【研究報告】

A Simple Model Calculation of Gas-Forming Bacteria Swarms in the Intestine

Norio TARAO

Department of Rehabilitation, Seirei Christopher University

ABSTRACT

A new mathematical model for chemotactically aggregating bacteria, which generate several aroma gases in an intestine with surrounding food, has been presented. This model makes it possible to simulate the destruction of bacteria caused by the lack of an attractant (feed), and our calculation has shown some of their traveling zones. The outbreak and the annihilation caused by the over aggregation and the proliferation are also calculated numerically as the result of this analysis. The interaction between the attractant and the bacteria is considered using successive approximation, as in our previous paper. This model calculation makes it possible to simulate some bowel obstructions (ileus) caused by gas-forming bacteria

Key word：Chemotaxis, Bacteria, Colony, Intestinal digestion, Ileus, Gas-Forming Bacteria

1. INTRODUCTION

Recently the problems of swallowing are getting healthcare professionals' attention in our aged society along with the use of QOLT (Quality of Life and Technology) for geriatric care; therefore gastroenterological science is becoming more and more important to senior care. Intestinal digestion is one of the most essential qualifications for healthy life, especially in aging people, however it sometimes happens that some symptoms of ileus caused by growing bacteria gas-formation disturb the transport system of the digested material in the intestine. At the very least, burnt cheese happens to damage the comfortable relationship among friends and hurts good QOL. These problems are seem to be caused by bowel gases with gas-forming bacteria, however their mechanism is not clear at this stage. In this article, we have restricted the gas forming process as follows[1)]: Indole $C_8H_7N\uparrow$ and 3-Methlindole $C_9H_9N\uparrow$ would be broken down by the following process. One of the amino-acid essential Tryptophan $C_{11}H_{12}N_2O_2$ makes 3-Indolepropionnic acid $C_{11}H_{11}NO_2\uparrow$ or Tryptamine $C_{10}H_{12}N_2\uparrow$ + carbon dioxide gas $CO_2\uparrow$. These chemical reactions are known to be activated by the catalyst activation of gas-forming bacteria. We have assumed the chemical reaction rates of gas generation are proportional to the products between "source material concentrations" and "number density of bacteria". On the other hand, the swarming process of gas-forming bacteria is very important to investigating the mechanism of dynamic movement of gases in the intestine. These processes have been investigated by a lot of authors theoretically since half a century ago: About 40 years ago, Keller and Segel[12)] proposed an analytical model of chemotaxis, which was used in the theoretical biology as the most popular model for chemical control of cell movement. On the other hand, since Nicholson[3)] proposed the first competition theory, many authors[4-6)] have indulged in the whimsy of calculating the population problem of insects or animals, in which the fluctuations of the insects' number between restricted limits are determined by the balance between that insects' capacity to increase and the environmental checks to this increase. In the light of the above two approaches, we made a theoretical model of the aggregation of microorganisms in our previous paper, concerning the growth of swarming bacteria toward scraps stuck in the gap between teeth and infections speck in other organs. The equation of the previous model has involved a consuming term and a proliferation term, and the results of the calculation have exhibited the empirical logistic curves to maximum colonies. However the consuming term and the proliferation term in it are so modest that neither outbreak nor annihilation could be seen in the previous calculation, for all that many of the published studies of predation concentrate on discrete parts of them. Therefore, we have used the more violent terms, so that they should induce some travelling zones of bacteria caused by the lack of a feed, in some cases of the larger mortality parameter. Using this term it might be possible to calculate the bubble size change by gas-forming bacteria in the inhomogeneous food in the intestine.

This paper is organized as follows. In section 2 we describe the mathematical model of our calculation, and in section 3 we show the method of the numerical calculation from the model. The result,

the discussion and concluding remarks follow in section 4.

2. The model

The geometry of the bacteria swarming model is spherical symmetric except for the formed gas distribution. The main assumptions of this calculation are as follows.

2.1 The Assumptions of the bacteria swarming model

We have assumed the following assumptions for this calculation.

(A) At the center of the model, a lump of an attractant having a rigid radius of "*a*" is fixed at a constant density. And, although the attractant diffuses into bacteria, the density of the central attractant does not change.

(B) Far from the central attractant, the number density of the bacteria is assumed to be a fixed value of n_0, and the density of the attractant there is also assumed to be a fixed value of C_B.

(C) At the beginning (t=0) the density of the bacteria everywhere around the central lump of the attractant is constant (the same number density of n_0 as the background density) and at the next moment a very thin membrane of the packed bacteria (the number density is n_{max}) is induced by the attractant containing the central sphere of the attractant.

(D) The maximum number density of the bacteria is a constant independently of the surrounding attractant concentration.

(E) The diffusive velocity of the attractant is assumed to be much faster than that of the bacteria, and the quasi-stationary diffusion of the attractant corresponding to "the almost static arrangement of bacteria" is assumed to be induced by the distribution of the bacteria. The process of this diffusion is assumed to obey the differential equation, which we show later.

(F) The movement of the bacteria is governed by the gradient of the attractant obeying the differential equation which will be shown later.

(G) The bacteria should be killed instantaneously by the lack of the feed (attractant) therefore we have used a modified step-function of n/c, thus the bacteria will be killed at a constant rate when "the ratio of the number density of the bacteria to the density of the attractant n/c " exceeds a value, and the bacteria will not be killed without the lack of the feed. The concrete consuming term of the bacteria will be described in the equation (9) later.

(H) The proliferation of the bacteria is described by the following equation.

(I) The incremental radius of the gas sphere produced by bacteria with food is proportional to the product cn in the vicinity of the attractant center.

(J) The effects of the yield stress of the surrounding fluid and the surface tension on the expansion of the generated gas bubble is negligibly small, therefore we have assumed the pressure in any bubble is the same as the circumjacent one.

Where $\varepsilon_1 n$ is a proliferation rate of the bacteria at very high density of the attractant (feed), and $\varepsilon_1 cn/\mu$ is a proliferation rate of the bacteria at very low density of the attractant; the rate is proportional to cn . This proliferation model was first introduced Sherrat[7], and the one used in this article is more sensitive to the density of the attractant than his.

2.2 The Boundary Conditions and the initial Conditions

From the above assumption, the boundary conditions and the initial conditions have been summarized by the following relations:

At the surface of the sphere of the lump of the

central attractant,

$r \geq a \cdots\cdots (1)$

$n = n_{\max}$ at $r = a$ .....(2)

$c = c_0$ at $r = a$ .....(3)

Far from the central attractant,

$n = \mathsf{n}_0$ at $r \to \infty$ .....(4-1),

$c = \mathsf{c}_\mathsf{B}$. at $r \to \infty$ ....(4-2).

At t=0 the density of bacteria around the attractant

$n = n_0$ at $r = 0$, and everywhere $r > a$ .....(5)

Considering the assumption of initial density distribution of the attractant, a step-function should be set for the starting density. However this function is extremely difficult for the numerical calculation, and moreover, the merit of introducing the step-function is very little (restricted at just after t =0). Therefore, we have assumed a more practical function, as follows;

$$c = \frac{a\ (c_0 - c_\mathsf{B})}{r} \exp\{-\varepsilon_3\ (r-a)\} + c_\mathsf{B} \cdots\cdots (6)$$

This function reduces exponentially to background density c_B far from the central attractant and behaves like the solution of an ordinary diffusing equation in the vicinity of the central attractant. Of course, this solution can not satisfy exactly the differential equation in the following subsection. The difference from the correct solution is very small, except for the initial moment.

2.3 The differential equations describing the number density of bacteria and the density of the attractant

According to Ford et al.[8],we use the following differential equations, which represent the number density of bacteria during the aggregation and the proliferation (destruction) very simply.

$$\frac{\partial n}{\partial t} = \frac{\partial}{\partial x}\left\{ D_\mathsf{n} \frac{\partial n}{\partial x} \right\} - \frac{\partial}{\partial x}(Vn) \cdots\cdots (7\text{-}1)$$

$$V = \chi \frac{\partial c}{\partial x} \cdots\cdots (7\text{-}2)$$

Where the first term of (7-1) represents the diffusion effect by the movement of the bacteria only, and the second term represents the flow induced by the gradient of the attractant (V is the local mean velocity of the bacteria induced by the gradient of the attractant).

The equation which represents the variation of the density of the attractant is

$$\frac{\partial c}{\partial t} = D_C \frac{\partial^2 c}{\partial x^2} - D_E\, n \cdots\cdots (8)$$

Where D_n, D_C are the coefficients corresponding to the diffusion coefficients of the bacteria and the attractant respectively, and D_E is the coefficient of the attractant consumption which is caused by the predation by the bacteria.

Modifying the equations (7) and (8) for a three dimensional spherical equation, using the distance from the center "r", we have the following equations. In the first equation, we have subtracted the consuming term, which makes the assumption (G) concrete, and we have added the proliferation term explained in the assumption (H).

$$\frac{\partial n}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2 \left\{ D_\mathsf{n}(c) \frac{\partial n}{\partial r} - \chi(c)\, n \frac{\partial c}{\partial r} \right\} \right] +$$

$$\varepsilon_1 \left(\frac{c}{\mu + c} \right) n - \frac{\mathsf{R}_\mathsf{E} n \left(1 - e^{-n/c\mathsf{R}} \right)}{1 + e^{-n/c\mathsf{R}}} \qquad \cdots\cdots (9)$$

$$\frac{\partial c}{\partial t} = D_\mathsf{C}(n) \frac{1}{r^2}\frac{\partial}{\partial r}\left\{ r^2 \frac{\partial c}{\partial r} \right\} - n D_E(c) \cdots\cdots (10).$$

Where the functional form of the above constants are as follows:

$$D_n(c) = 1 + 4c\,C_n \Big/ (c + C_n)^2 \quad \cdots\cdots (11),$$

$$\chi(c) = K_1 / c \quad \cdots\cdots (12),$$

$$D_C(n) = D_{c0} \Big/ (1 + \varepsilon_2 n) \quad \cdots\cdots (13),$$

$$D_E(c) = \Gamma c \Big/ (c + C_2) \quad \cdots\cdots (14),$$

and $D_n(c)$ in equation (l1) was first introduced by Lapidus[16] experimentally.

3. Numerical Calculation

For a practical calculation of the above equations we have used the following successive approximation; using the assumption (E) we have transformed Eq. (10) under the boundary condition (4-2), and have used the following equation (the second term in the right side of equation (10) can be assumed to be zero).

$$c = \frac{ac_0}{r} - \frac{1}{r}\int_a^r r'^2 \rho(r')\,dr' + \int_a^r r'\rho(r')\,dr' + c_B \quad \text{.....(15),}$$

where is the distribution of the bacteria and is represented as;

$$\rho(r') = \frac{n(r')(1+\varepsilon_2 n)\Gamma c(r')}{Dc\{c(r') + C_2\}} \quad \text{.....(16).}$$

Namely, the number density of the bacteria changes corresponding to the density of the attractant, however we fixed the number density of the bacteria for the moment and calculated the density of the attractant from Eq.(15) and Eq.(16) at the individual moment (we have calculated the distribution function of the bacteria $p(r')$ from the number density of the bacteria at that moment from Eq. (l6), using the density of the attractant at the preceding moment, and using this $p(r')$ we have calculated the density of the attractant from Eq. (15), and then we have calculated again the distribution of the bacteria $p(r')$ from this density of attractant, and we have repeated these process). These processes were repeated until the self-consistent stationary state of the density of the attractant was attained.

Then the number density at the next moment was calculated from the final density distribution of the attractant at that moment using Eq.(9). Throughout this paper we have used the physical value in c.g.s. Units according the paper by Ford et al.[8] in the practical calculation as follows.

Table 1.

Symbol	Physical Value	Unit
n_0	5.0×10^{6}	cell/cm^3
n_{max}	1.0×10^{11}	cell/cm^3
c_0	1.0×10^{-7}	mol/cm^3 (mM)
c_B	1.0×10^{-11}	mol/cm^3 (mM)
C_2	2.0×10^{-7}	mol/cm^3 (mM)
C_n	1.0×10^{-7}	mol/cm^3 (mM)
ε_1	0.8	cm^3/ mol
ε_2	1.0×10^{-9}	cm^3/ mol
ε_3	1.0×10^{-5}	cm^3/ mol
D_{c0}	3.0×10^{-5}	cm^2/s
a	1.0×10^{-2}	cm
Γ	1.0×10^{-18},1.0×10^{-22}	mol/(cell･s)
K_1	5.0×10^{6}	cm^2/s
R	5.0×10^{6}	non
R_E	5.0×10^{6}	non

Where R_E is the mortality rate of bacteria in the moment when lack of the feed is extreme, and we used R to represent the sensitivity of the consuming function of the bacteria [$R=1/(n_0 c_B)$ for the background].

4. Results and Discussion

We show the growth of the packed area of the bacteria and the travelling zones of the desk-don and the outbreak in Fig'1-Fig.4. From these figures, we can see that the number density of bacteria at a certain place decays exponentially according to the distance from the central attractant.

In case where the mortality parameter R_E is larger than 0.2, there exist some empty zones of the bacteria. This mechanism is a little different between two types of predation; the types of predation of Fig-1 and Fig.2-Fig.4 are different. This means that consuming the feed by bacteria contributes to the destruction of the bacteria in relation to their mortality. The consuming speed of the type in Eq. (14) is faster than that of Lapidus[16] in the case of starvation. The predation function represented in Eq.(14) is named Ho1lings Type-I function[9]. Although this analysis itself cannot be useful for medical treatment, we can apply this modeling to some other problems; we will show a few examples:

1. The population problem of epidemics can be analyzed replacing immunity with predation.

2. The war problem between macrophage and bacteria.

3. Analysis of the growth of tumor cell population or that of swarming bacteria.[10)-18)]

4. The model studies of acute leukemia chemotherapy.[19)-23)]

An important aspect of our current and future studies is the investigation of the real behavior of these microorganisms or infected people, therefore we should analyze the above mentioned mechanisms.

Using these data of swarming bacteria and the condensation of the attractant, we have calculated the buoyant velocity of the spherical gas bubble

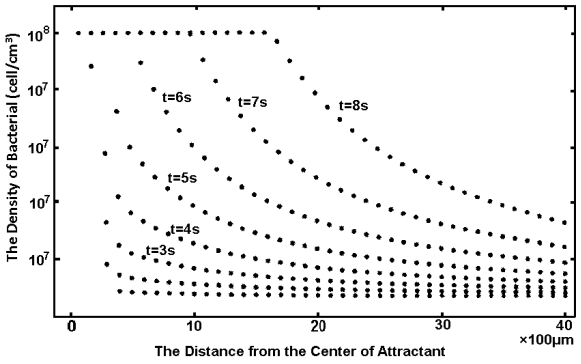

Fig.1 The Density Distribution of the Bacteria on the Radial Coordinate from Centre.

The radius of the packed bacteria region in the vicinity of the central core is expanding in the course of time. (5s~8s) (In the case of $\Gamma=10^{-18}$ [mol/(cell･s)])

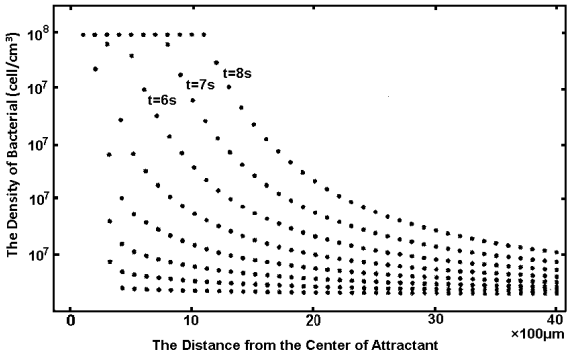

Fig.2 The Density Distribution of the Bacteria on the Radial Coordinate from Centre.

The radius of the packed bacteria region in the vicinity of the central core is expanding in the course of time. (6s~8s) (In the case of $\Gamma=10^{-22}$ [mol/(cell･s)])

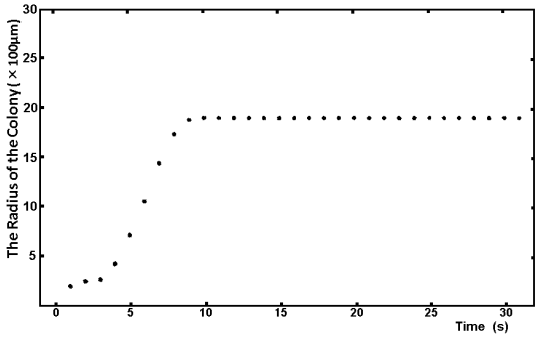

Fig.3 The Radial Growth of the Bacteria Core region at the Central Attractant.

The radius of the packed bacteria region in the vicinity of the central core is expanding in the course of time. (In the case of $\Gamma=10^{-18}$ [mol/(cell･s)], $1\times10^{8}> n >3\times10^{7}$ cell/cm^3)

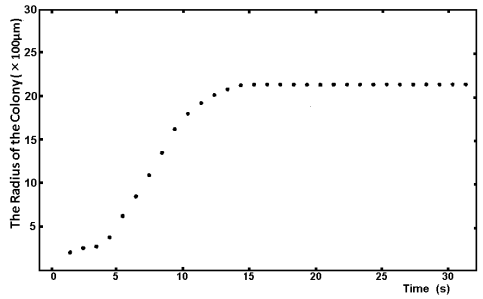

Fig.4 The Radial Growth of the Bacteria Core region at the Central Attractant.

The radius of the packed bacteria region in the vicinity of the central core is expanding
in the course of time. (In the case of $\Gamma=10^{-22}$ [mol/(cell･s)], $1\times10^{8}> n >3\times10^{7}$ cell/cm^3)

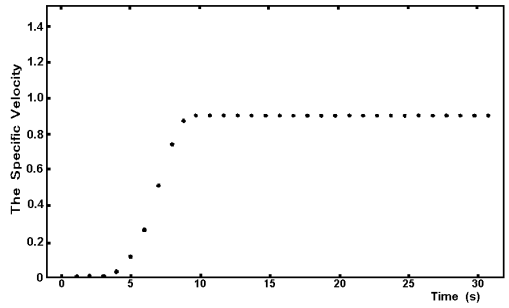

Fig.5 The Time-Dependence of the buoyant Velocity of the Gas Bubble.

The velocity becomes constant at about 9s when the bubble is getting at the no-growing area with tenuous bacteria. (In the case of $\Gamma=10^{-18}$ [mol/(cell･s)], The medium viscosity 0.01 Pa･s, $1\times10^{8}> n >3\times10^{7}$ cell/cm^3)

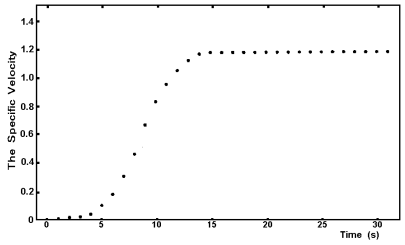

Fig.6 The Time-Dependence of the buoyant Velocity of the Gas Bubble.

The velocity becomes constant at about 12s when the bubble is getting at the no-growing area with tenuous bacteria. (In the case of $\Gamma=10^{-22}$ [mol/(cell･s)], The medium viscosity 0.01 Pa･s, $1\times10^{8}> n >3\times10^{7}$ cell/cm^3)

through the surrounding food in the vicinity of the central core region: The quasi-stationary buoyant velocity can be calculated using Hadamard's Formula for liquid droplets[27]. The practical absorption of the bubble strongly depends on the yield stress and the surface tension of the surrounding liquid (food in this calculation), therefore we cannot estimate whether the ileus condition is attained with this calculation. However we can estimate the interval period for the position change of the body to prevent ileus; the interval should be shorter than the amount of time for bubbles to cross the inner radius of the intestine in these conditions.

5. Concluding Remarks

Using a new mathematical model for chemotactically aggregating bacteria, we have calculated the buoyant velocities of bubbles produced by bacteria in the intestine. This swarming model has a new consuming term, which kills the bacteria instantaneously by the lack of feed, besides simplifying the physical condition of the surrounding food around the bacteria. We have also estimated the generated gas size, assuming the chemical reaction rates of gas generation are proportional to the products between the source material condensations and the swarming bacteria number density. In this calculation we have used a modified step-functional term which reveals some traveling zones of the annihilation of the bacteria, as many authors investigated[24)-26)] the traveling bands of chemotactic bacteria, whereas the zones break out in our cases of the large mortality parameter in the new term. The buoyant velocities introduced in this calculation make it possible to estimate the position change interval period and would be useful to prevent the ileus in the intestine.

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腸内バクテリア集合によるガス発生の簡単なモデル計算

多羅尾範郎

聖隷クリストファー大学　リハビリテーション学部

要　旨

腸内の食物中の誘引物質に群がるバクテリアの挙動を擬似実験する新しい走化性数学的モデルで、発生ガスの成長と浮上速度を計算した。この計算は、ガスによる腸閉塞を防止するための体位変換の時間間隔を見積もるのに役立つと期待される。