A MODEL FOR STREP THROAT INFECTION: DYNAMICS OF CONTINGENCY GENE SELECTION IN AN INFECTED HOST

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To Tong, Tyler and my parents

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CHAPTER I

INTRODUCTION

Streptococcus pyogenes is a highly prevalent bacterial pathogen throughout the world. It often causes infection of the throat in hosts that leads to pharyngitis ("strep" throat) [5, 30]. School-aged children are the most affected. Signs and symptoms usually occur within several days of exposure. They include fever, sore throat, a swollen tender neck and swollen tonsils. Some people with strep throat may develop a rash called scarlet fever. If some patients with strep throat are untreated, these infections may result in serious kidney complications and heart disease [35, 23, 36]. The tissues in the throat constitute the primary habitat for *S. pyogenes*, where it is successful in reproductive growth and transmission of progeny to new hosts [1, 13].

Bacteria have the reputation of being primitive, unsophisticated types. But "this microscopic menagerie of organisms has the uncanny ability to rapidly adapt to vastly different environments and evade host immune systems" [33]. While random mutation has been thought to explain this ability, Richard Moxon, of Oxford University, believes that bacteria have a more resourceful and quicker system. He has identified a set of contingency genes, which contain a region with a higher rate of mutation than other areas of the genome with much lower mutation rates (so-called "housekeeping" genes) [24, 20]. Each gene can be turned on or off, and the switching mechanism is random mutation within the switch region. Each time a bacterium divides, one mutation within a switched-on genes' switch region might turn the gene sequence to inactivity, effectively turning the gene off. On the other hand, a mutation in a switched-off genes' switch region might switch back on and restore that gene's activity [2, 3].

Contingency genes provide an intriguing potential explanation of why a population of bacteria can rapidly adapt to the hosts. According to Moxon's hypothesis, random flipping genes on and off creates unique genotypic combinations in the rapidly reproducing population [1, 37, 32, 22]. Biologists have explored the idea that contingency genes play an important role in adaptation to the hosts by emergence of populations of genotypic

variations. Therefore, we wish to set up a mathematical model that can describe populations of genotypic combinations with binary switches in contingency genes. This model can be directly applied to strep throat infection.

Based on the hypothesis of contingency genes, we construct a model for strep throat infection to compute the bacterial populations of genotype combinations in an infected host. The model consists of a system of 2^n nonlinear ordinary differential equations, one for each genotype class, where n is the number of contingency genes. After the ODE model has been introduced in Chapter II, we perform some theoretical analysis for the steady state and the solutions of the model in Chapter III. We will prove that the solution to the model is unique and there is an exponentially asymptotically stable equilibrium solution. In Chapter IV, we also perform numerical analysis for the model. The graphs for the bacterial population are obtained for up to 10 contingency genes and involve the large-scale computation of the differential equations system. All these graphs show how the bacterial population evolves from the initial state with all turned-off genes to a state with all turned-on genes. Simulations are performed to investigate how the domination of the class with all turned-on genes is affected by the mutation frequency, the selection rates, the number of contingency genes and the carrying capacity of the population. In order to do numerical simulations for higher than 10 contingency genes, a modified model is constructed in Chapter V. The modified model only consists of $n + 1$ nonlinear ordinary differential equations, which is greatly reduced compared to the model in Chapter II. By using the modified model, we can compute the bacterial population of combinations with more than one hundred contingency genes. We prove the consistency of the solutions of the first model and the modified one. Also, the asymptotic behavior of the first model and the modified one is the same under the conditions for the mutation frequency and selection rates. We perform some simulations to investigate consistency of the time to domination by the switched-on genotypes with observed mutation frequencies and selection rates. Assuming that different genotypes have different carrying capacities, we introduce carrying capacity coefficients to the first model and the modified one. The results from analysis of the models demonstrate the ability of the bacterial population to adapt to the host within a realistically observed time frame of 3-6 days [11].

CHAPTER II

CONSTRUCTION OF THE MODEL

II.1 Background of Contingency Genes

"All organisms are faced with the perpetual challenge of maintaining their fitness in diverse and changing environments. To meet this challenge, populations of organisms must possess mechanisms and strategies for responding to changes in their environments. These include phenotypic acclimation, by which an individual organism modifies some aspect of its behavior, morphology or metabolism in response to environmental change, and genetic adaptation, whereby the genetic composition of a population may change as a result of natural selection" [24].

Natural selection has produced genetic mechanisms that facilitate acclimation to a wide variety of environments [31]. Provided that environmental factors (such as nutrients, temperature, acidity) remain within certain limits, then changes in external environment may be accomodated by regulation of gene expression. However, given the diversity and unpredictability of environmental changes, these stereotypic responses are unlikely to contribute more than one limited subset of the phenotypic state necessary for long-term evolutionary success [15]. Confronted with a persisting unfavorable environment in which classical regulation of gene expression cannot provide an adequate response, a population of bacteria may face extinction unless it can adapt genetically by natural selection [8, 13].

"Pathogenic bacteria face especially stringent tests of their adaptive potential, due to the characteristic diversity nature and polymorphic nature of their hosts' immune responses" [24]. Given their relatively large population sizes and short generation times, pathogenic bacteria would seem to have considerable advantages over their hosts in adaptability and evolutionary flexibility [15, 39].

In 1994, the article [24] reviewed evidence indicating that "pathogenic bacteria have evolved mechanisms for increasing the frequency of random variations in those genes that are involved in critical interactions with their hosts". Having elevated mutation rates in a specific subset of genes may be highly advantageous, allowing certain phenotypic traits to

respond rapidly, by natural selection, to unpredictable changes in the environment. Such genes have been termed contingency genes by Moxon [17].

Contingency genes provide an explanation of why a population of bacteria can rapidly adapt to the host. They contain a region with a higher rate of mutation than other areas of the genome [21]. Each gene can switch on or off. Contingency genes enable at least a few bacteria in a given population to adapt to new environments. The variety of traits encoded by contingency genes includes "those governing recognition by the immune system, general mobility, movement toward chemical cues, attachment to and invasion of host cells, acquisition of nutrients and sensitivity to antibiotics" [2]. Contingency genes make up a very small fraction of a bacterium's DNA, but they can provide a vast amount of flexibility in functioning [24]. Moxon says that contingency genes function like a library of thousands to millions of genotype variants [9]. With one of these genes, the bacterium has two variations. Two genes provide four alternations. If only 10 of the 2000 genes in typical bacterium were contingency genes, for instance, the bacterium would be able to display 2^{10} different combinations of turned on and off genes. Such diversity ensures that at least one bacterium in a population can survive its host's immune defenses and then can replicate to produce a new, thriving colony [33, 5, 39].

We want to explore contingency gene selection in pathogen adaptation to human hosts. A model is developed that allows stochastic on/off switches of contingency genes and consequent selection of advantaged phenotypes.

II.2 Introduction of the Model

The objective of the model is to investigate contingency genes' adaptation to infected hosts. We want the model to be directly applicable to strep throat infection. Strep throat is very contagious. An effort should be made to avoid contact with infected people, since there is no single way to avoid the infection otherwise [11, 30]. The model explains clustering of strep throat cases in families, since genetic similarities of siblings allow more rapid adaptation to hosts.

Contingency genes can be switched on or off. We denote a turned-off contingency gene to be '0', and a turned-on contingency gene to be '1'. Random mutation provides a background

source of the contingency gene combinations. If we consider two contingency genes, there are four genotypic combinations (0,0), (1,0), (0,1) and (1,1). In order to get all genotypes with three contingency genes, we only need to consider that one more contingency gene is added to four genotypic variations with two contingency genes. The added contingency gene has on or off possibilities. These two possibilities are considered in those four variations, then we can get eight variations. The following diagram interprets how to get eight genotype classes with three contingency genes from four genotype classes with two contingency genes.

$$\begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ 1 & 1 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \Rightarrow \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 1 & 1 & 0 \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ 1 & 1 \end{bmatrix} + \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \Rightarrow \begin{bmatrix} 0 & 0 & 1 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix}$$

Figure 1: $2^3 = 8$ combinations with three contingency genes.

More generally, we can get 2^n genotype classes with n contingency genes from all 2^{n-1} combinations with $n-1$ contingency genes.

To explore dynamics of genotype selection in infected hosts, we consider mutation and selection processes of streptococcal bacteria.

In the mutation process, we introduce the mutation frequency denoted by f, which is the probability for one contingency gene to be switched from on to off or from off to on. During each division of an individual cell, any contingency gene can be switched from on to off or from off to on. Suppose that a bacterium in class (0,1,1) mutates to (0,0,1), the probability of this mutation process is $(1-f)f(1-f)$, where the first and third genes do not change and the second gene is switched from on to off.

In the selection process, each genotype class has its selection coefficient. We assume that the selection coefficient of the class with all host-specific genes turned on is bigger than the other selection coefficients because this class is necessary for the bacterial population to cause the inflammation that propagates the infection and gives it a selective advantage.

The bacterial population cannot increase forever since the population has a limited carrying capacity shared by all the strains in a host. We incorporate this constraint on the bacterial population growth as a nonlinearity in the equation for each genotype [28].

II.3 Ordinary Differential Equations

Before we state the model, Table 1 shows all terms in use.

Table 1: Variables, Parameters and Functions

Term	**Description**
C	carrying capacity parameter
t	time in hours
$\vec{P}(t)$	the bacterial population densities of genotypes as a 2^n-dimensional vector
$\lvert\vec{P}(t)\rvert$	the summation of the bacterial population densities of genotypes
$\vec{P}_0$	the initial condition at time 0
f	the mutation frequency
A	a $2^n \times 2^n$ Markov matrix of the mutation frequencies
S	a $2^n \times 2^n$ diagonal matrix with selection coefficients on its diagonal entries

An ordinary differential equations model is constructed to compute the bacterial population in an infected host. The model is shown as follows:

$$\frac{d\vec{P}(t)}{dt} = A \cdot \vec{P}(t) + S \cdot \vec{P}(t) - \frac{|\vec{P}(t)|}{C}\vec{P}(t), \quad t \geq 0, \quad \vec{P}(0) = \vec{P}_0.$$

To explain this ODE model more clearly, we consider the case of three contingency genes. Any contingency gene has the ability to be turned from off to on or from on to off by a mutation process. For convenience, a turned-off contingency gene is denoted by '0' and a turned-on contingency gene is denoted by '1'. Suppose that initially, the contingency genes in all cells are all turned off. The population density of cells with three contingency genes at time t is denoted by $P(t, 0, 0, 0)$. In general, the population density of the genotype class (i, j, k) at time t is denoted by $P(t, i, j, k)$, where i, j, k is either 0 or 1. For three contingency

genes, the bacterial population densities of 2^3 genotypic combinations are shown as follows:

$$\vec{P}(t) = \begin{bmatrix} P(t,0,0,0) \\ P(t,1,0,0) \\ P(t,0,1,0) \\ P(t,1,1,0) \\ P(t,0,0,1) \\ P(t,1,0,1) \\ P(t,0,1,1) \\ P(t,1,1,1) \end{bmatrix}.$$

From the above, every entry in $\vec{P}(t)$ represents the bacterial population density of one genotype class. Let $|\vec{P}(t)|$ be the summation of the population densities of every combination at time t, *i.e.* $|\vec{P}(t)| = \sum_{i,j,k=0}^{1} P(t,i,j,k)$. For the general case of n contingency genes, $\vec{P}(t)$ is defined analogously.

In this model, mutation and selection processes are both included with the constraint on population growth due to a limited carrying capacity. Firstly, the mutation process is considered. The mutation process is described by a Markov matrix A (at this moment ignoring the selection process and the constraint on population growth):

$$\frac{d\vec{P}(t)}{dt} = A \cdot \vec{P}(t),$$

where the Markov matrix A for three contingency genes is

$$\begin{bmatrix} (1-f)^3 & (1-f)^2 f & (1-f)^2 f & (1-f)f^2 & (1-f)^2 f & (1-f)f^2 & (1-f)f^2 & f^3 \\ (1-f)^2 f & (1-f)^3 & (1-f)f^2 & (1-f)^2 f & (1-f)f^2 & (1-f)^2 f & f^3 & (1-f)f^2 \\ (1-f)^2 f & (1-f)f^2 & (1-f)^3 & (1-f)^2 f & (1-f)f^2 & f^3 & (1-f)^2 f & (1-f)f^2 \\ (1-f)f^2 & (1-f)^2 f & (1-f)^2 f & (1-f)^3 & f^3 & (1-f)f^2 & (1-f)f^2 & (1-f)^2 f \\ (1-f)^2 f & (1-f)f^2 & (1-f)f^2 & f^3 & (1-f)^3 & (1-f)^2 f & (1-f)^2 f & (1-f)f^2 \\ (1-f)f^2 & (1-f)^2 f & f^3 & (1-f)f^2 & (1-f)^2 f & (1-f)^3 & (1-f)f^2 & (1-f)^2 f \\ (1-f)f^2 & f^3 & (1-f)^2 f & (1-f)f^2 & (1-f)^2 f & (1-f)f^2 & (1-f)^3 & (1-f)^2 f \\ f^3 & (1-f)f^2 & (1-f)f^2 & (1-f)^2 f & (1-f)f^2 & (1-f)^2 f & (1-f)^2 f & (1-f)^3 \end{bmatrix}.$$

The $2^n \times 2^n$ markov matrix A for n contingency genes is defined analogously.

Consider the first component $P(t,0,0,0)$ at time t :

$$\frac{dP(t,0,0,0)}{dt} = (1-f)^3 \cdot P(t,0,0,0) + (1-f)^2 f \cdot P(t,1,0,0) + (1-f)^2 f \cdot P(t,0,1,0) + (1-f) f^2 \cdot P(t,1,1,0)$$
$$+ (1-f)^2 f \cdot P(t,0,0,1) + (1-f) f^2 \cdot P(t,1,0,1) + (1-f) f^2 \cdot P(t,0,1,1) + f^3 \cdot P(t,1,1,1).$$

It can be seen that the growth rate of the population density of every combination at time t is the summation of the product of the population density of every combination at time t and the probability of the corresponding mutation process.

Secondly, the selection process is considered without the mutation process and the constraint on population growth. In the selection process, the form of the selection matrix S for the populations of genotypic combinations at time t is assumed to be diagonal. For the selection process without the mutation process and the constraint on population growth, the growth rate of the population at time t can be expressed as follows:

$$\frac{d\vec{P}(t)}{dt} = S \cdot \vec{P}(t),$$

where S is a matrix with the selection coefficients. For three contingency genes, S has the following form:

$$S = \begin{bmatrix} s_1 & 0 & \dots & 0 \\ 0 & s_2 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & s_8 \end{bmatrix}.$$

The $2^n \times 2^n$ diagonal matrix S for n contingency genes is defined analogously.

A combination of all turned-on contingency genes is necessary for the bacterial population to adapt to the host and it has a selective advantage. Thus, the selection coefficient for the combination of all turned-on genes is bigger than the other selection coefficients. In the matrix S for three contingency genes, we can, for example, choose $s_1 = s_2 = \ldots = s_7 < s_8$. From the diagonal matrix S and the differential equation for the selection process, the

growth rate of the population of the first combination at time t is shown as follows:

$$\frac{dP(t,0,0,0)}{dt} = s_1 \cdot P(t,0,0,0).$$

The growth rate of the population of every combination at time t is linearly dependent on the population of the corresponding combination at time t. Thus the selection in the ith combination depends on a selection coefficient s_i particular to that combination.

The bacterial population cannot grow exponentially forever in an infected host, because the host has a limited carrying capacity for the population of bacteria. Thus, the constraint on population growth also needs to be considered in this model. The form of the constraint on population growth is the nonlinear term $-\frac{|\vec{P}(t)|}{C} \cdot \vec{P}(t)$, which means that mortality increases as the total population $|\vec{P}(t)|$ increases. The effect of the logistic nonlinearity is to cause the population to stabilize to a unique globally attracting equilibrium, which is dependent on the carrying capacity parameter C.

From the special case of three contingency genes, we can draw similar interpretations for n contingency genes. $\vec{P}(t)$ has 2^n entries which correspond to the population densities of the 2^n genotypes at time t. A is a $2^n \times 2^n$ Markov matrix whose entries correspond to the mutation frequencies of on/off switching. S is a $2^n \times 2^n$ diagonal matrix whose entries correspond to genotype selection. The growth rate of $\vec{P}(t)$ involves the combined effects of the three separate processes: mutation, selection and logistic constraint. If the mutation frequency f is very small, then $A\vec{P}(t) \approx \vec{P}(t)$, and if the total population $|\vec{P}(t)|$ is near the carrying capacity C, then the logistic nonlinearity $\frac{-|\vec{P}(t)|}{C}\vec{P}(t) \approx -\vec{P}(t)$. These two processes thus balance each other in the differential equation for $\vec{P}(t)$, and $\vec{P}(t) \approx e^{tS}\vec{P}_0$. Thus, the doubling time of the ith contingency gene class is approximately $\dfrac{\ln 2}{s_i}$.

CHAPTER III

STEADY STATE AND SOLUTION

III.1 Steady State

The ODE model has been constructed to compute the bacterial population densities with n contingency genes in an infected host and it is shown as follows:

$$\frac{d\vec{P}(t)}{dt} = A \cdot \vec{P}(t) + S \cdot \vec{P}(t) - \frac{|\vec{P}(t)|}{C} \cdot \vec{P}(t), \qquad t \geq 0, \qquad \vec{P}(0) = \vec{P}_0 \in R_+^{2^n} \backslash \{0\}, \qquad (1)$$

where A is a $2^n \times 2^n$ Markov matrix, C is a carrying capacity parameter specific to the host, $\vec{P}_0$ is the initial population vector, $\vec{P}(t) \in R_+^{2^n}$, and S is a $2^n \times 2^n$ diagonal matrix as follows:

$$S = \begin{bmatrix} s_1 & 0 & \dots & 0 \\ 0 & s_2 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & s_{2^n} \end{bmatrix}.$$

Definition 1. *The notation $|\cdot|$ means $|\vec{x}| = \sum_{i=1}^{n} x_i$ for any $\vec{x} \in R^n$.*

Definition 2. *A square matrix is defined as a Markov matrix if every entry is a positive number, the sum of the entries in any row is equal to 1 and the sum of the entries in any column is also equal to 1 [18].*

Definition 3. *A steady state (equilibrium) of (1) is a vector $\vec{x}_0 \in R^{2^n}$ such that $A\vec{x}_0 + S\vec{x}_0 = \frac{|\vec{x}_0|}{C}\vec{x}_0$.*

Theorem 1. *Let A be a Markov matrix, let S be a diagonal matrix with all positive entries on the diagonal, and let $C > 0$. If $\lambda > 0$ is an eigenvalue of $M = C(A + S)$, then $\vec{x}$ is a steady state of (1), where $M\vec{x} = \lambda\vec{x}$ and $|\vec{x}| = \lambda$.*

Proof. If λ is an eigenvalue of M, there exists an eigenvector $\vec{x}_0$ such that $M\vec{x}_0 = \lambda\vec{x}_0$.

Assume that $|\vec{x}_0| = 1$, take $t = \lambda$, and let $\vec{u} = t\vec{x}_0$, it follows that

$$M\vec{u} = M \cdot t\vec{x}_0 = \lambda \cdot \lambda\vec{x}_0 = \lambda \cdot \vec{u}$$

Obviously, $\vec{u}$ is an eigenvector of M and $|\vec{u}| = \lambda$ and we obtain

$$\begin{aligned} M\vec{u} &= \lambda\vec{u} \\ C(A+S)\cdot\vec{u} &= \lambda\vec{u} \\ (A+S)\cdot\vec{u} &= \frac{\lambda}{C}\vec{u} \\ A\cdot\vec{u} + S\cdot\vec{u} &= \frac{|\vec{u}|}{C}\vec{u} \end{aligned}$$

Hence, it follows that $\vec{u}$ is a steady state of (1) and $M\vec{u} = \lambda\vec{u}$ with $\lambda = |\vec{u}|$. □

III.2 An Abstract Logistic Equation

First, we investigate the stability of equilibrium solutions to an abstract logistic equation in a Banach space. The formulation of the abstract problem allows an application to the ODE model we construct. Let X be a Banach space lattice with norm $\|\cdot\|$ and let X_+ denote the cone of nonnegative elements of X [40]. We require the following hypotheses:

(H.1) $T(t)$, $t \geq 0$ is a strongly continuous semigroup of bounded linear operators on X with infinitesimal generator A and $T(t)x \in X_+$ for $x \in X_+$.

(H.2) There exist a real number λ_0 and a direct sum decomposition $X = X_0 \oplus X_1$ with associated projections P_i, $P_iX = X_i$, $i = 0, 1$, such that $P_iT(t) = T(t)P_i$, $i = 0, 1$, $T(t)P_0 = e^{\lambda_0 t} \cdot P_0, t \geq 0$, and for some constants $M \geq 1$, $\omega < \lambda_0$, $|T(t)P_1| \leq Me^{\omega t}|P_1|, t \geq 0$.

(H.3) $\mathcal{F}$ is a bounded linear functional on X such that $\mathcal{F}x > 0$ for $x \in X_+\backslash\{0\}$.

(H.4) η is a continuous increasing function from $[0, \infty)$ onto $[0, \infty)$.

Consider the abstract logistic equation

$$w'(t) = Aw(t) - \eta(\mathcal{F}w(t))w(t), \quad t \geq 0, \quad w(0) = x. \tag{2}$$

The proof of the following theorem is given in [38], but for the sake of completeness we provide a proof.

Theorem 2. *Let (H.1)-(H.4) hold and let $x \in X_+ \cap D(A)$ such that $P_0x \in X_+\backslash\{0\}$. There exists a unique continuously differentiable function $w : [0,\infty) \to X_+\backslash\{0\}$ such that w satisfies the equation (2). If $\lambda_0 < 0$, then $\lim_{t\to\infty} w(t) = 0$, and if $\lambda_0 \geq 0$, then $\lim_{t\to\infty} w(t) = \dfrac{\eta^{-1}(\lambda_0)P_0x}{\mathcal{F}P_0x}$.*

Proof. We first claim:

(i) $T(t)x \in X_+\backslash\{0\}$ and $\mathcal{F}(T(t)x) > 0$ for $t \geq 0$.

If $T(t_1)x = 0$ for some t_1, then $0 = P_0T(t_1)x = e^{\lambda_0 t_1}P_0x$, which contradicts $P_0x \in X_+ - \{0\}$.

We also claim:

(ii) $\lim_{t\to\infty} \dfrac{\mathcal{F}(T(t)Ax)}{\mathcal{F}(T(t)x)} = \lambda_0$.

Since

$$\begin{aligned} & \frac{\mathcal{F}(T(t)Ax)}{\mathcal{F}(T(t)x)} \\ = \ & \frac{\mathcal{F}(\lambda_0 e^{\lambda_0 t}P_0x + T(t)P_1Ax)}{\mathcal{F}(e^{\lambda_0 t}P_0x + T(t)P_1x)} \\ = \ & \frac{\mathcal{F}(\lambda_0 P_0x + e^{-\lambda_0 t}T(t)P_1Ax)}{\mathcal{F}(P_0x + e^{-\lambda_0 t}T(t)P_1x)}, \end{aligned}$$

then $\lim_{t\to\infty} \dfrac{\mathcal{F}(T(t)Ax)}{\mathcal{F}(T(t)x)} = \lim\limits_{t\to\infty} \dfrac{\mathcal{F}(\lambda_0P_0x)}{\mathcal{F}P_0x} = \lambda_0$.

We next show that for each $t_1 > 0$ there exists a continuous function $F : [0,\infty) \to [0,\infty)$ such that for $0 \leq t \leq t_1$,

$$F(t) = \exp[-\int_0^t \eta(F(s))ds]\mathcal{F}(T(t)x). \tag{3}$$

Let W be the closed convex subset of the Banach Space $C([0,t_1],R)$ consisting of functions F such that $\|F\|_{C[0,t_1]} \leq |\mathcal{F}|(|P_0| + M\max\{1, e^{\lambda_0 t_1}\}|P_1|)$.

Define $K : W \to W$ by

$$(KF)(t) = \exp\left[-\int_0^t \eta(F(s))ds\right] \mathcal{F}(T(t)x), \quad F \in W, \quad 0 \le t \le t_1.$$

By the hypothesis K is a continuous mapping of W into itself. Also, the image of K is compact by the Arzela-Ascoli Theorem [10]. By the Schauder-Leray Theorem [29], K has a fixed point F in W.

We want to claim that this fixed point of K is unique. It is known that F satisfies

$$F'(t) = [G(t) - \eta(F(t))]F(t),$$

where $G(t) = \dfrac{\mathcal{F}(T(t)Ax)}{\mathcal{F}(T(t)x)}$. Suppose that F and $\widehat{F}$ are both fixed points of K. Since η is increasing,

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}[F(t) - \widehat{F}(t)]^2 &= G(t)[F(t) - \widehat{F}(t)]^2 \\ &- [\eta(F(t))F(t) - \eta(\widehat{F}(t))\widehat{F}(t)][F(t) - \widehat{F}(t)] \\ &\le \left(\sup_{0\le\tau\le t_1} G(\tau)\right)[F(t) - \widehat{F}(t)]^2. \end{aligned}$$

Since $F(0) = \widehat{F}(0)$, this last differential inequality implies that $F \equiv \widehat{F}$ on $[0, t_1]$. Since t_1 is arbitrary, we conclude that there exists a unique function $F : [0, \infty) \to [0, \infty)$ satisfying (3). Define $w : [0, \infty) \to X_+\backslash\{0\}$ by

$$w(t) = \exp[-\textstyle\int_0^t \eta(F(s))ds]T(t)x, \quad t \ge 0.$$

It is obtained that $w(t) \in D(A)$, since $x \in D(A)$. Also, $\mathcal{F}w(t) = F(t)$. Then we can conclude that w is the unique continuously differentiable function satisfying (2).

If $\lambda_0 < 0$, then $T(t)x \to 0$ as $t \to \infty$, so that $w(t) \to 0$ as $t \to \infty$. If $\lambda_0 \ge 0$, then let $\epsilon > 0$ and set $\delta = \eta(\eta^{-1}(\lambda_0) + \epsilon) - \lambda_0$. Since (ii), there exists $t_1 > 0$ such that $t > t_1$, then $|G(t) - \lambda_0| < \dfrac{\delta}{2}$, where $G(t) = \dfrac{\mathcal{F}(T(t)Ax)}{\mathcal{F}(T(t)x)}$. Suppose that $t \ge t_1$ and $F(t) \ge \eta^{-1}(\lambda_0) + \epsilon$ and since η is an increasing function, then $\eta(F(t)) \ge \eta(\eta^{-1}(\lambda_0) + \epsilon) = \lambda_0 + \delta > G(t) + \dfrac{\delta}{2}$.

Therefore, $G(t) - \eta(F(t)) < -\frac{\delta}{2}$.

We want to claim that for some $t > t_1$, $F(t) \leq \eta^{-1}(\lambda_0) + \epsilon$.

If for all $t > t_1$, $F(t) > \eta^{-1}(\lambda_0) + \epsilon$, then $F'(t) = [G(t) - \eta(F(t))]F(t) < -\frac{\delta}{2}F(t)$. By differential inequality theorem [6], $F(t) \leq e^{-\frac{\delta}{2}t} F(t_1)$, then as $t \to \infty$, $F(t) \to 0$. This yields a contradiction.

So there exists $t_2 > t_1$ such that $F(t_2) < \eta^{-1}(\lambda_0) + \epsilon$ and let t_3 be infimum of all such t_2.

Then, we have $t_3 > t_2$ and $F(t_3) \geq \eta^{-1}(\lambda_0) + \epsilon > F(t)$, where $t \in (t_2, t_3)$. By the above, $F'(t_3) \geq 0$. However, $F'(t_3) < 0$ since $F'(t_3) < -\frac{\delta}{2}F(t_3) \leq 0$. This yields a contradiction. Hence, $F(t) < \eta^{-1}(\lambda_0) + \epsilon$ for all $t > t_2$.

A similar argument shows that $F(t) > \eta^{-1}(\lambda_0) - \epsilon$ for all $t >$ some t_2'.

Therefore, $\lim_{t\to\infty} F(t) = \eta^{-1}(\lambda_0)$.

From (3), we have that

$$\begin{aligned} & \lim_{t\to\infty} \exp[\lambda_0 t - \int_0^t \eta(F(s))ds] \\ = & \lim_{t\to\infty} \frac{F(t)}{\mathcal{F}(e^{-\lambda_0 t}T(t)x)} \\ = & \frac{\eta^{-1}(\lambda_0)}{\mathcal{F}P_0 x}, \end{aligned}$$

which implies that $\lim_{t\to\infty} w(t) = \frac{\eta^{-1}(\lambda_0)P_0 x}{\mathcal{F}P_0 x}$.

□

III.3 Uniqueness and Equilibrium of Solution

Definition 4. *A square matrix A is irreducible if for every m, n, $(A^k)_{mn} > 0$ for some positive integer k [18].*

Definition 5. *R_+^n is defined by nonnegative elements in R^n.*

Definition 6. *F is a positive bounded linear functional on R^n if $F(\vec{x}) \geq 0$ for every $\vec{x} \in R_+^n$ and there exists a positive real number t such that $|F(\vec{x})| \leq t \cdot |\vec{x}|$ for every $\vec{x} \in R^n$ [7].*

Definition 7. *$\{W(t)\}_{t\geq 0}$ is a strongly continuous semigroup of (nonlinear) operators on R^n iff $\forall t \geq 0$, $W(t)$ is a continuous (nonlinear) operator from R^n to R^n, $W(0) = I$, $W(t+s) = W(t)W(s)$, and $W(t)\vec{x}$ is continuous in $t \in [0,\infty)$ for each fixed $\vec{x} \in R^n$ [27]. $\{W(t)\}_{t\geq 0}$ is called positive iff $W(t)\vec{x} \in R^n_+$ for $\vec{x} \in R^n_+$.*

Definition 8. *Let A be an $n \times n$ matrix and define $T(t) = \sum_{i=0}^{\infty} \frac{(tA)^i}{i!}$ for $t \geq 0$, $\{T(t)\}_{t\geq 0}$ is a strongly continuous semigroup of $n \times n$ matrices, and A is called the infinitesimal generator of $\{T(t)\}_{t\geq 0}$.*

Definition 9. *A direct sum decomposition of a linear space X is a representation $X = X_1 \oplus X_2$, if $\forall x \in X$, there exist $x_1 \in X_1$ and $x_2 \in X_2$ such that $x = x_1 + x_2$ and $X_1 \cap X_2 = \{0\}$, where X_1 and X_2 are linear subspaces of X. A linear operator P from X to X is a projection if $P^2 = P$.*

Definition 10. *λ_0 is a dominant eigenvalue of an $n \times n$ matrix A if $\lambda_0 > Re\lambda_i$, $i = 1, 2, \ldots, n$, and λ_i is any other eigenvalue of A.*

Lemma 1. *Suppose that A is an $n \times n$ irreducible matrix, $\vec{u}_0 \in R^n_+ \backslash \{0\}$, and F is a positive bounded linear functional on R^n. There exists a unique continuously differentiable solution to the differential equation*

$$\frac{d\vec{u}(t)}{dt} = A\vec{u}(t) - F(\vec{u}(t))\vec{u}(t), \quad t \geq 0, \quad \vec{u}(0) = \vec{u}_0. \tag{4}$$

Further, $\lim_{t\to\infty} \vec{u}(t) = \frac{\lambda_0 \vec{x}_0}{F(\vec{x}_0)}$, where $\vec{x}_0$ is the unique eigenvector of A such that $|\vec{x}_0| = 1$ corresponding to the real positive dominant eigenvalue of A.

Proof. Since A is an irreducible matrix, there exists a real positive dominant eigenvalue λ_0 with 1-dimensional eigenspace by the theorem of Perron and Frobenius [28]. Since the eigenspace of λ_0 is 1-dimensional, there is a unique eigenvector $\vec{x}_0$ of λ_0 such that $|\vec{x}_0| = 1$. Let X_1 be the eigenspace of λ_0 and X_2 be the direct sum complement of X_1 in R^n, *i.e.* $X_1 \oplus X_2 = R^n$.

Let P_i be the projection from R^n onto X_i, $i = 1, 2$. Then

$$P_i R^n = X_i, \quad P_i A = A P_i.$$

We define $T(t), t \geq 0$ to be the strongly continuous semigroup of bounded linear operators on $X = R^n$ with infinitesimal generator A. Then $T(t)$ satisfies hypotheses (H.1) and (H.2).

We consider η as the identity function $\eta(x) = x$. By Theorem 2, there exists a unique continuously differentiable solution $\vec{u}$ to the equation (4), and the conclusions of lemma 1 hold. □

Theorem 3. *Let A be a Markov matrix, let S be a diagonal matrix with all positive entries on the diagonal, $C > 0$, $\vec{P}_0 \in R^n_+ \backslash \{0\}$, and $\vec{P}(t) = [P_1(t), P_2(t), \ldots, P_n(t)]^t$ satisfy (1). Then*

$$\lim_{t\to\infty} \frac{P_i(t)}{P_n(t)} = \frac{x_i}{x_n}, \quad \lim_{t\to\infty} \sum_{i=1}^{n} P_i(t) = \lambda_0 C, \quad (i = 1, 2, \ldots, n-1)$$

where $\vec{x} = (x_1, x_2, \ldots, x_n)^t$ is an eigenvector of $M = C(A+S)$ with the dominant eigenvalue λ_0.

Proof. Since every entry of $A + S$ is positive, then every entry of M is also positive for $C > 0$, as is M^k for every positive integer k. By the definition of irreducible matrix, M is an irreducible matrix. By the theorem of Perron and Frobenius [28], there exists a dominant eigenvalue $\lambda_0 > 0$ and $\vec{x}_0 \neq \vec{0}$ such that $M\vec{x}_0 = \lambda_0 \vec{x}_0$.

By lemma 1 and since $\vec{P}(t)$ satisfies (1),

$$\lim_{t\to\infty} \vec{P}(t) = \frac{\lambda_0 C \vec{x}}{|\vec{x}|}.$$

Also, it follows that

$$\lim_{t\to\infty} \frac{P_i(t)}{P_n(t)} = \frac{\frac{\lambda_0 C x_i}{|\vec{x}|}}{\frac{\lambda_0 C x_n}{|\vec{x}|}} = \frac{x_i}{x_n}, \quad i = 1, 2, \ldots, n-1$$

$$\lim_{t\to\infty} \sum_{i=1}^{n} P_i(t) = \frac{\lambda_0 C |\vec{x}|}{|\vec{x}|} = \lambda_0 C.$$

□

Definition 11. *Let $\{W(t)\}_{t\geq 0}$ be a strongly continuous semigroup of (nonlinear) operators on R^n and let u^* be an equilibrium of (4). u^* is an exponentially asymptotically stable equilibrium solution of (4) if there exists $M > 0, \delta > 0$, such that $\forall t > 0$, $|\vec{u}(t) - u^*| < Me^{-\delta t}$.*

Consider (4), let X be the linear space R^n and let X_+ denote R^n_+.

Theorem 4. *Let hypotheses (H.1) and (H.2) hold, $\lambda_0 > 0$, $\vec{x} \in X_+\backslash\{0\}$, and $\{W(t)\}_{t\geq 0}$ be a strongly continuous semigroup of positive (nonlinear) operators on X. Let $W(t)\vec{x} = \vec{u}(t)$, where $\vec{u}(t)$ is the solution of equation (4). Then*

$$W(t)\vec{x} = \vec{u}(t) \to \vec{p}* := \frac{\lambda_0 P_0 \vec{x}}{F(P_0\vec{x})}, \quad as \quad t \to \infty.$$

Moreover, $\vec{p}*$ is an exponentially asymptotically stable equilibrium solution.

Proof. Let $\vec{x} \in X_+\backslash\{0\}$. By [6, 19], the solution of equation (4) is given by

$$\vec{u}(t) = W_0(t)\vec{x} = \frac{T(t)\vec{x}}{1 + \int_0^t F(T(s)\vec{x})ds},$$

where $T(t)\vec{x} = e^{\lambda_0 t}P_0\vec{x} + T(t)P_1\vec{x}$ by the hypotheses. And by using L'Hospital's rule [16], we obtain

$$\vec{u}(t) \to \vec{p}* = \frac{\lambda_0 P_0 \vec{x}}{F(P_0\vec{x})}, \quad as \quad t \to \infty$$

It remains to prove that $\vec{p}*$ is exponentially asymptotically stable. In order to do this, we now show that

$$\frac{T(t)\vec{x}}{1 + \int_0^t F(T(s)\vec{x})ds} - \frac{\lambda_0 P_0 \vec{x}}{F(P_0\vec{x})} \to 0, \quad as \quad t \to \infty$$

exponentially on bounded sets of $X_+ \backslash\{0\}$. Consider the following expression:

$$\begin{aligned}
& \left\| \frac{T(t)\vec{x}}{1 + \int_0^t F(T(s)\vec{x})ds} - \frac{\lambda_0 P_0 \vec{x}}{F(P_0\vec{x})} \right\| \\
\leq & \left\| \frac{T(t)\vec{x}}{1 + \int_0^t F(T(s)\vec{x})ds} - \frac{\lambda_0 T(t)\vec{x}}{e^{\lambda_0 t}F(P_0\vec{x})} \right\| + \left\| \frac{\lambda_0 T(t)\vec{x}}{e^{\lambda_0 t}F(P_0\vec{x})} - \frac{\lambda_0 P_0 \vec{x}}{F(P_0\vec{x})} \right\| \\
\leq & \left\| \frac{T(t)\vec{x}}{e^{\lambda_0 t}} \right\| \cdot \left| \frac{e^{\lambda_0 t}}{1 + \int_0^t F(T(s)\vec{x})ds} - \frac{\lambda_0}{F(P_0\vec{x})} \right| + \left| \frac{\lambda_0}{F(P_0\vec{x})} \right| \cdot \left\| \frac{T(t)\vec{x}}{e^{\lambda_0 t}} - P_1\vec{x} \right\|
\end{aligned}$$

It remains to prove that

$$\left| \frac{e^{\lambda_0 t}}{1 + \int_0^t F(T(s)\vec{x})ds} - \frac{\lambda_0}{F(P_0\vec{x})} \right| \to 0, \quad as \quad t \to \infty$$

exponentially on bounded sets of $X_+\backslash\{0\}$. But

$$\left|\frac{e^{\lambda_0 t}}{1+\int_0^t F(T(s)\vec{x})ds}-\frac{\lambda_0}{F(P_0\vec{x})}\right|=\left|\frac{1}{e^{-\lambda_0 t}+\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds}-\frac{1}{\frac{F(P_0\vec{x})}{\lambda_0}}\right|,$$

so it remains to show that

$$\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-\frac{F(P_0\vec{x})}{\lambda_0}\right|\to 0,\quad as\quad t\to\infty$$

exponentially on bounded sets of $X_+\backslash\{0\}$. Since

$$\begin{aligned}
&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-\frac{F(P_0\vec{x})}{\lambda_0}\right|\\
=&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-\frac{F(P_0\vec{x})}{\lambda_0}+\frac{F(e^{-\lambda_0 t}P_0\vec{x})}{\lambda_0}-\frac{F(e^{-\lambda_0 t}P_0\vec{x})}{\lambda_0}\right|\\
=&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-F(\int_0^t e^{-\lambda_0 s}P_0\vec{x}ds)-\frac{F(e^{-\lambda_0 t}P_0\vec{x})}{\lambda_0}\right|\\
\leq&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-F(\int_0^t e^{-\lambda_0 s}P_0\vec{x}ds)\right|+\left|\frac{F(e^{-\lambda_0 t}P_0\vec{x})}{\lambda_0}\right|,
\end{aligned}$$

so it only remains to consider the term

$$\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-F(\int_0^t e^{-\lambda_0 s}P_0\vec{x}ds)\right|$$

Since $\int_0^t e^{-\lambda_0 s}ds=\int_0^t e^{-\lambda_0(t-l)}dl$, we have

$$\begin{aligned}
&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-F(\int_0^t e^{-\lambda_0 s}P_0\vec{x}ds)\right|\\
=&\left|\int_0^t e^{-\lambda_0 t}F(T(s)\vec{x})ds-F(\int_0^t e^{-\lambda_0(t-s)}P_0\vec{x}ds)\right|\\
=&\left|\int_0^t e^{-\lambda_0(t-s)}F(e^{-\lambda_0 s}T(s)\vec{x}-P_0\vec{x})ds\right|\\
\leq&\left|\int_0^{\frac{t}{2}} e^{-\lambda_0(t-s)}F(e^{-\lambda_0 s}T(s)P_1\vec{x})ds\right|+\left|\int_{\frac{t}{2}}^t e^{-\lambda_0(t-s)}F(e^{-\lambda_0 s}T(s)P_1\vec{x})ds\right|\\
\leq&\frac{e^{-\frac{\lambda_0 t}{2}}}{\lambda_0}\sup_{s\in[0,\frac{t}{2}]}\left|F(e^{-\lambda_0 s}T(s)P_1\vec{x})\right|+\frac{1}{\lambda_0}\sup_{s\in[\frac{t}{2},t]}\left|F(e^{-\lambda_0 s}T(s)P_1\vec{x})\right|
\end{aligned}$$

$$\leq \quad ||F||\frac{e^{-\frac{\lambda_0 t}{2}}}{\lambda_0}M|P_1\vec{x}| + ||F||\frac{e^{\frac{(\omega-\lambda_0)t}{2}}}{\lambda_0}M|P_1\vec{x}|$$

and the result follows. □

Theorem 5. *Let A be a Markov matrix, let S be a diagonal matrix with all positive entries on the diagonal, let $C > 0$, and let $\vec{P}_0 \in R^n_+\backslash\{0\}$. Then there exists a unique exponentially asymptotically stable equilibrium solution to the ODE model (1).*

Proof. In the ODE model (1), $A + S$ is an irreducible matrix since every entry of $A + S$ is positive. It is obvious that $F(\vec{P}(t)) = \dfrac{|\vec{P}(t)|}{C}$ is a linear bounded positive functional on R^n. There exists a unique exponentially asymptotically stable equilibrium solution for (1) by Lemma 1 and Theorem 4. □

CHAPTER IV

NUMERICAL ANALYSIS

In this chapter, we investigate how the bacterial population evolves from the initial state with all contingency genes turned off to a state with all genes turned on. Simulations for the model demonstrate how the domination for the class with all genes turned on depends on the mutation frequency, selection coefficients, the number of contingency genes, and the carrying capacity.

IV.1 Values for Parameters

From the combinations with $n-1$ and n contingency genes, we can obtain the Markov matrix A_i with i contingency genes from the Markov matrix with $i-1$ contingency genes. It is shown as follows (i=2,...,n):

$$A_1 = \begin{bmatrix} 1-f & f \\ f & 1-f \end{bmatrix},$$

$$A_i = \begin{bmatrix} A_{i-1}\cdot(1-f) & A_{i-1}\cdot f \\ A_{i-1}\cdot f & A_{i-1}\cdot(1-f) \end{bmatrix}.$$

We can easily get any Markov matrix with any number of contingency genes. Therefore, we can use *Mathematica* to convert the ODE system (1) to a program for the numerical simulations (see http://people.vanderbilt.edu/$\sim$ yan.zhao).

In Chapter II, it is mentioned that contingency genes have a higher rate of mutation than other areas of genome. Contingency genes have a spontaneous mutation rate generally yielding a phenotype switch several orders of magnitude faster than the 10^{-6} mutations per doubling that is the common background [2].

In the system of equations, S is a $2^n \times 2^n$ diagonal matrix with the selection coefficients and we suppose that $s_1 = s_2 = \ldots = s_{2^n-1} < s_{2^n}$ since the combination with all turned-on contingency genes has a selective advantage. In the selection process without the mutation process or constraint on population growth, the differential equation for $y(t)$, the population for a particular combination at time t (which is meaured in hours), with the initial condition

$y(0) = y_0$, is shown as follows:

$$\frac{dy(t)}{dt} = s \cdot y(t), \qquad y(0) = y_0 \tag{5}$$

where s is a selection coefficient particular to the combination. The solution of (5) is $y(t) = y_0 \cdot e^{st}$. Based on the fact that it takes approximately 20 minutes for every cell division [26], it follows that

$$2y_0 = e^{s \cdot \frac{1}{3}} \cdot y_0, \qquad s = \frac{\ln 2}{0.33}.$$

Now, we just take the values of s_i $(i = 1, 2, \ldots, 2^n - 1)$ to be $\frac{\ln 2}{0.33}$ and $s_{2^n} = 1.1 \cdot s_1$.

We suppose that initially contingency genes in mother cells are all turned off. Then, the values for parameters which are used are shown in Table 2.

Table 2: Values for Parameters Used in Numerical Simulations

carrying capacity parameter	mutation frequency	selection coefficients s_i (i=1,2,...,2^n)	initial condition $\vec{P}_0$
C=10^{10}	$f = \frac{1}{1000}$	$s_1 = \ldots = s_{2^n-1} = \frac{\ln 2}{0.33}$, $s_{2^n} = \frac{\ln 2}{0.3}$	$P(0,0,\ldots,0) = 1000$, $P(0,i_1,i_2,\ldots,i_n) = 0$, $(i_1,i_2,\ldots,i_n = 1,0)$

IV.2 Graphical Results from Numerical Simulations

According to the given values of the parameters and the ODE model (1), we can compute the bacterial population of all the combinations by the numerical solutions to the ordinary differential equations using *Mathematica*.

First, the number of contingency genes is considered to be three, the bacterial population for each class and the total population of all eight classes are easily obtained and the graphs for the population of each genotype combination and the total population are shown in Figure 2 and Figure 3.

From the graphs, the following statements can be made:

(1) Even if the initial population of the class (1,1,1) is 0, it eventually dominates and

the class (0,0,0) decreases to a very low level.

(2) It takes about 5 days for the class (1,1,1) to dominate the bacterial population.

(3) The graphs for the classes (1,0,0), (0,1,0), (0,0,1) are the same, so are the graphs for the classes (1,1,0), (0,1,1), (1,0,1). In fact, there are only four distinct graphs for the bacterial population of eight genotypic classes.

(4) The total population of all the classes cannot increase forever, *i.e.* there is a limitation for it is determined by the carrying capacity.

For three contingency genes, more model simulations are done and indicate that the observed time of approximately 4-6 days for the dominant genotype class to take over is consistent with mutation frequencies in the range of 10^{-5} to 10^{-3} and the ratio of dominant to non-dominant selection coefficients in the range of 1.08 to 1.15.

By applying the same numerical method, the bacterial population graphs with different numbers of contingency genes can also be obtained. The following conclusions can be drawn for any number of genes based on all the known population graphs with different numbers of contingency genes from two to ten.

(1) A combination of all turned-on genes eventually dominates the bacterial population and a combination of all turned-off genes falls to a very low level. The combination of all turned-on genes is called a dominant class.

(2) The time it takes for the dominant genotype class to take over is longer if the number of contingency genes is bigger.

(3) There will be some overlapped population graphs for all the combinations with a certain number of contingency genes. The graphs for the combinations with the same number of turned-on genes or equivalently the same number of turned-off genes are the same. Thus, there are only $n+1$ distinct population graphs out of 2^n combinations with n contingency genes.

More simulations are done for the case that the number of contingency genes is ten. The time to domination by the genotype combination with all turned-on genes is 5-6 days, provided that the mutation frequency for a single switch is 10^{-4} to 10^{-3} and the dominant to non-dominant selection coefficient ratios are in the range 1.08-1.15. The number of equations in the system increases on the order 2^n as the number of contingency genes n increases,

which necessitates large-scale computing for higher values of n. In the next chapter, we investigate a modified system of equations for more efficient numerical simulations.

IV.3 Convergence Rate for the Dominant Class

An exponentially asymptotically stable solution of (1) has been discussed in chapter III. Hence, $\vec{p}* = \dfrac{\lambda_1 C\vec{x}}{|\vec{x}|}$ is the exponentially asymptotically solution for the system (1), where λ_1 is the dominant eigenvalue of $A+S$, $\vec{x}$ is the eigenvector of $A+S$ with the dominant eigenvalue λ_1 and $|\vec{x}| = \sum_{i=1}^{2^n} x_i$ for $\vec{x} \in R^{2^n} \backslash \{0\}$.

According to Theorem 4, it is known that

$$\left\| \vec{P}(t) - \vec{p}* \right\| \leq \widehat{M} e^{-\delta t}, \quad t \geq 0 \tag{6}$$

where $\vec{P}(t)$ is the solution of (1), $\widehat{M}$ and δ are constants independent of $\vec{P}_0$, and $\vec{p}*$ is the steady state of (1). Suppose that the number of contingency genes is n, let $\vec{P}(0) \in R_+^{2^n}$, let $\epsilon > 0$, and let t_ϵ^* be defined as $\inf_{t \geq 0} \left\| \vec{P}(t) - \vec{p}* \right\| \leq \epsilon$. In the application, the model simulations show $|\vec{p}*| \approx 3.3 \times 10^{10}$, so ϵ is chosen to be approximately $0.03|\vec{p}*|$, *i.e.* $\epsilon = 10^9$. Let $t_{10^9}^*$ be the time for the total population of all the genotype classes to be within approximately 97% of the limiting steady state.

The bacterial population increases with time and the dominant class eventually dominates the bacterial population, so it is necessary to know how fast the population of the dominant class converges to the steady state. It is seen that the number of contingency genes, selection coefficients and mutation frequency change the time for the dominant combination to take over, separately.

Firstly, we discuss how the number of contingency genes affects the convergence rate of the dominant class. We apply the same numerical method with different numbers of contingency genes to determine the relationship between the time needed for the dominant class to converge to the steady state and the number of contingency genes, and also obtain the dominant eigenvalue λ_1 as shown in Table 3:

Table 3: Convergence Time for the Dominant Class

the number of contingency genes	t^* s.t. $\lvert P(t^*) - p^* \rvert \leq 10^9$	dominant eigenvalue λ_1
2	86 hr	3.31029
3	117 hr	3.31019
4	147 hr	3.31009
5	175 hr	3.30999
6	203 hr	3.30989
7	230 hr	3.30979
8	255 hr	3.30969
9	281 hr	3.30959
10	305 hr	3.30949

A graph is shown in Figure 4, and it indicates that the convergence rate for the dominant class is linearly dependent on the number of contingency genes under the conditions in Table 2.

Secondly, how the selection coefficients affect the convergence rate is investigated. As it is mentioned before, the selection coefficient particular to the dominant class is bigger than the other selection coefficients which are equal. Under the conditions that the number of genes is 3, f=0.0001, and $C = 10^{10}$, two cases are discussed as follows:

1. $s[2^3] = \frac{\ln 2}{0.3}$, $s[i] = \frac{s[2^3]}{j}$, $i = 1, 2, \ldots, 7$, $j = 1.1, 1.125, \ldots, 1.475, 1.5$, *i.e.* the ratio of dominant to non-dominant changes in the range 1.1 to 1.5 for the fixed dominant selection coefficient.

2. $s[2^3] = \frac{\ln 2}{j}$, $j = 0.3, 0.35, \ldots, 0.95, 1.0$, $s[i] = \frac{s[2^3]}{1.1}$,$i = 1, 2, \ldots, 7$, *i.e.* the dominant selection coefficient changes in the same ratio of non-dominant to dominant.

For the above two different cases, ${t^*}_\epsilon$ can be found as before for $\epsilon = 10^9$. Figure 5 shows the first case, and Figure 6 shows the second case.

Finally, the relationship between the mutation frequency and convergence rate is discussed. Under the conditions that the number of contingency genes is 3 and with the parameters in Table 2, the mutation frequency is varied with values from 10^{-5} to 10^{-3}. With the same numerical methods as before, ${t^*}_\epsilon$ can be found as before $\epsilon = 10^9$ and Figure 7 is shown. In this figure, it is indicated that the convergence rate has a log-linear relationship with the mutation frequency.

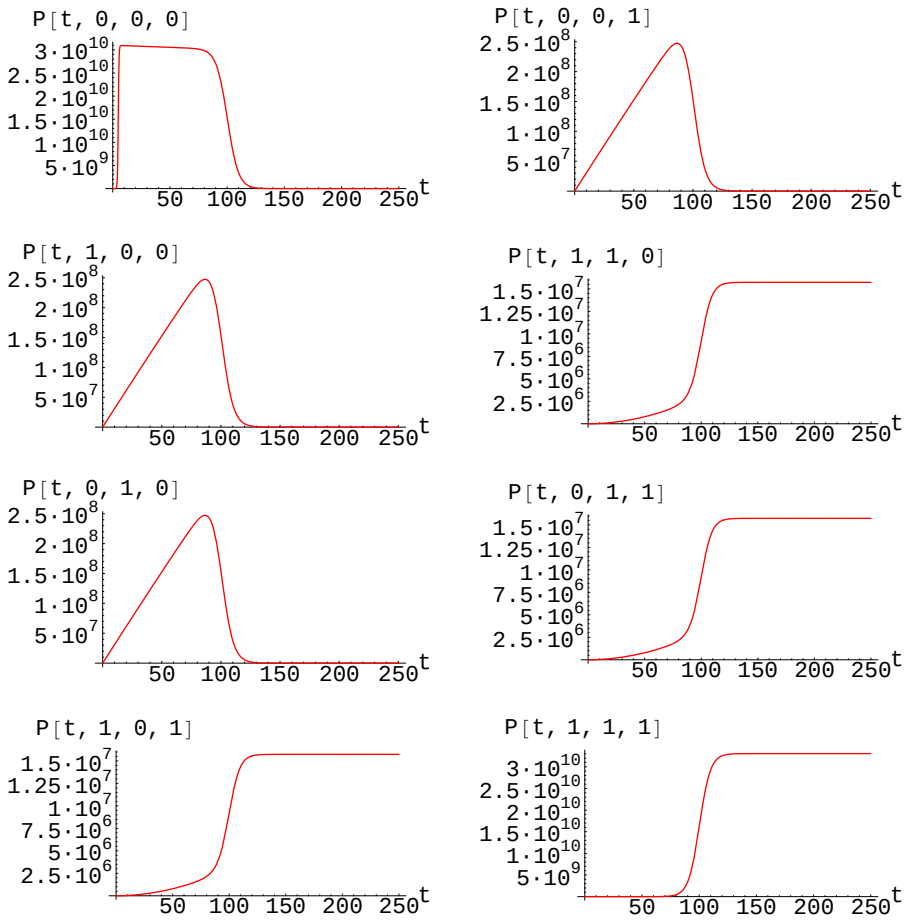

Figure 2: Populations of 8 genotype combinations (n=3, t:hour).

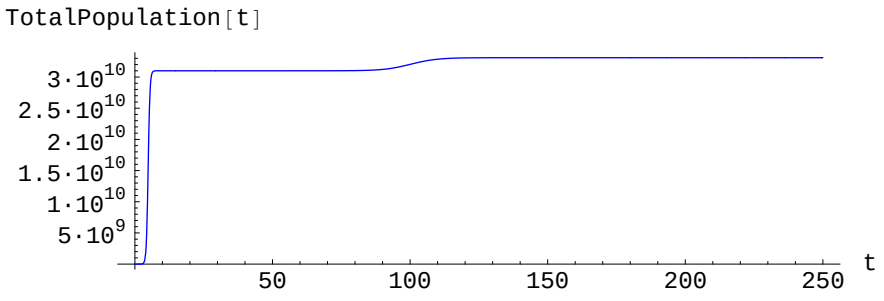

Figure 3: Total population of 8 genotype combinations (n=3, t:hour).

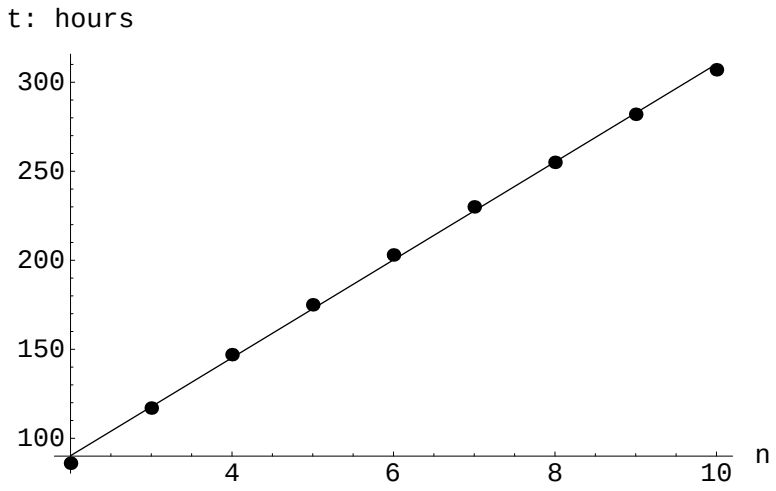

Figure 4: The linear relationship between the number of contingency genes and the time in hours for the dominant genotype class to attain 97% of its asymptotic limit.

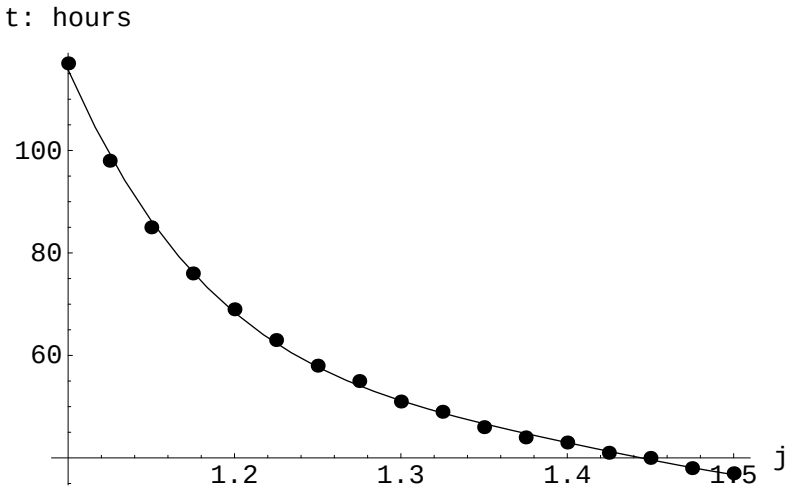

Figure 5: The inverse relationship between j (the ratio of dominant to nondominant selection coefficient) and the time in hours for the dominant genotype class to attain 97% of its asymptotic limit.

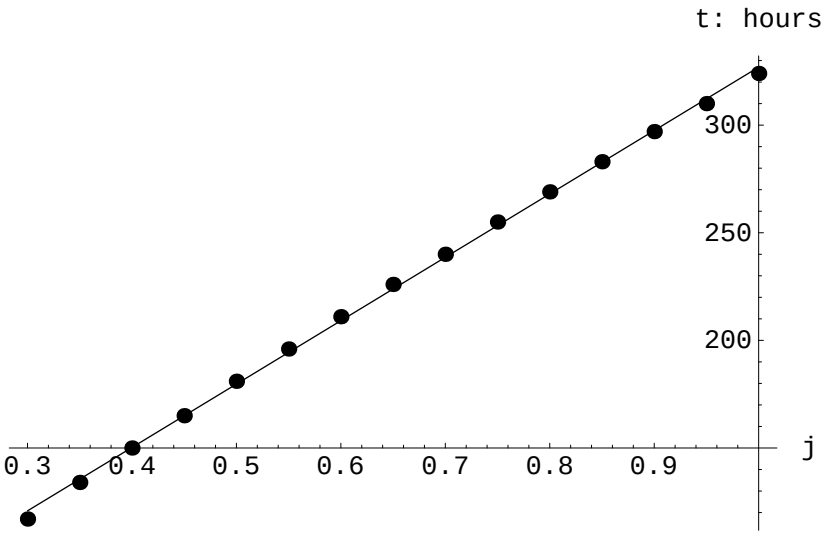

Figure 6: The linear relationship between the dominant selection coefficient $\frac{\ln 2}{j}$ with the fixed ratio of dominant to nondominat selection coefficients and the time in hours for the dominant genotype class to attain 97% of its asymptotic limit.

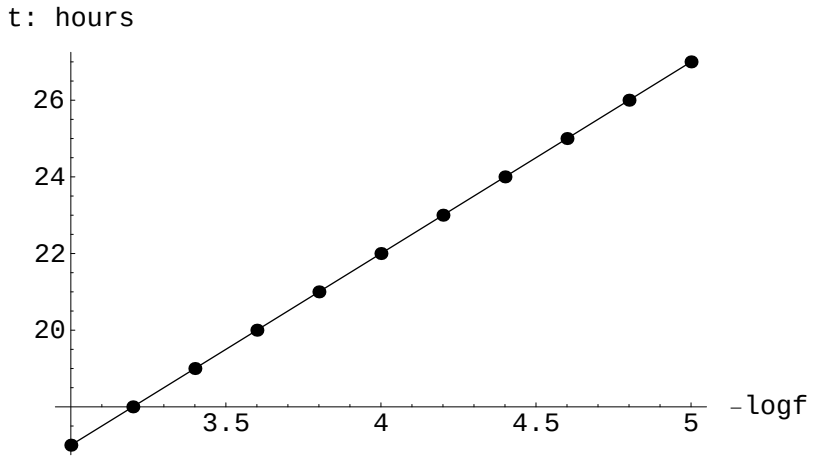

Figure 7: The log-linear relationship between the mutation frequency and the time in hours for the dominant genotype class to attain 97% of its asymptotic limit.

CHAPTER V

A MODIFIED SYSTEM OF EQUATIONS

V.1 Construction of a Modified System

In Chapter II and IV, we have constructed the ODE system for the bacterial population and also given some model simulations. However, this ODE system does not allow an efficient way for computing the case of higher than 10 contingency genes, since the system increases in the order 2^n as the number of contingency genes n increases. We wish to modify the system for improving the efficiency of the computations. From the graphical results in Chapter IV, the populations for the combinations with the same number of turned-on genes have the same graphs. According to this fact, we introduce a new notation for the average value of populations for the combinations with the same number of turned-on genes. Then we can reduce the number of ordinary differential equations in the first model by applying the new notations to the first model.

We consider a simple case of two contingency genes in the ODE system. The system for two contingency genes is shown as follows, where $s_1 = s_2 = s_3 < s_4$:

$$\begin{pmatrix} \frac{d}{dt}P(t,0,0) \\ \frac{d}{dt}P(t,1,0) \\ \frac{d}{dt}P(t,0,1) \\ \frac{d}{dt}P(t,1,1) \end{pmatrix} = \begin{pmatrix} (1-f)^2 & (1-f)f & (1-f)f & f^2 \\ (1-f)f & (1-f)^2 & f^2 & (1-f)f \\ (1-f)f & f^2 & (1-f)^2 & (1-f)f \\ f^2 & (1-f)f & (1-f)f & (1-f)^2 \end{pmatrix} \cdot \begin{pmatrix} P(t,0,0) \\ P(t,1,0) \\ P(t,0,1) \\ P(t,1,1) \end{pmatrix}$$

$$+ \begin{pmatrix} s_1 & 0 & 0 & 0 \\ 0 & s_2 & 0 & 0 \\ 0 & 0 & s_3 & 0 \\ 0 & 0 & 0 & s_4 \end{pmatrix} \cdot \begin{pmatrix} P(t,0,0) \\ P(t,1,0) \\ P(t,0,1) \\ P(t,1,1) \end{pmatrix} - \frac{|P(t,0,0)+P(t,1,0)+P(t,0,1)+P(t,1,1)|}{C} \cdot \begin{pmatrix} P(t,0,0) \\ P(t,1,0) \\ P(t,0,1) \\ P(t,1,1) \end{pmatrix}.$$

From the above, we can get the following four ordinary differential equations:

$$\begin{aligned} \frac{d}{dt}P(t,0,0) &= (1-f)^2P(t,0,0) + (1-f)fP(t,1,0) + (1-f)fP(t,0,1) + f^2P(t,1,1) + \\ &\quad s_1P(t,0,0) - \frac{P(t,0,0)+P(t,1,0)+P(t,0,1)+P(t,1,1)}{C}P(t,0,0), \end{aligned} \tag{7}$$

$$\frac{d}{dt}P(t,1,0) = (1-f)fP(t,0,0) + (1-f)^2P(t,1,0) + f^2P(t,0,1) + (1-f)fP(t,1,1) + s_2P(t,1,0) - \frac{P(t,0,0)+P(t,1,0)+P(t,0,1)+P(t,1,1)}{C}P(t,1,0), \quad (8)$$

$$\frac{d}{dt}P(t,0,1) = f^2P(t,0,0) + (1-f)fP(t,1,0) + (1-f)fP(t,0,1) + (1-f)^2P(t,1,1) + s_3P(t,0,1) - \frac{P(t,0,0)+P(t,1,0)+P(t,0,1)+P(t,1,1)}{C}P(t,0,1), \quad (9)$$

$$\frac{d}{dt}P(t,1,1) = f^2P(t,0,0) + (1-f)fP(t,1,0) + (1-f)fP(t,0,1) + (1-f)^2P(t,1,1) + s_4P(t,1,1) - \frac{P(t,0,0)+P(t,1,0)+P(t,0,1)+P(t,1,1)}{C}P(t,1,1). \quad (10)$$

To reduce the number of equations, we introduce new notations for the bacterial population at time t as follows:

$$G_0(t) = P(t,0,0), G_1(t) = \frac{P(t,1,0)+P(t,0,1)}{2}, G_2(t) = P(t,1,1).$$

Add the equation (8) and (9) together and divide it by two, then the new ordinary differential equations with new notations can be obtained as follows when $s_1 = s_2 = s_3 < s_4$:

$$\begin{aligned}
\frac{dG_0(t)}{dt} &= (1-f)^2G_0(t) + 2(1-f)fG_1(t) + f^2G_2(t) + s_1G_0(t) - \frac{G_0(t)+2G_1(t)+G_2(t)}{C}G_0(t),\\
\frac{dG_1(t)}{dt} &= (1-f)fG_0(t) + ((1-f)^2+f^2)G_1(t) + f^2G_2(t) + s_2G_1(t) - \frac{G_0(t)+2G_1(t)+G_2(t)}{C}G_1(t),\\
\frac{dG_2(t)}{dt} &= f^2G_0(t) + 2(1-f)fG_1(t) + (1-f)^2G_2(t) + s_4G_2(t) - \frac{G_0(t)+2G_1(t)+G_2(t)}{C}G_2(t).
\end{aligned}$$

Suppose that

$$\vec{G}(t) = \begin{pmatrix} G_0(t) \\ G_1(t) \\ G_2(t) \end{pmatrix}, \widetilde{A_2} = \begin{pmatrix} (1-f)^2 & 2(1-f)f & f^2 \\ (1-f)f & (1-f)^2+f^2 & (1-f)f \\ f^2 & 2(1-f)f & (1-f)^2 \end{pmatrix}, \widetilde{S_2} = \begin{pmatrix} \widetilde{s_1} & 0 & 0 \\ 0 & \widetilde{s_2} & 0 \\ 0 & 0 & \widetilde{s_3} \end{pmatrix}, \text{ where}$$

$\widetilde{s_1} = \widetilde{s_2} = s_1$, $\widetilde{s_3} = s_4$. We define $|\vec{G}(t)|_0 = G_0(t) + 2G_1(t) + G_2(t)$. Then we can get a modified ODE model for the bacterial population with two contingency genes at time t as follows:

$$\frac{d\vec{G}(t)}{dt} = \widetilde{A_2} \cdot \vec{G}(t) + \widetilde{S_2} \cdot \vec{G}(t) - \frac{|\vec{G}(t)|_0}{C} \cdot \vec{G}(t), \quad t \geq 0, \quad \vec{G}(0) = \vec{G}_0.$$

By following the same approach for bacteria with three contingency genes, we can also reduce the number of ordinary differential equations. The equations for three contingency genes are shown, where $|\vec{P}(t)| = \sum_{i,j,k=0}^{1} P(t,i,j,k)$ and $s_1 = s_2 = \ldots = s_7 < s_8$:

$$\begin{aligned}\frac{d}{dt}P(t,0,0,0) &= (1-f)^3P(t,0,0,0) + (1-f)^2fP(t,1,0,0) + (1-f)^2fP(t,0,1,0) + (1-f)\\ &\quad f^2P(t,1,1,0) + (1-f)^2fP(t,0,0,1) + (1-f)f^2P(t,1,0,1) + (1-f)f^2\\ &\quad P(t,0,1,1) + f^3P(t,1,1,1) + s_1P(t,0,0,0) - \frac{|\vec{P}(t)|}{C}P(t,0,0,0), \qquad (11)\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}P(t,1,0,0) &= (1-f)^2fP(t,0,0,0) + (1-f)^3P(t,1,0,0) + (1-f)f^2P(t,0,1,0) + (1-f)^2\\ &\quad fP(t,1,1,0) + (1-f)f^2P(t,0,0,1) + (1-f)^2fP(t,1,0,1) + f^3P(t,0,1,1)\\ &\quad + (1-f)f^2P(t,1,1,1) + s_2P(t,1,0,0) - \frac{|\vec{P}(t)|}{C}P(t,1,0,0), \qquad (12)\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}P(t,0,1,0) &= (1-f)^2fP(t,0,0,0) + (1-f)f^2P(t,1,0,0) + (1-f)^3P(t,0,1,0) +\\ &\quad (1-f)^2fP(t,1,1,0) + (1-f)f^2P(t,0,0,1) + f^3P(t,1,0,1) + (1-f)^2f\\ &\quad P(t,0,1,1) + (1-f)f^2P(t,1,1,1) + s_3P(t,0,1,0) - \frac{|\vec{P}(t)|}{C}P(t,0,1,0), \qquad (13)\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}P(t,1,1,0) &= (1-f)f^2P(t,0,0,0) + (1-f)^2fP(t,1,0,0) + (1-f)^2fP(t,0,1,0) +\\ &\quad (1-f)^3P(t,1,1,0) + f^3P(t,0,0,1) + (1-f)f^2P(t,1,0,1) + (1-f)f^2P(t,0,1,1)\\ &\quad + (1-f)^2fP(t,1,1,1) + s_4P(t,1,1,0) - \frac{|\vec{P}(t)|}{C}P(t,1,1,0), \qquad (14)\end{aligned}$$

$$\frac{d}{dt}P(t,0,0,1) = (1-f)^2 fP(t,0,0,0) + (1-f)f^2 P(t,1,0,0) + (1-f)f^2 fP(t,0,1,0) + f^3 P(t,1,1,0) + (1-f)^3 P(t,0,0,1) + (1-f)^2 fP(t,1,0,1) + (1-f)^2 fP(t,0,1,1) + (1-f)f^2 P(t,1,1,1) + s_5 P(t,0,0,1) - \frac{|\vec{P}(t)|}{C} P(t,0,0,1), \quad (15)$$

$$\frac{d}{dt}P(t,1,0,1) = (1-f)f^2 P(t,0,0,0) + (1-f)^2 fP(t,1,0,0) + f^3 P(t,0,1,0) + (1-f)f^2 P(t,1,1,0) + (1-f)^2 fP(t,0,0,1) + (1-f)^3 P(t,1,0,1) + (1-f)f^2 P(t,0,1,1) + (1-f)^2 fP(t,1,1,1) + s_6 P(t,1,0,1) - \frac{|\vec{P}(t)|}{C} P(t,1,0,1), \quad (16)$$

$$\frac{d}{dt}P(t,0,1,1) = (1-f)f^2 P(t,0,0,0) + f^3 P(t,1,0,0) + (1-f)^2 fP(t,0,1,0) + (1-f)f^2 P(t,1,1,0) + (1-f)^2 fP(t,0,0,1) + (1-f)f^2 P(t,1,0,1) + (1-f)^3 P(t,0,1,1) + (1-f)^2 fP(t,1,1,1) + s_7 P(t,0,1,1) - \frac{|\vec{P}(t)|}{C} P(t,0,1,1), \quad (17)$$

$$\frac{d}{dt}P(t,1,1,1) = f^3 P(t,0,0,0) + (1-f)f^2 fP(t,1,0,0) + (1-f)f^2 fP(t,0,1,0) + (1-f)^2 f P(t,1,1,0) + (1-f)f^2 P(t,0,0,1) + (1-f)^2 fP(t,1,0,1) + (1-f)^2 fP(t,0,1,1) + (1-f)^3 P(t,1,1,1) + s_8 P(t,1,1,1) - \frac{|\vec{P}(t)|}{C} P(t,1,1,1). \quad (18)$$

We define the new notations for the bacterial population at time t as follows:

$$G_0(t) = P(t,0,0,0), \quad G_1(t) = \frac{P(t,1,0,0) + P(t,0,1,0) + P(t,0,0,1)}{3},$$

$$G_2(t) = \frac{P(t,1,1,0) + P(t,1,0,1) + P(t,0,1,1)}{3}, \quad G_3(t) = P(t,1,1,1).$$

We add (12), (13) and (15) and divide it by three and do the same for (14), (16) and

(17). A modified model for the bacterial poplation with three contingency genes at time t is then obtained.

$$\begin{pmatrix} \frac{d}{dt}G_0(t) \\ \frac{d}{dt}G_1(t) \\ \frac{d}{dt}G_2(t) \\ \frac{d}{dt}G_3(t) \end{pmatrix} = \begin{pmatrix} (1-f)^3 & 3(1-f)^2 f & 3(1-f)f^2 & f^3 \\ (1-f)^2 f & (1-f)^3 + 2(1-f)f^2 & 2(1-f)f^2 + f^3 & (1-f)f^2 \\ (1-f)f^2 & 2(1-f)^2 f + f^3 & (1-f)^3 + 2(1-f)f^2 & (1-f)^2 f \\ f^3 & 3(1-f)f^2 & 3(1-f)^2 f & (1-f)^3 \end{pmatrix} \cdot \begin{pmatrix} G_0(t) \\ G_1(t) \\ G_2(t) \\ G_3(t) \end{pmatrix}$$

$$+ \begin{pmatrix} \widetilde{s}_1 & 0 & 0 & 0 \\ 0 & \widetilde{s}_2 & 0 & 0 \\ 0 & 0 & \widetilde{s}_3 & 0 \\ 0 & 0 & 0 & \widetilde{s}_4 \end{pmatrix} \cdot \begin{pmatrix} G_0(t) \\ G_1(t) \\ G_2(t) \\ G_3(t) \end{pmatrix} - \frac{|\vec{G}(t)|_0}{C} \cdot \begin{pmatrix} G_0(t) \\ G_1(t) \\ G_2(t) \\ G_3(t) \end{pmatrix},$$

where $|\vec{G}(t)|_0 = G_0(t) + 3G_1(t) + 3G_2(t) + G_3(t)$, $\widetilde{s}_1 = \widetilde{s}_2 = \widetilde{s}_3 = s_1, \widetilde{s}_4 = s_8$.

For the more general case when the number of contingency genes is considered to be n, we define

$$\vec{G}(t) = \begin{pmatrix} G_0(t) \\ G_1(t) \\ G_2(t) \\ \vdots \\ G_n(t) \end{pmatrix}, \quad G_i(t) = \frac{\sum P_i(t)}{\binom{n}{i}}, \; 0 \le i \le n, \text{ where } P_i(t) \text{ is the bacterial population}$$

of any combination with i turned-on genes at time t, and $|\vec{G}(t)|_0 = \sum_{i=0}^{n} \binom{n}{i} G_i(t)$.

We apply the same method as the above for two and three contingency genes to reduce the number of the ordinary differential equations, which is 2^n if n contingency genes are considered. Supposed that C is a carrying capacity parameter specific to the host and $\vec{G}(t)$ is the bacterial population, a modified system of ordinary differential equations is constructed as follows:

$$\frac{d\vec{G}(t)}{dt} = \widetilde{A} \cdot \vec{G}(t) + \widetilde{S} \cdot \vec{G}(t) - \frac{|\vec{G}(t)|_0}{C} \cdot \vec{G}(t), \quad t \ge 0, \quad \vec{G}(0) = \vec{G}_0, \tag{19}$$

where $\widetilde{A}$ is a matrix in terms of mutation frequencies, $\widetilde{S}$ is a diagonal matrix with selection coefficients. $\widetilde{A}$ and $\widetilde{S}$ will be defined in the case of n contingency genes. If the number of contingency genes is n, $\widetilde{A}$ is an $n+1$ by $n+1$ matrix, $\widetilde{S}$ is a diagonal matrix with

$n+1$ entries on the diagonal such that $\widetilde{s}_1 = \widetilde{s}_2 = \ldots = \widetilde{s}_i = \ldots = \widetilde{s}_n < \widetilde{s}_{n+1}$ and $|\vec{G}(t)|_0 = \sum_{i=0}^{n} \binom{n}{i} G_i(t)$. In the modified model, mutation and selection processes are both included with the constraint on population growth due to a limited carrying capacity. However, the mutation process in the modified model is different from the first one. Each entry of $\widetilde{A}$ represents more mutation processes than each entry of A in the first model. By the definition of $G_i(t)$, *i.e.* the average value of bacterial populations of all the combinations with i turned-on genes, we can assume $G_i(t) = P(t, \underbrace{1, \ldots, 1}_{i}, \overbrace{0, \ldots, 0}^{n})$. Each entry in A is the probability of the mutation process from one combination to the other combination of bacteria. However, $\widetilde{A}(i,j)$, where $1 \leq i \leq n+1$ and $1 \leq j \leq n+1$, is the sum of all the probabilities of the mutation processes from $(\underbrace{1, 1, \ldots, 1}_{j-1}, 0, \ldots, 0)$ to all $\binom{n}{i-1}$ combinations with $i-1$ turned-on genes. For the purpose of illustration, four contingency genes are considered in the modified model. Suppose we want to compute $\widetilde{A}(3,2)$ by using the diagram, which is shown as follows:

$$
\begin{array}{rcl}
 & & (1,1,0,0) \\
 & & (1,0,1,0) \\
(1,0,0,0) & \rightarrow & (0,1,1,0) \\
 & & (1,0,0,1) \\
 & & (0,1,0,1) \\
 & & (0,0,1,1)
\end{array}
$$

the probability of the mutation from (1,0,0,0) to (1,1,0,0)=$(1-f)^3 f$

the probability of the mutation from (1,0,0,0) to (1,0,1,0)=$(1-f)^3 f$

the probability of the mutation from (1,0,0,0) to (0,1,1,0)=$(1-f) f^3$

the probability of the mutation from (1,0,0,0) to (1,0,0,1)=$(1-f)^3 f$

the probability of the mutation from (1,0,0,0) to (0,1,0,1)=$(1-f) f^3$

the probability of the mutation from (1,0,0,0) to (0,0,1,1)=$(1-f) f^3$

$\widetilde{A}(3,2)$ is the sum of the above probabilities, i.e. $\widetilde{A}(3,2) = 3(1-f)^3 f + 3(1-f) f^3$.

$\widetilde{A}$ for four contingency genes can be obtained in the following:

$$\begin{pmatrix} (1-f)^4 & 4(1-f)^3 f & 6(1-f)^2 f^2 & 4(1-f)f^3 & f^4 \\ (1-f)^3 f & (1-f)^4 + 3(1-f)^2 f^2 & 2(1-f)^3 f + 2(1-f)f^3 & 3(1-f)^2 f^2 + f^4 & (1-f)f^3 \\ (1-f)^2 f^2 & 3(1-f)^3 f + 3(1-f)f^3 & (1-f)^4 + 4(1-f)^2 f^2 + f^4 & 3(1-f)^3 f + 3(1-f)f^3 & (1-f)^2 f^2 \\ (1-f)f^3 & 3(1-f)^2 f^2 + f^4 & 2(1-f)^3 f + 2(1-f)f^3 & (1-f)^4 + 3(1-f)^2 f^2 & (1-f)^3 f \\ f^4 & 4(1-f)f^3 & 6(1-f)^2 f^2 & 4(1-f)^3 f & (1-f)^4 \end{pmatrix}.$$

Therefore, we can calculate every entry of $\widetilde{A}$ for any number of contingency genes. For n contingency genes, $\widetilde{A}(i,j)$ is the sum of all the probabilities of the mutation processes from $(\underbrace{1,1,\ldots,1}_{j-1},0,\ldots,0)$ to all the genotypic combinations with $i-1$ turned-on contingency genes.

Theorem 6. *Let $\widetilde{A}$ be an $(n+1)\times(n+1)$ matrix with all positive entries, let $\widetilde{S}$ be an $(n+1)\times(n+1)$ diagonal matrix with all positive entries on the diagonal, let $C>0$, let $\vec{G}_0 \in R_+^{n+1}/\{0\}$. There exists a unique continuously differentiable function w: $[0,\infty) \to R_+^{n+1}/\{0\}$ such that w satisfies (19). Also, the unique solution of (1) can be obtained by the solution to (19) under the assumption that $G_i(t)$ is the bacterial population of any combination with i turned-on genes, $i=0,1,\ldots,n$.*

Proof. Since every entry of $\widetilde{A}+\widetilde{S}$ is positive, then every entry of $(\widetilde{A}+\widetilde{S})^k$ is positive for every positive integer k. By the definition of irreducible matrix, $\widetilde{A}+\widetilde{S}$ is an irreducible matrix. According to the definition of $|\vec{G}(t)|$ and positivity of C, it is obvious that $\dfrac{|\vec{G}(t)|_0}{C}$ is a positive bounded linear functional on R^{n+1}. Therefore, there exists a unique continuously differentiable function w to satisfy (19) by Lemma 1.

The solution of (1) gives a solution to (19) by the formula $G_i(t) = \dfrac{\sum P_i(t)}{\binom{n}{i}}$, where $P_i(t)$ is the population of any combination of bacteria with i turned-on genes at time t. By the uniqueness of the solution to (19), $G_i(t)$ must have this formula. If we assume that $G_i(t)$ is the bacterial population of any combination with i turned-on genes, we can also get the solution to (1) from the solution of (19). □

V.2 Asymptotic Behavior

Let $w^n(i)$ be a set of natural numbers, where n is the number of contingency genes and i is the number of turned-on genes in the genotypic combinations, $0 \leq i \leq n$.

Define $w^n(i)$ as follows: $w^2(0) = \{1\}, \quad w^2(1) = \{2,3\}, \quad w^2(2) = \{4\}$,

$w^n(0) = \{1\}, \forall n = 2,3,4,\ldots, \quad w^n(n) = \{2^n\}, \forall n = 2,3,4,\ldots,$

$w^n(i) = \{w^{n-1}(i), w^n(i-1) + 2^{n-1}\}, \forall n = 2,3,4,\ldots, 1 \leq i \leq n-1.$

If $n = 2$, we can express the population of bacteria as a function of time as follows:

$$\vec{P}(t) = \begin{pmatrix} P(t,0,0) \\ P(t,1,0) \\ P(t,0,1) \\ P(t,1,1) \end{pmatrix} = \begin{pmatrix} P_1(t) \\ P_2(t) \\ P_3(t) \\ P_4(t) \end{pmatrix}.$$

$w^2(0)$ is the set of the subscript of the combination with all tuned-off genes, $w^2(1)$ is the set of the subscripts of the combinations with one turned-on genes and $w^2(2)$ is the set of the subscript of the combination with two turned-on genes if the number of contingency genes is two.

If $n = 3$, $w^3(0) = \{1\}, \quad w^3(1) = \{2,3,5\}, \quad w^3(2) = \{4,6,7\}$ and $w^3(3) = \{8\}$.

In the general case, $w^n(i)$ is the set of the subscripts of the combinations with i ($i = 0,1,\ldots,n$) turned-on genes if the number of contingency genes is n.

Definition 12. *A real matrix A is called nonnegative if all its entries are nonnegative [4].*

Definition 13. *A nonnegative square matrix is called row stochastic, or simply stochastic, if all its row sums are 1 [4].*

Lemma 2. *If $A = (a_{ij})$ is a row stochastic matrix, and $\omega = \min_i(a_{ii})$, then $|\lambda - \omega| \leq 1 - \omega$, for any eigenvalue λ of A.*

Proof. Let λ be any eigenvalue of an $n \times n$ stochastic matrix A, and let $x = (x_1, x_2, \ldots, x_n)^t$ be a corresponding eigenvector. Let $0 < |x_m| = \max_i(|x_i|)$. Then $\lambda x = Ax$, and, in particular,

$$\lambda x_m = \textstyle\sum_{j=1}^{n} a_{mj} x_j$$

and therefore,

$$\lambda - a_{mm} = \sum_{j \neq m} a_{mj}(\frac{x_j}{x_m}).$$

Now, by the triangle inequality,

$$\begin{aligned} |\lambda - a_{mm}| &\leq \sum_{j \neq m} a_{mj} |\frac{x_j}{x_m}| \\ &\leq \sum_{j \neq m} a_{mj} \\ &= 1 - a_{mm}. \end{aligned}$$

Since A is stochastic, thus

$$\begin{aligned} |\lambda - \omega| &= |\lambda - a_{mm} + a_{mm} - \omega| \\ &\leq |\lambda - a_{mm}| + |a_{mm} - \omega| \\ &\leq (1 - a_{mm}) + (a_{mm} - \omega) \\ &= 1 - \omega. \end{aligned}$$

□

Suppose that C is a carrying capacity parameter specific to an infected host, and recall the earlier ordinary differential equations model to compute the bacterial population:

$$\frac{d\vec{P}(t)}{dt} = A \cdot \vec{P}(t) + S \cdot \vec{P}(t) - \frac{|\vec{P}(t)|}{C} \cdot \vec{P}(t), \quad t \geq 0, \quad \vec{P}(0) = \vec{P}_0, \tag{20}$$

where A is a $2^n \times 2^n$ Markov matrix , S is a $2^n \times 2^n$ diagonal matrix with selection coefficients and $|\vec{P}(t)| = \sum_{i=1}^{2^n} P_i(t)$ is the total population of bacteria if n contingency genes are considered. Also, we get a modified ODE model in the following:

$$\frac{d\vec{G}(t)}{dt} = \widetilde{A} \cdot \vec{G}(t) + \widetilde{S} \cdot \vec{G}(t) - \frac{|\vec{G}(t)|_0}{C} \cdot \vec{G}(t), \quad t \geq 0, \quad \vec{G}(0) = \vec{G}_0, \tag{21}$$

where $\widetilde{A}$ is an $(n+1)\times(n+1)$ matrix in terms of mutation frequencies, $\widetilde{S}$ is an $(n+1)\times(n+1)$ diagonal matrix with selection coefficients and $|\vec{G}(t)|_0 = \sum_{i=0}^{n} \binom{n}{i} G_i(t)$.

Lemma 3. *Let* $\vec{P}_0 \in R_+^{2^n}\backslash\{0\}$, $\vec{G}_0 \in R_+^{n+1}\backslash\{0\}$, *and let* $\vec{P}(t) = [P_1(t), P_2(t), \ldots, P_{2^n}(t)]^t$ *satisfy (1),* $\vec{G}(t) = [G_0(t), G_1(t), \ldots, G_n(t)]^t$ *satisfy (19). If* λ_0 *is a dominant eigenvalue of* $A + S$ *and* $\widetilde{\lambda}_0$ *is a dominant eigenvalue of* $\widetilde{A} + \widetilde{S}$, *then* $\lambda_0 = \widetilde{\lambda}_0$.

Proof. According to the relationship between $\vec{P}(t)$ and $\vec{G}(t)$, *i.e.* $G_i(t) = \dfrac{\sum P_i(t)}{\binom{n}{i}}$, $0 \le i \le n$, we have $|\vec{G}(t)|_0 = |\vec{P}(t)|$, where $t > 0$. Therefore $\lim_{t\to\infty} |\vec{G}(t)|_0 = \lim_{t\to\infty} |\vec{P}(t)|$.

It is obvious that $A + S$ and $\widetilde{A} + \widetilde{S}$ are both irreducible matrices. Assume that $C = 1$ in (1) and (19), by Lemma 1, we can get

$$\lim_{t\to\infty} \vec{P}(t) = \frac{\lambda_0 x}{|x|}, \text{ where } x \text{ is an eigenvector of } A + S \text{ with } \lambda_0,$$
$$\lim_{t\to\infty} \vec{G}(t) = \frac{\widetilde{\lambda}_0 \widetilde{x}}{|\widetilde{x}|_0}, \text{ where } \widetilde{x} \text{ is an eigenvector of } \widetilde{A} + \widetilde{S} \text{ with } \widetilde{\lambda}_0.$$

From the above,

$$\lim_{t\to\infty} |\vec{P}(t)| = \frac{\lambda_0 \sum_{i=1}^{2^n} (x)_i}{|x|} = \frac{\lambda_0 |x|}{|x|} = \lambda_0,$$

$$\lim_{t\to\infty} |\vec{G}(t)|_0 = \frac{\widetilde{\lambda}_0 \sum_{i=0}^{n} \binom{n}{i} (\widetilde{x})_i}{|\widetilde{x}|_0} = \frac{\widetilde{\lambda}_0 |\widetilde{x}|_0}{|x|_0} = \widetilde{\lambda}_0,$$

Since $\lim_{t\to\infty} |\vec{G}(t)|_0 = \lim_{t\to\infty} |\vec{P}(t)|$, it is obtained that $\lambda_0 = \widetilde{\lambda}_0$. □

Theorem 7. *Let* $\vec{P}_0 \in R_+^{2^n}\backslash\{0\}$, $\vec{G}_0 \in R_+^{n+1}\backslash\{0\}$, *and let* $\vec{P}(t) = [P_1(t), P_2(t), \ldots, P_{2^n}(t)]^t$ *satisfy (1),* $\vec{G}(t) = [G_0(t), G_1(t), \ldots, G_n(t)]^t$ *satisfy (19). If* $0 < f < 1 - \dfrac{1}{\sqrt[n-1]{2}}$, *then* $\lim_{t\to\infty} G_i(t) = \lim_{t\to\infty} P_j(t)$, *where* $j \in w^n(i)$, $G_i(t) = \dfrac{\sum_{j\in w^n(i)} P_j(t)}{\binom{n}{i}}$, *where* n *is the number of contingency genes and* $n \ge 2$.

Proof. Assume that $C = 1$ and $x = (x_1, x_2, \ldots, x_i, \ldots, x_{2^n})^t$ is a normalized eigenvector of $A + S$ with the dominant eigenvalue λ_0, by Lemma 1

$$\lim_{t\to\infty} \vec{P}(t) = \lambda_0 x.$$

We want to show $x_{j_1} = x_{j_2}$, $\forall j_1, j_2 \in w^n(i)$, where $i = 0, 1, \ldots, n$. When the number of contingency genes is n, we denote $A^{(n)}$ to be A in (1) and let $S^{(n)}$ be S in (1).

If $n = 2$, $A^{(2)}$ and $S^{(2)}$ are $2^2 \times 2^2$ matrices and $\lambda_0^{(2)}$ is a dominant eigenvalue of $A^{(2)}+S^{(2)}$, $x^{(2)}$ is the corresponding eigenvector with $|x^{(2)}| = 1$,

$$(A^{(2)} + S^{(2)})x^{(2)} = \lambda_0^{(2)} x^{(2)},$$

$$\begin{pmatrix} (1-f)^2+s_1 & (1-f)f & (1-f)f & f^2 \\ (1-f)f & (1-f)^2+s_1 & f^2 & (1-f)f \\ (1-f)f & f^2 & (1-f)^2+s_1 & (1-f)f \\ f^2 & (1-f)f & (1-f)f & (1-f)^2+s_4 \end{pmatrix} \cdot \begin{pmatrix} x_1^{(2)} \\ x_2^{(2)} \\ x_3^{(2)} \\ x_4^{(2)} \end{pmatrix} = \begin{pmatrix} \lambda_0^{(2)} x_1^{(2)} \\ \lambda_0^{(2)} x_2^{(2)} \\ \lambda_0^{(2)} x_3^{(2)} \\ \lambda_0^{(2)} x_4^{(2)} \end{pmatrix}.$$

From the above, we can get four equations and subtract the third equation from the second one. The result is shown as follows:

$$[(1-f)^2 + s_1 - f^2](x_2^{(2)} - x_3^{(2)}) = \lambda_0^{(2)}(x_2^{(2)} - x_3^{(2)}).$$

Suppose that $\lambda_0^{(2)} = (1-f)^2 + s_1 - f^2$, in the first equation, we can have

$$\begin{aligned} [(1-f)^2 + s_1 - f^2]x_1^{(2)} &= [(1-f)^2 + s_1]x_1^{(2)} + f(1-f)x_1^{(2)} + f(1-f)x_3^{(2)} + f^2 x_4^{(2)} \\ -f^2 x_1^{(2)} &= f(1-f)x_1^{(2)} + f(1-f)x_3^{(2)} + f^2 x_4^{(2)}. \end{aligned}$$

Since $0 < f < 1$ and $x_1^{(2)}, x_2^{(2)}, x_3^{(2)}, x_4^{(2)} > 0$, $\lambda_0^{(2)} \neq (1-f)^2 + s_1 - f^2$. Then, $x_2^{(2)} = x_3^{(2)}$.

In the other word, $x_{j_1}^{(2)} = x_{j_2}^{(2)}$, $\forall j_1, j_2 \in w^2(1) = \{2, 3\}$.

If $n = 3$, $w^3(1) = \{2, 3, 5\}, w^3(2) = \{4, 6, 7\}$, so we need to show that $x_2^{(3)} = x_3^{(3)} = x_5^{(3)}$ and $x_4^{(3)} = x_6^{(3)} = x_7^{(3)}$. $A^{(3)}$ and $S^{(3)}$ are $2^3 \times 2^3$ matrices and $\lambda_0^{(3)}$ is a dominant eigenvalue of $A^{(3)} + S^{(3)}$, $x^{(3)}$ is the corresponding eigenvector with $|x^{(3)}| = 1$,

$$(A^{(3)} + S^{(3)})x^{(3)} = \lambda_0^{(3)} x^{(3)} \tag{22}$$

Observe that

$$A^{(3)} = \begin{pmatrix} A^{(2)}(1-f) & A^{(2)}f \\ A^{(2)}f & A^{(2)}(1-f) \end{pmatrix}.$$

In (22), we can get eight equations, subtract the third equation from the second one, and subtract the seventh equation from the sixth one, then we can get the following:

$$\begin{pmatrix} (1-f)^3 + s_1 - f^2(1-f) & (1-f)^2 f - f^3 \\ (1-f)^2 f - f^3 & (1-f)^3 + s_1 - f^2(1-f) \end{pmatrix} \begin{pmatrix} x_2^{(3)} - x_3^{(3)} \\ x_6^{(3)} - x_7^{(3)} \end{pmatrix} = \begin{pmatrix} \lambda_0^{(3)}(x_2^{(3)} - x_3^{(3)}) \\ \lambda_0^{(3)}(x_6^{(3)} - x_7^{(3)}) \end{pmatrix},$$

$$\left(\begin{pmatrix} \lambda_0^{(3)} - s_1 & 0 \\ 0 & \lambda_0^{(3)} - s_1 \end{pmatrix} + \begin{pmatrix} (1-f)^3 - f^2(1-f) & (1-f)^2 f - f^3 \\ (1-f)^2 f - f^3 & (1-f)^3 - f^2(1-f) \end{pmatrix} \right) \begin{pmatrix} x_2^{(3)} - x_3^{(3)} \\ x_6^{(3)} - x_7^{(3)} \end{pmatrix} = 0,$$

$$\left(\begin{pmatrix}\lambda_0^{(3)}-s_1 & 0\\ 0 & \lambda_0^{(3)}-s_1\end{pmatrix}+(1-2f)\begin{pmatrix}(1-f) & f\\ f & (1-f)\end{pmatrix}\right)\begin{pmatrix}x_2^{(3)}-x_3^{(3)}\\ x_6^{(3)}-x_7^{(3)}\end{pmatrix}=0.$$

We can transform the matrices on the left side to the Jordan canonical form [14]:

$$Q_{(3)}((\lambda_0^{(3)}-s_1)I_2+(1-2f)\begin{pmatrix}1 & 0\\ 0 & 1-2f\end{pmatrix})Q_{(3)}^{-1}\begin{pmatrix}x_2^{(3)}-x_3^{(3)}\\ x_6^{(3)}-x_7^{(3)}\end{pmatrix}=0.$$

Denote B to be

$$(\lambda_0^{(3)}-s_1)I_2+(1-2f)\begin{pmatrix}1 & 0\\ 0 & 1-2f\end{pmatrix}.$$

From the first equation in (22), it is obvious that $\lambda_0^{(3)}>s_1$. Since $f\neq\frac{1}{2}$ and $\lambda_0^{(3)}>s_1$,

$$\det(B)\neq 0,$$
$$\det(Q_{(3)}BQ_{(3)}^{-1})\neq 0.$$

Therefore, $x_2^{(3)}=x_3^{(3)}$ and $x_6^{(3)}=x_7^{(3)}$.

We subtract the fifth equation from the third one in (22) and subtract the sixth equation from the fourth one in (22):

$$\begin{pmatrix}(1-f)^3+s_1-f^2(1-f) & (1-f)^2f-f^3\\ (1-f)^2f-f^3 & (1-f)^3+s_1-f^2(1-f)\end{pmatrix}\begin{pmatrix}x_3^{(3)}-x_5^{(3)}\\ x_4^{(3)}-x_6^{(3)}\end{pmatrix}=\begin{pmatrix}\lambda_0(x_3^{(3)}-x_5^{(3)})\\ \lambda_0(x_4^{(3)}-x_6^{(3)})\end{pmatrix}.$$

In the same way, we can get $x_3^{(3)}=x_5^{(3)}$ and $x_4^{(3)}=x_6^{(3)}$.

Thus, we have proved that $x_{j_1}=x_{j_2}$, $\forall j_1,j_2\in w^3(i), i=1,2$.

If $n=4$, $A^{(4)}+S^{(4)}$ has a normalized eigenvector $x^{(4)}$ with a dominant eigenvalue $\lambda_0^{(4)}$.

$$(A^{(4)}+S^{(4)})x=\lambda_0 x \tag{23}$$

Let $H^{(3)}=\begin{pmatrix}1-f & f\\ f & 1-f\end{pmatrix}$ and $H^{(n)}=\begin{pmatrix}H^{(n-1)}(1-f) & H^{(n-1)}f\\ H^{(n-1)}f & H^{(n-1)}(1-f)\end{pmatrix}$, $n=4,5,6,\ldots$.

We can apply the same method to $n=4$, subtract one equation from the other one in

(23) for four times and get the following:

$$\left(\begin{pmatrix} \lambda_0^{(4)}-s_1 & 0 & 0 & 0 \\ 0 & \lambda_0^{(4)}-s_1 & 0 & 0 \\ 0 & 0 & \lambda_0^{(4)}-s_1 & 0 \\ 0 & 0 & 0 & \lambda_0^{(4)}-s_1 \end{pmatrix} + (1-2f)\cdot \begin{pmatrix} H^{(3)}(1-f) & H^{(3)}f \\ H^{(3)}f & H^{(3)}(1-f) \end{pmatrix}\right)\cdot$$

$$\begin{pmatrix} x_2^{(4)}-x_3^{(4)} \\ x_6^{(4)}-x_7^{(4)} \\ x_{10}^{(4)}-x_{11}^{(4)} \\ x_{14}^{(4)}-x_{15}^{(4)} \end{pmatrix} = 0,$$

$$((\lambda_0^{(4)}-s_1)I_4 + (1-2f)H^{(4)})\cdot \begin{pmatrix} x_2^{(4)}-x_3^{(4)} \\ x_6^{(4)}-x_7^{(4)} \\ x_{10}^{(4)}-x_{11}^{(4)} \\ x_{14}^{(4)}-x_{15}^{(4)} \end{pmatrix} = 0.$$

We can transform the above matrix to the Jordan canonical form and get the following:

$$(\lambda_0^{(4)}-s_1)I_4 + (1-2f)H^{(4)} = Q_{(4)}((\lambda_0^{(4)}-s_1)I_4 + (1-2f)\widetilde{H}^{(4)})Q_{(4)}^{-1}.$$

Since $H^{(3)}$ is a row stochastic matrix, $H^{(4)}$ is also a row stochastic matrix by its definition. Every entry of $H^{(4)}$ is real and it is symmetric , so $H^{(4)}$ has real eigenvalues [14]. Then entries on the diagonal of $\widetilde{H}^{(4)}$ are real eigenvalues of $H^{(4)}$. By Lemma 2, for any eigenvalue λ of $H^{(4)}$, $|\lambda-\omega| \leq 1-\omega$, where $\omega = \min_i(H_{ii}^{(4)})$. Since λ is real and $\omega = (1-f)^2$, thus,

$$2(1-f)^2 - 1 \leq \lambda \leq 1.$$

It is known that if $0 < f < 1 - \dfrac{1}{\sqrt{2}}$, then $0 < (1-f)^2 < 1$, and $0 < (1-f)^2 - 1 < 1$. Therefore, $0 < \lambda \leq 1$.

From the first equation in (23), it is obvious that $\lambda_0^{(4)} > s_1$. The entries on the diagonal of $(\lambda_0^{(4)}-s_1)I_4 + (1-2f)\widetilde{H}^{(4)}$ are all positive, so,

$$\det((\lambda_0^{(4)}-s_1)I_4 + (1-2f)\widetilde{H}^{(4)}) \neq 0,$$

then,

$$\det(Q_{(4)}((\lambda_0^{(4)} - s_1)I_4 + (1-2f)\widetilde{H}^{(4)})Q_{(4)}^{-1}) \neq 0.$$

Therefore, $x_2^{(4)} = x_3^{(4)}$, $x_6^{(4)} = x_7^{(4)}$, $x_{10}^{(4)} = x_{11}^{(4)}$ and $x_{14}^{(4)} = x_{15}^{(4)}$.

We can use the same way to obtain the following results:

$$x_3^{(4)} = x_5^{(4)}, x_4^{(4)} = x_6^{(4)}, x_{11}^{(4)} = x_{13}^{(4)}, x_{12}^{(4)} = x_{14}^{(4)},$$

$$x_2^{(4)} = x_9^{(4)}, x_4^{(4)} = x_{11}^{(4)}, x_6^{(4)} = x_{13}^{(4)}, x_8^{(4)} = x_{15}^{(4)}.$$

Therefore, we have proved the followings:

(i) For $w^4(1) = \{2, 3, 5, 9\}$, $x_2^{(4)} = x_3^{(4)} = x_5^{(4)} = x_9^{(4)}$.

(ii) For $w^4(2) = \{4, 6, 7, 10, 11, 13\}$, $x_4^{(4)} = x_6^{(4)} = x_7^{(4)} = x_{10}^{(4)} = x_{11}^{(4)} = x_{13}^{(4)}$.

(iii) For $w^4(3) = \{8, 12, 14, 15\}$, $x_8^{(4)} = x_{12}^{(4)} = x_{14}^{(4)} = x_{15}^{(4)}$.

If the number of contingency genes is n, we use induction and assume that $x_{j_1}^{(n)} = x_{j_2}^{(n)}$, $\forall j_1, j_2 \in w^n(i), 1 \leq i \leq n-1$. Suppose that $\lambda_0^{(n)}$ is a dominant eigenvalue of the matrix $A^{(n)} + S^{(n)}$ and $x^{(n)}$ is the corresponding eigenvector with $|x^{(n)}| = 1$. Then we have

$$(A^{(n)} + S^{(n)})x^{(n)} = \lambda_0^{(n)} x^{(n)}. \tag{24}$$

From the above equations (24), we have $n-1$ systems of linear equations like the following:

$$((\lambda_0^{(n)} - s_1)I_{2^{(n-2)}} + (1-2f)H^{(n)}) \begin{pmatrix} x_{j_1^{(1)}}^{(n)} - x_{j_2^{(1)}}^{(n)} \\ x_{j_1^{(2)}}^{(n)} - x_{j_2^{(2)}}^{(n)} \\ \vdots \\ x_{j_1^{(2^{n-2})}}^{(n)} - x_{j_2^{(2^{n-2})}}^{(n)} \end{pmatrix} = 0. \tag{25}$$

Now, we consider the number of contingency genes is $n+1$. We suppose that $\lambda_0^{(n+1)}$ is a dominant eigenvalue of the matrix $A^{(n+1)} + S^{(n+1)}$ and $x^{(n+1)}$ is the corresponding eigenvector with $|x^{(n+1)}| = 1$. Then,

$$(A^{(n+1)} + S^{(n+1)})x^{(n+1)} = \lambda_0^{(n+1)} x^{(n+1)}. \tag{26}$$

From the above equations (26), we can get $n-1$ systems of linear equations by the rela-

tionship between $w^n(i)$ and $w^{n+1}(i)$. The following is one of these $n-1$ systems:

$$\left((\lambda_0^{(n+1)}-s_1)I_{2^{(n-1)}}+(1-2f)\begin{pmatrix}H^{(n)}(1-f) & H^{(n)}f\\ H^{(n)}f & H^{(n)}(1-f)\end{pmatrix}\right)\begin{pmatrix}x_{j_1^{(1)}}^{(n+1)}-x_{j_2^{(1)}}^{(n+1)}\\ x_{j_1^{(2)}}^{(n+1)}-x_{j_2^{(2)}}^{(n+1)}\\ \vdots\\ x_{j_1^{(2^{n-2})}}^{(n+1)}-x_{j_2^{(2^{n-2})}}^{(n+1)}\\ x_{j_1^{(1)}+2^{n-1}}^{(n+1)}-x_{j_2^{(1)}+2^{n-1}}^{(n+1)}\\ x_{j_1^{(2)}+2^{n-1}}^{(n+1)}-x_{j_2^{(2)}+2^{n-1}}^{(n+1)}\\ \vdots\\ x_{j_1^{(2^{n-2})}+2^{n-1}}^{(n+1)}-x_{j_2^{(2^{n-2})}+2^{n-1}}^{(n+1)}\end{pmatrix}=0.$$

By the first equation in (26), we can have $\lambda_0^{(n+1)}>s_1$.

Since $H^{(n+1)}=\begin{pmatrix}H^{(n)}(1-f) & H^{(n)}f\\ H^{(n)}f & H^{(n)}(1-f)\end{pmatrix}$ is a row stochastic matrix, by lemma 2, any eigenvlaue λ of $H^{(n+1)}$ satisfies

$$2\omega-1\le\lambda\le 1,\quad \omega=\min_i(H_{ii}^{(n+1)})=(1-f)^{n-1}.$$

Also, we know that $0<f<1-\frac{1}{\sqrt[n-1]{2}}$, thus, $0<\lambda\le 1$.

We transform $(\lambda_0^{(n+1)}-s_1)I_{2^{(n-1)}}+(1-2f)\cdot H^{(n+1)}$ by using the Jordan canonical form $\widetilde{H}^{(n+1)}$ of $H^{(n+1)}$ as follows:

$$(\lambda_0^{(n+1)}-s_1)I_{2^{(n-1)}}+(1-2f)\cdot H^{(n+1)}=Q_{(n+1)}((\lambda_0-s_1)I_{2^{(n-1)}}+(1-2f)\widetilde{H}^{(n+1)})Q_{(n+1)}^{-1}.$$

All entries on the diagonal of $\widetilde{H}^{(n+1)}$ are eigenvalues of $H^{(n+1)}$ and $\lambda_0^{(n+1)}>s_1$, so

$$\det(Q_{(n+1)}((\lambda_0^{(n+1)}-s_1)I_{2^{(n-1)}}+(1-2f)\widetilde{H}^{(n+1)})Q_{(n+1)}^{-1})\neq 0.$$

We obtain that

$$\begin{aligned}x_{j_1^{(i)}}^{(n+1)}&=x_{j_2^{(i)}}^{(n+1)},\quad i=1,2,\ldots,2^{n-2},\\ x_{j_1^{(i)}+2^{n-1}}^{(n+1)}&=x_{j_2^{(i)}+2^{n-1}}^{(n+1)},\quad i=1,2,\ldots,2^{n-2}.\end{aligned}$$

Since we have $n-1$ systems of linear equations, we can get $n-1$ kinds of results like

the above. Also, we can obtain the nth system of linear equations from (26):

$$((\lambda_0^{(n+1)} - s_1)I_{2^{(n-1)}} + (1-2f)H^{(n+1)}) \begin{pmatrix} x_{j_1^{(1)}}^{(n+1)} - x_{2^{n-1}+1}^{(n+1)} \\ \vdots \\ x_{2^{n-1}}^{(n+1)} - x_{j_2^{(2^{n-1})}}^{(n+1)} \end{pmatrix} = 0.$$

By applying Lemma 2, we can get that

$$x_{j_1^{(1)}}^{(n+1)} = x_{2^{n-1}+1}^{(n+1)}, \ldots, x_{2^{n-1}}^{(n+1)} = x_{j_2^{(2^{n-1})}}^{(n+1)}.$$

By the definition of $w^{n+1}(i)$, we have proved that

$$x_{j_1} = x_{j_2}, \quad \forall j_1, j_2 \in w^{n+1}(i), \quad i = 1, 2, \ldots, n.$$

From all the above, for any number of contingency genes n, $A^{(n)} + S^{(n)}$ has a normalized eigenvector $x = (x_1, x_2, \ldots, x_{2^n})^t$ with a dominant eigenvalue λ_0. Also, the components in x have the following relationship:

$$x_{j_1} = x_{j_2}, \quad \forall j_1, j_2 \in w^n(i), \quad i = 1, 2, \ldots, n-1.$$

By lemma 1 and the above results,

$$\lim_{t\to\infty} \sum_{j \in w^n(i)} P_j(t) = \lambda_0 \sum_{j \in w^n(i)} x_j = \lambda_0 \binom{n}{i} x_j.$$

Since $G_i(t) = \dfrac{\sum_{j \in w^n(i)} P_j(t)}{\binom{n}{i}}$ by its definition, we have

$$\lim_{t\to\infty} G_i(t) = \lambda_0 x_j.$$

Also, suppose that $\widetilde{A} + \widetilde{S}$ has a normalized eigenvector $\widetilde{x} = (\widetilde{x}_0, \widetilde{x}_1, \ldots, \widetilde{x}_n)^t$ with a dominant eigenvalue $\widetilde{\lambda}_0$. By lemma 1,

$$\lim_{t\to\infty} G_i(t) = \widetilde{\lambda}_0 \widetilde{x}_i.$$

Since $\widetilde{\lambda}_0 = \lambda_0$ by lemma 3, it is obtained that $\widetilde{x}_i = x_j$.

We have

$$\lim_{t\to\infty} P_j(t) = \lambda_0 x_j = \widetilde{\lambda}_0 \widetilde{x}_i = \lim_{t\to\infty} G_i(t), \quad \forall j \in w^n(i), \quad i = 1, 2, \ldots, n-1.$$

If $j \in w^n(0)$ or $w^n(n)$, it is obvious that $\lim_{t\to\infty} P_j(t) = \lim_{t\to\infty} G_i(t)$, where $i = 0, n$. □

V.3 Numerical Simulations for the Modified Model

We can also perform numerical simulations for the modified system by using *Mathematica*. The number of equations in the modified system increases in the same order as the number of contingency genes. The modified system improves the computation efficiency significantly. Thus, we can obtain the graphs for the populations of genotype combinations with more than 10 contingency genes.

It is known that the incubation period of GAS pharyngitis is 3-6 days [24, 25]. We therefore perform simulations for more than 10 contingency genes to observe the values for the mutation frequency, selection coefficients, in order to be consistent with the domination time about 3-6 days. In all the following simulations, we assume the carrying capacity parameter C to be 10^{10}.

Table 4 and Table 5 show estimations for the values of mutation frequencies, and selection coefficients for the dominant class to converge within 4-6 days when 20 contingency genes and 30 contingency genes are considered, respectively.

Table 4: Estimations for 20 Contingency Genes

mutation frequency	s_i,i=1,2,...,20	s_{21}	convergence time for the dominant class
0.0013-0.033	$3\ln 2/0.33$	$3\ln 2/0.3$	100hr-144hr
0.0015-0.01	$3.5\ln 2/0.33$	$3.5\ln 2/0.3$	96hr-144hr
0.03-0.048	$3.5\ln 2/0.33$	$3.5\ln 2/0.3$	90hr-144hr
0.0018-0.003	$4\ln 2/0.33$	$4\ln 2/0.3$	96hr
0.048-0.066	$4\ln 2/0.33$	$4\ln 2/0.3$	96hr-144hr

Table 5: Estimations for 30 Contingency Genes

mutation frequency	s_i,i=1,2,...,30	s_{31}	convergence time for the dominant class
0.0048-0.025	$3.5 \ln 2/0.33$	$3.5 \ln 2/0.3$	100hr-144hr
0.0048-0.03	$4 \ln 2/0.33$	$4 \ln 2/0.3$	100hr-130hr
0.0056-0.02	$5 \ln 2/0.33$	$5 \ln 2/0.3$	96hr-120hr
0.003-0.046	$5 \ln 2/0.33$	$5 \ln 2/0.3$	96hr-120hr
0.0057-0.007	$5.5 \ln 2/0.33$	$5.5 \ln 2/0.3$	90hr
0.065-0.6	$5.5 \ln 2/0.33$	$5.5 \ln 2/0.3$	96hr

From the tables, contingency genes switch on or off much faster and each cell divides much more quickly. In Chapter II, it is known that the doubling time of the ith genotype class is appoximately $\frac{\ln 2}{s_i}$. Therefore, the doubling time of the dominant class is about 5 minutes if a higher number of contingency genes is considered.

We have discussed how the mutation frequencies and selection coefficients affect the bacterial population in an infected host. Since the computation has been significantly improved, we can deal with more than one hundred contingency genes. However, when we performed simulations for 34 contingency genes if the carrying capacity parameter C is 10^{10}, there are fractional values that are less than 1 for the populations of some genotype combinations in Figure 8. These are unrealistic results. If we change the value for the carrying capacity parameter from 10^{10} to 10^{14}, the new results are shown in Figure 9. From the above, we can tell the carrying capacity parameter affects the existence of genotype combinations. We will further the discussion about the effect of the carrying capacity parameter on the bacterial populations.

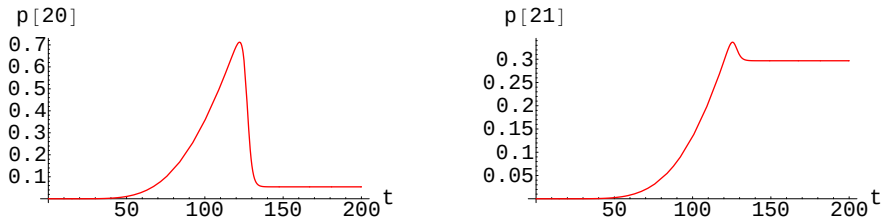

Figure 8: Populations for 34 contingency genes when $C = 10^{10}$.

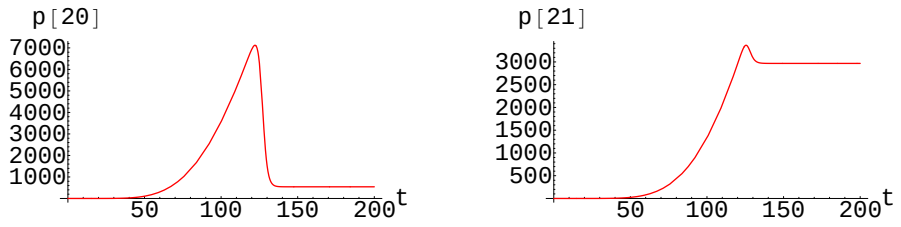

Figure 9: Populations for 34 contingency genes when $C = 10^{14}$.

V.4 Carrying Capacity Coefficients

From previous numerical simulations, we observe from the graphs that the value for the carrying capacity parameter has an effect on the existence of genotype combinations if a larger number of contingency genes is considered. All the simulations have been performed under the condition that all the genotypic combinations share the same carrying capacity parameter specific to the host. Due to the adaptation for the bacteria to the host's immune system [24, 25], different genotypic classes have different resource utilizations in the host. In Chapter IV, the graphical results show that the classes with the same number of turned-on contingency genes have the same graph for the bacterial population, which indicates that these classes have the same ability to adapt to the infected host. Based on this fact, we suppose that the combinations with the same number of turned-on contingency genes have the same carrying capacity parameter. Then we introduce carrying capacity coefficients for genotypic classes. From numerical simulations in Chapter IV, the combinations with more turned-on congtingency genes have higher resource utilizations in the host. We also suppose that the carrying capacity coefficient has a lower value for the combinations with a larger number of turned-on contingency genes.

For simplicity, we introduce three carrying capacity coefficients c_0, c_1, c_2 to the first model with two contingency genes, where c_0 is the carrying capacity coefficient for the class (0,0), c_1 is the coefficient for the classes (0,1) and (1,0), c_2 is the coefficient for the class (1,1). A new model is shown as follows:

$$\begin{bmatrix} \frac{d}{dt}P(t,0,0) \\ \frac{d}{dt}P(t,1,0) \\ \frac{d}{dt}P(t,0,1) \\ \frac{d}{dt}P(t,1,1) \end{bmatrix} = \begin{bmatrix} (1-f)^2+s_1 & f(1-f) & (1-f)f & f^2 \\ f(1-f) & (1-f)^2+s_2 & f^2 & (1-f)f \\ (1-f)f & f^2 & (1-f)^2+s_3 & f(1-f) \\ f^2 & (1-f)f & f(1-f) & (1-f)^2+s_4 \end{bmatrix} \begin{bmatrix} P(t,0,0) \\ P(t,1,0) \\ P(t,0,1) \\ P(t,1,1) \end{bmatrix}$$

$$-\frac{|c_0P(t,0,0)+c_1P(t,1,0)+c_1P(t,0,1)+c_2P(t,1,1)|}{C}\begin{bmatrix}P(t,0,0)\\P(t,1,0)\\P(t,0,1)\\P(t,1,1)\end{bmatrix},$$

where c_0, c_1, c_2 are carrying capacity coefficients, and $c_0 > c_1 > c_2$.

If n contingency genes are considered, the new model to compute the bacterial population is the following:

$$\frac{d\vec{P}(t)}{dt} = A\cdot\vec{P}(t) + S\cdot\vec{P}(t) - \frac{|\sum c_iP_i(t)|}{C}\cdot\vec{P}(t), \quad t\geq 0, \quad \vec{P}(0)=\vec{P}_0, \tag{27}$$

where A is a $2^n\times 2^n$ Markov matrix , S is a $2^n\times 2^n$ diagonal matrix with selection coefficients, $P_i(t)$ is the population of combinations with i turned-on contingency genes and c_i is the corresponding carrying capacity coefficient, $c_0 > c_1 > \ldots > c_n$.

Theorem 8. *Let A be a $2^n \times 2^n$ Markov matrix, let S be a $2^n \times 2^n$ diagonal matrix with all positive entries on the diagonal, let $C > 0$, $c_i > 0, i = 0, 1, \ldots, n$, let $\vec{P}_0 \in R_+^{2^n}/\{0\}$. There exists a unique continuously differentiable function u: $[0,\infty) \to R_+^{2^n}/\{0\}$ such that u satisfies (27).*

Proof. Since every entry of $A + S$ is positive, every entry of $(A + S)^k$ is positive for any positive integer k. By the definition of irreducible matrix, $A + S$ is an irreducible matrix. According to the definition of $|\vec{P}(t)|$ and the positivity of C, it is obvious that $\frac{|\sum c_iP_i(t)|}{C}$ is a positive bounded linear functional on R^{2^n}. Therefore, there exists a unique continuously differentiable function u that satisfies (27) by Lemma 1. □

We can compute the bacterial population of every genotype combination by using *Mathematica* as before. Here, four contingency genes are considered. We assume that the selection coefficients and carrying capacity coefficients are the same for all combinations with the same number of turned-on contingency genes. The values for the parameters used in numerical solutions are shown in Table 6.

Table 6: Parameters Used in Figure 10

carrying capacity parameter	$C = 10^8$
mutation frequency	$f = 0.0001$
selection coefficients	$s_1 = 1.5 \ln 2/0.4, s_2 = s_3 = s_5 = s_9 = 1.5 \ln 2/0.39$ $s_4 = s_5 = s_7 = s_{10} = s_{11} = s_{13} = 1.5 \ln 2/0.36$ $s_8 = s_{12} = s_{14} = s_{15} = 1.5 \ln 2/0.32, s_{16} = 1.5 \ln 2/0.31$
carrying capacity coefficients	$c_0 = 10, c_1 = 8, c_2 = 6, c_3 = 4, c_4 = 2$
initial conditions	$P(0,0,0,0) = 100, P(0,i_1,i_2,i_3,i_4) = 0, (i_1,\ldots,i_4 = 1,0)$

It is found that we get the same graph for the population of combinations with the same number of turned-on genes. Thus there are five distinct graphs for the population of 16 genotypic combinations.

The graph for the total population is shown below (see Figure 10). From the graph, the total population obtains three increasing levels. The first level happens at about 5 hours, the second one happens at about 32 hours and goes up smoothly, and the last one happens at about 80 hours.

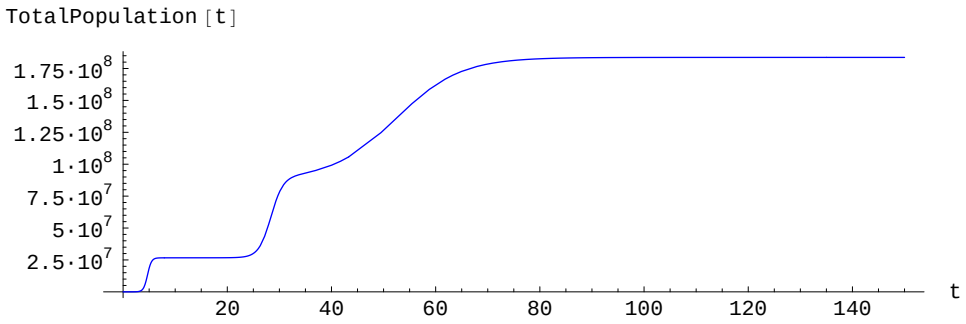

Figure 10: The total population of 16 genotypic combinations with 4 contingency genes.

If we want to get the population graph of bacteria with more than 10 contingency genes when the carrying capacity coefficients are considered, a modified model is needed. Thus, we add carrying capacity coefficients to the modified model we discussed before. The model is shown as follows:

$$\frac{d\vec{G}(t)}{dt} = \widetilde{A} \cdot \vec{G}(t) + \widetilde{S} \cdot \vec{G}(t) - \frac{|\sum c_i G_i(t)|_0}{C} \cdot \vec{G}(t), \quad t \geq 0, \quad \vec{G}(0) = \vec{G}_0, \tag{28}$$

where c_i is a carrying capacity coefficient for $G_i(t)$, which is the average population of all the combinations with i turned-on contingency genes, and $c_0 > c_1 > \ldots > c_n$.

The dominant variant is much more important than other variants since it is necessary to adapt to the host immune environment. We want to determine how fast the population of the dominant variant converges. The convergence time for the dominant variant has been defined before. Upon the condition that the combinations with the same number of contingency genes share the same carrying capacity, we wish to find out how the convergence time changes if the selection coefficients and mutation frequency are both changed. The case of 20 contingency genes is used as an example. The parameters used for simulations are shown in Table 7 in which $\{d_j\}$ is an arithmatic progression with the first term 0.1 and common difference 0.01, and $\{h_j\}$ is an arithmatic progression with the first term 3 and common difference 0.1. We take C to be 10^{10}.

Table 7: Parameters Used in Figure 11

mutation frequency	$f = 3 \times 10^{(-2-h_j)}$ $h_j = 3 + 0.1(j-1), \quad j = 1, 2, \ldots, 11$
selection coefficients	$s_i = 3.64 + d_j, \quad i = 1, 2, \ldots, 20$ $s_{21} = 3.64 + 20d_j$ $d_j = 0.1 + 0.01(j-1), \quad j = 1, 2, \ldots, 11$
carrying capacity coefficients	$c_i = 11 - 0.5i, \quad i = 1, 2, \ldots, 21$

In Figure 11, x-axis represents selection coefficients, y-axis represents the mutation frequency and z-axis is the convergence time for the dominant variant with 20 contingency genes.

We change the number of contingency genes from 6 to 20 and the values for mutation frequency respectively. The values for parameters are shown in Table 8 and we assume C to be 10^{10}.

Figure 12 shows how the convergence time changes under the condition that the number of contingency genes increases from 6 to 20 and the mutation frequency is log-linearly decreasing.

Table 8: Parameters Used in Figure 12

mutation frequency	$f = 3 \times 10^{(-2-h_j)}$ $h_j = 3 + 0.1(j-1), \quad j = 1, 2, \ldots, 11$
selection coefficients	$s_i = 3.64, \quad i = 1, 2, \ldots, g$ $s_{g+1} = 3.64 + 0.1g$
carrying capacity coefficients	$c_i = 11 - 0.5i, \quad i = 1, 2, \ldots, g+1$

Also, we want to know what the convergence time will be as the number of contingency genes increases while the selection coefficients are changing. The number of genes is varied from 3 to 30. Table 9 tells us the values for the parameters we need to use and $C = 10^{10}$. Thus, we can obtain the graph (see Figure 13).

Table 9: Parameters Used in Figure 13

mutation frequency	$f = 3 \times 10^{(-3)}$
selection coefficients	$s_i = 1.82 + d_j, \quad i = 1, 2, \ldots, g$ $s_{g+1} = 1.82 + g \times d_j$ $d_j = 0.1 + 0.01(j-1), \quad j = 1, 2, \ldots, 11$
carrying capacity coefficients	$c_i = 22 - 0.5i, \quad i = 1, 2, \ldots, g+1$

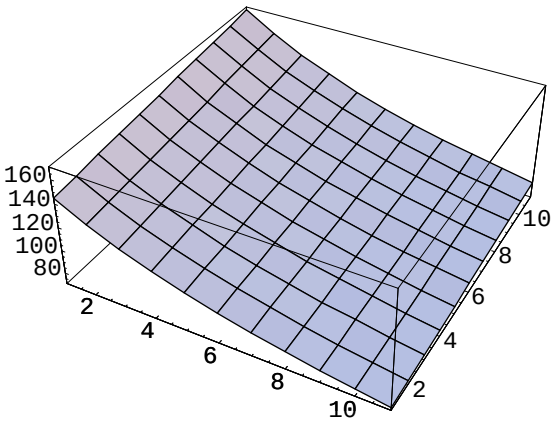

Figure 11: The behavior of the convergence time for the dominant genotype class of 20 contingency genes with the changed selection coefficients in x-axis and mutation frequency in y-axis.

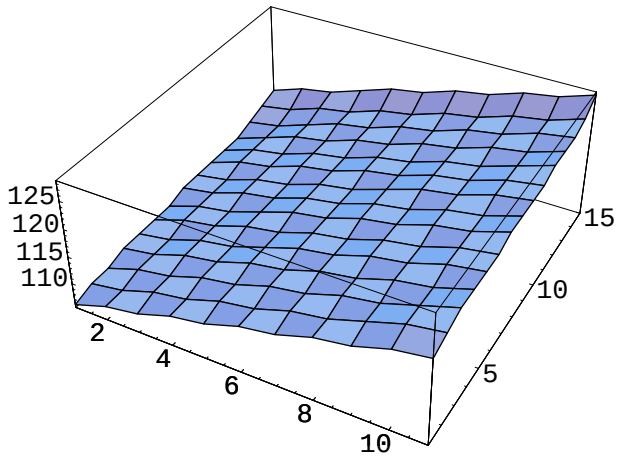

Figure 12: The behavior of the convergence time for the dominant genotype class with the log-linearly decreased mutation frequency in x-axis and the increased number of contingency genes in y-axis.

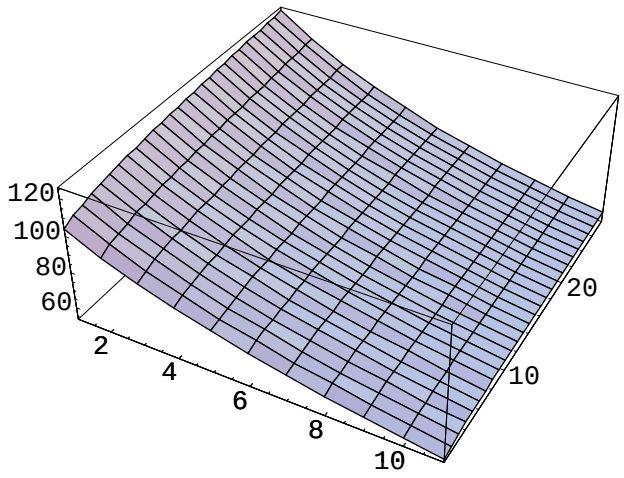

Figure 13: The behavior of the convergence time for the dominant genotype class with the changed selection coefficients in x-axis and the increased number of contingency genes in y-axis.

CHAPTER VI

CONCLUSION

A mathematical model is developed to explore contingency genes' adaptation to the bacterial pathogen *Streptococcus pyogenes* in infected hosts. We perform theoretical and numerical analyses for the model. From the theoretical analysis, a unique nontrivial exponentially asymptotically stable equilibrium solution is obtained for the model. We do numerical simulations to illustrate the solutions of the model by using *Mathematica*. The graphical solutions demonstrate that the bacterial population can evolve from the initial state with all turned-off genes to a state with all turned-on genes very quickly because of highly mutable contingency genes. The class with all turned-on genes causes inflammation in the infected host and the coughing that then propagates the disease. More simulations are performed to demonstrate how the population of the class with all turned-on genes is dependent on selection rates, the number of contingency genes and mutation frequency. To increase the efficiency of the computation and allow a greater number of contingency genes, a modified model is constructed by reducing the number of equations in the ODE model. We provide more simulations for a larger number of contingency genes. The results show how the bacterial population can adapt to the infected hosts in a realistic time frame, dependent on mutation frequencies, selection rates, the number of contingency genes, and the carrying capacity parameter.

Strep thoat is an infection caused by streptococcal bacteria. It can spread within close contacts, so that it is important to isolate the patients with strep throat [34]. Our model explains the clustering of cases in a family, in which the genetic similarity of siblings allows more rapid adaptation to hosts. Patients with strep throat usually need antibiotics treatment, which lasts for about ten days. It is very important that the antibiotics medication is followed to completion even though recovery may seem complete after three to four days, since contingency genes have the ability of surviving the host defense. The studies of the ODE model increase our understanding of the important role of contingency genes in quick adaptation to the bacterial pathogen. The simulations of this model demonstrate

the process of contingency gene evolution in bacteria. Specifically, a large number of contingency genes (as in Table 4 and 5) can be switched on and attain domination within 4-6 days with realistic mutation frequencies and doubling times.

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