall or the membrane, which is assumed to be equilibrated with the concentration, C_w, and α_w [$g\,m^{-3}\,mmHg^{-1}$] is the solubility of the gas into the wall or the membrane. Using the relations of $C_w = \alpha_m p_w$ and