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The Within-Host Population Dynamics of Normal Flora in the Presence of an Invading Pathogen and Antibiotic Treatments

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Abstract A mathematical competition model between normal flora and an invading pathogen was devised to allow analysis of bacterial infections in a host. The normal flora includes the various microorganisms that live on or within the host and act as a primary human immune system. Despite the important role of the normal flora, no mathematical study has been undertaken on models of the interaction between it and invading pathogens against a background of antibiotic treatment. To quantify key elements of bacterial behavior in a host, pairs of nonlinear differential equations were used to describe three categories of human health conditions, namely, healthy, latent infection, and active infection. In addition, a cutoff value was proposed to represent the minimum population level required for survival. The recovery of normal flora after antibiotic treatment was also included in the simulation because of its relation to human health recovery. The significance of each simulation parameter for the bacterial growth model was investigated. The devised simulation showed that bacterial proliferation rate, carrying capacity, initial population levels, and competition intensity have a significant effect on bacterial behavior. Consequently, a model was established to describe competition between normal flora and an infiltrating pathogen. Unlike other population models, the recovery process described by the devised model can describe the human health recovery mechanism.

Key words: Population dynamics, antibiotic treatments, recovery process, normal flora, cutoff value

The emergence of antibiotic-resistant bacteria is a problem to both public health and the individual host. As bacterial pathogens have become resistant to antibiotic treatments because of the increasing use of antibiotics, the number of incurable bacterial diseases has been increasing [18]. Despite the recent introduction of several new antibiotics and enormous efforts to reduce the transmission of antibiotic-resistant bacteria within hospitals and the community, the incidence of antibiotic-resistant infections has continued to increase [4]. Therefore, the optimal use of antibiotics and proper health care policies are of key importance.

Mathematical modeling has been widely used to solve this problem and thus has made substantial contributions to our understanding of within-host microorganism population dynamics and of the epidemiological dynamics of infections [1, 7, 15–17, 19]. Thus far, many researchers have evaluated the relationships between antibiotic use and antimicrobial resistance at the level of both an individual patient and a community [2, 3, 5, 6, 8–10, 12–14, 21, 22]. A particularly interesting approach was reported by Webb *et al.* [22], who proposed a two-level population model, which represents the growth of plasmid-free (nonresistant) and plasmid-bearing (resistant) bacteria, to quantify the key elements of nosocomial (hospital acquired) infections. Frequently, a bacterial pathogen is drug resistant because it has a plasmid bearing one or more resistance genes. Such plasmids are called R-plasmids (resistance plasmids). Once a bacterial cell acquires an R-plasmid, it may be transferred to other cells rapidly via normal gene exchange processes [20]. Indeed, the genes encoding drug resistance are present in both bacterial chromosome and plasmids. In order to simplify their model, Webb *et al.* [22] assumed that the emergence of resistance could only occur through the acquisition of plasmids, and other mechanisms (*e.g.*, chromosomal mutation and efflux pumps) were omitted.

Moreover, the normal flora is also of interest. The interaction between a host and a microorganism is a dynamic process in which each protagonist acts to maximize its survival. The human race has many symbiotic microorganisms that comprise the normal flora; approximately 10^{14} individual microbes exist in the normal human body [20]. In general,

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these symbiotic microorganisms occupy most of the niches available in the host and are well adapted to utilize available resources and nutrients, and thus they constitute the microbial species. Moreover, the normal flora can prevent pathogens from causing infections by microbial antagonism. For example, symbiotic microorganisms prevent pathogenic bacteria from growing by preoccupying a specific niche. However, an upset in the microbial balance can result in host infection by normally symbiotic microorganisms [20]. Thus, although these microorganisms offer a degree of protection from invading pathogens, they can become pathogenic under certain circumstances. This phenomenon is known as opportunistic infection [20]. However, in the present study, it was assumed that only infiltrating pathogens could cause disease and transfer R-plasmid. Thus, the normal flora and infiltrated pathogens only act as beneficial and harmful organisms, respectively. Therefore, behaviors of normal flora can affect competition balance between the dominant species and invading pathogens in the human body. For this reason, modeling of within-host population dynamics should consider the growth behavior of normal flora. However, despite the importance of these organisms, to the best of our knowledge, it has not been represented by a mathematical characterization and no interaction model is available describing the relations between normal flora and invading pathogens.

In this paper, we propose a simple mathematical competition model for normal flora and an invading pathogen. In addition, the effects of antibiotics on both of these components were investigated. The main aim of this study was to understand how symbiotic organisms affect pathogen colonization and which model parameters are most effective in destroying pathogenic bacteria. In addition, we investigated the recovery process of the proliferation rate of the normal flora after antibiotic treatment.

MATERIALS AND METHODS

Model Description

To apply the concept of normal flora to a model, the Gause (1934) competition model and the two-level bacterial population model by Webb *et al.* [22] were combined and modified. A schematic diagram of the competition model between normal flora and pathogens in the host is shown in Fig. 1. The three differential equations are as follows (1):

$$\frac{dn^-}{dt}=\left[-\frac{\tau n^+}{n^-+n^+}+\beta^- -\frac{(n^-+n^+)+\varepsilon n_{nm}}{\kappa}\right](n^- -\zeta)n^- +\gamma n^+ \quad (1A)$$

$$\frac{dn^+}{dt}=\left[-\frac{\tau n^-}{n^-+n^+}+\beta^+ -\frac{(n^-+n^+)+\varepsilon n_{nm}}{\kappa}-\gamma\right](n^+ -\zeta)n^+ \quad (1B)$$

$$\frac{dn_{nm}}{dt}=n_{nm}\left[\beta_{nm}-\frac{n_{nm}+\delta(n^-+n^+)}{\kappa_{nm}}\right](n_{nm}-\zeta) \quad (1C)$$

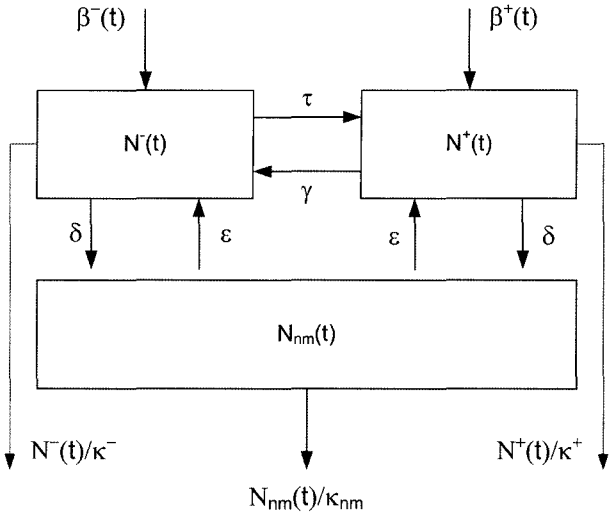

Fig. 1. A schematic diagram of the within-host population dynamics model.
Here, β is the proliferation rate, n the population level of each bacterial species, and plus (+) and (–) represent plasmid-bearing (resistant) and plasmid-free (nonresistant) bacteria, respectively. The subscript nm represents the normal flora. βκ is the carrying capacity, τ the recombination rate, γ the reversion rate, ε the competition intensity of normal flora to the pathogens, and δ the competition intensity of a pathogen to the normal flora.

Equation (1) represents the growth behavior of plasmid-free bacteria (1A), plasmid-bearing bacteria (1B), and normal flora (1C), respectively. The growth patterns of bacteria are interconnected with each other because the equation for each bacterial growth shares the population level as a common parameter. All the equations are changed to the simulation sheet (MATLAB Simulink Ver. 6) in the shape of a block diagram. As shown in Fig. 1, blocks connected with arrows represent three bacterial types; *e.g.*, normal flora, and nonresistant and resistant bacteria. The arrows represent flows that can be explained using some rate parameters, such as recombination rate (τ), reversion rate (γ), and competition intensities (ε, δ). The descriptions of model parameters are as follows:

n_{nm}, n^-, and n^+ represent each population level of normal flora, plasmid-free bacteria, and plasmid-bearing bacteria, respectively. Thus, $n^-/(n^-+n^+)$ is the fraction of plasmid-free bacteria, and $n^+/(n^-+n^+)$ the fraction of plasmid-bearing bacteria. β is the proliferation rate of each population in the host, and βκ is the carrying capacity (the total tolerable bacteria load). γ is the reversion rate of the plasmid-bearing bacteria to plasmid-free ones, and thus γn^+ describes the reversion process. Let τ be the recombination rate of the plasmid-free and plasmid-bearing bacteria. Then, $\tau n^- n^+/(n^-+n^+)$ represents the recombination process. ζ is the cut-off value of the minimum population level for survival, and the parameters ε and δ are the competition intensities. Specifically, ε is the effect of normal flora on the growth of pathogens, and δ is the effect of pathogen on the growth of

normal flora. The competition intensity is a concept similar to Gause's competitive exclusion principle, as normal flora and pathogens use resources in precisely the same way, and thus cannot coexist. Therefore, one species will drive the other into extinction with an intensity level.

Cutoff Value

Although an ordinary differential equation-based model is suitable for evaluating population dynamics or a time-dependent system, some complementary programming is needed to obtain reasonable data from the simulation. In the present study, a cutoff value is proposed to represent the minimum population level required for survival, which is similar to the concept underlying the Allee effect [11]. Usually, the analytical solution of an ordinary differential equation is in the form of an exponential. The bacterial population concerned will fall to zero if the value of the overall differential equation is negative as time approaches infinity. This means that in order to totally eliminate the pathogen, antibiotic treatment (the equation value is negative at infinity) is required for an infinite time. In addition, if a population level decreases to below 1, an exponential equation would return non-integer results, which is unrealistic. Figs. 2A and 2B show a comparison without and with the cut-off value, respectively.

Fig. 2B shows that extinguished bacteria cannot grow again. However, Fig. 2A shows that the population level of the bacteria increases even after the plasmid-free bacteria have been eliminated. This demonstrates that a simulation model without a cutoff value produces non-integer population levels at below a population of 1. For this reason, a cutoff value should be considered in the programming procedure in order to prevent wrong simulation results. Thus, in the present study, a bacteria is assumed to be absent after its level falls below 1. Therefore, bacteria counts were subjected to a cutoff value of 1 in our study.

Results and Discussion

Health Condition Classification

One of the main advantages of this model is its ability to describe a phenomenon intuitively when parameter values are suitably modified. In order to examine the relationship between a bacterial infection and a human health condition, the following three different classifications of individual health were used: normal health, latent infection, and active infection. This classification is important not only in terms of epidemiology but also in terms of the spreading mechanism of resistant bacteria, because the degree of pathogenic infiltration in the human body depends on individual health. Usually, most people in the community are healthy, which means that healthy people can suitably protect themselves against pathogenic bacteria. Conversely, pathogens can more easily infiltrate the body when health is depressed for some reason.

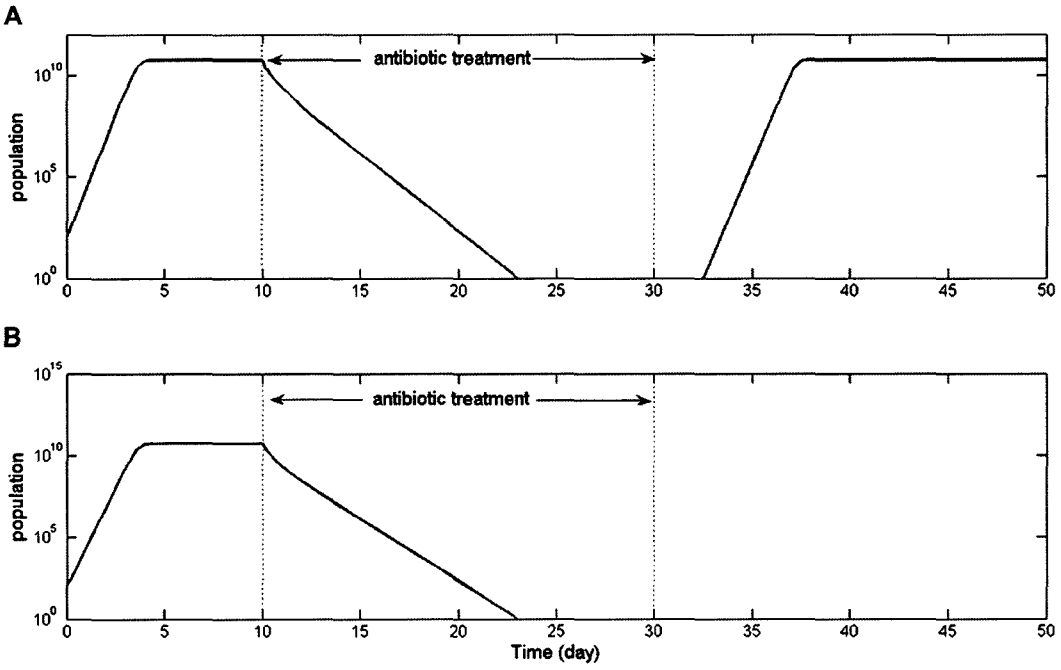

Fig. 2. The effect of cutoff value being applied (**B**) or not (**A**).
Only nonresistant bacterial behavior is shown. Here, $\beta^{-}=8$ ln (2), $\beta^{-}=-2$ after treatment, $\kappa^{-}=10^{10}$, initial population level=100, and cutoff value=1. Antibiotic treatment began on day 10 and lasted for 30 days. Note that the population increases again after 33 days even though the population was below 1 (bacteria eliminated) (**A**). In contrast, the treatment was successful in eliminating the nonresistant bacteria (**B**).

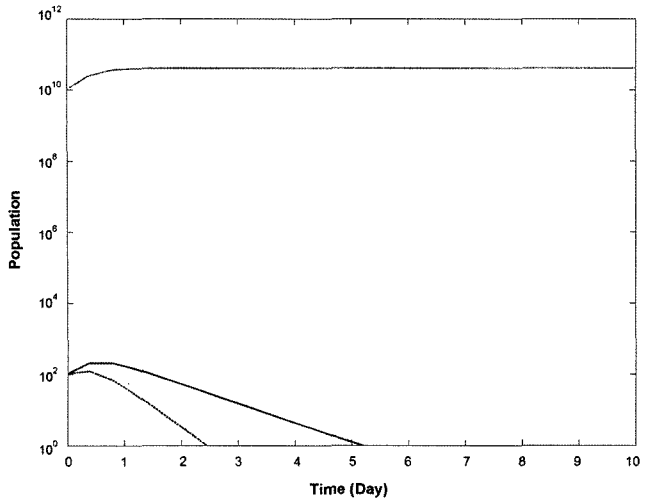

Fig. 3. Behavior of the normal flora (dotted line), and of nonresistant (dashed line) and resistant (straight line) bacteria of normal status.

The parameters are β_{nm}=6 ln(2), β^+=6 ln(2), β^-=4 ln(2), τ=0.001, γ=0.00001, ε=1.2, δ=0.4, and all $\kappa=10^{10}$. The initial population of the normal flora was 10^{10} and those of the two pathogens 100 apiece. Although the resistant bacteria have the same proliferation rate as the normal flora, the resistant strain was eliminated owing to the high initial population level of the normal flora.

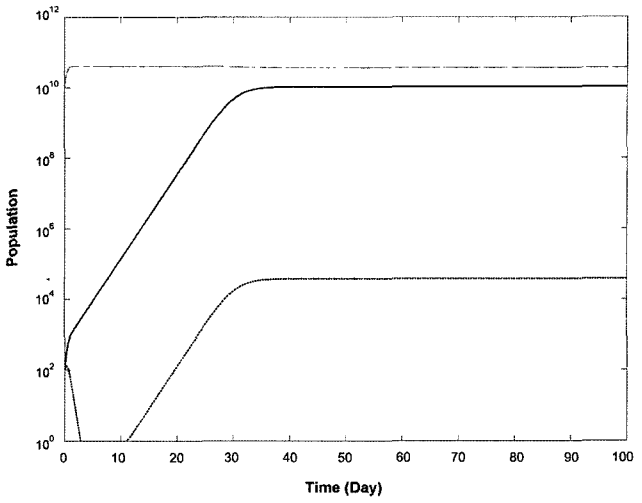

Fig. 4. Behavior of the normal flora (dotted line), and of nonresistant (dashed line) and resistant (straight line) bacteria of latent status.

The parameters are β_{nm}=6 ln(2), β^+=8 ln(2), β^-=4 ln(2), τ=0.001, γ=0.00001, ε=1.2, δ=0.4, and all $\kappa=10^{10}$. Initial population of the normal flora was 10^{10} and those of the two pathogens were 100 apiece. Interestingly, the extinguished nonresistant bacteria re-emerged owing to a reversion process, even though cutoff parameters had been applied to the simulation. In this case, the infiltrated pathogen will persist and converge to a steady state owing to competition with the normal flora.

A normal status means that a host is healthy. This indicates that the normal flora is the dominant bacteria in the host, and maintains equilibrium with the host immune system. Therefore, although the pathogens infiltrate the host, they will be extinguished as a result of the strong normal flora (Fig. 3). As shown in Fig. 3, the proliferation rates of normal flora, resistant bacteria, and nonresistant bacteria were set at 6ln(2), 6ln(2), and 4ln(2), respectively. The proliferation rate is a primary parameter of population growth. In other words, even if the initial population of a group of bacteria is low, it can become the dominant species if it has a high proliferation rate. Fig. 3 shows an interesting result; *i.e.*, even when the proliferation rates of normal flora and resistant bacteria are the same, the former remains as the dominant species because its initial population is higher than that of other species.

The latent infectious status is when infiltrated pathogens just maintain their population and do not cause any symptoms in their host. However, the pathogens can initiate an infection if the health of a host is depressed or they can exploit some weakness in the immune system. Fig. 4 shows that pathogens will persist and converge to a steady state under this condition. This result also shows an interesting growth characteristic of plasmid-free bacteria. When bacteria infiltrate a host, the nonresistant bacterial population level falls to less than 1 because of competition with the normal flora. Hence, the nonresistant bacteria vanish. However, as shown in Fig. 4, nonresistant bacteria would emerge again after 10 days even after applying the cutoff parameter. This phenomenon might be caused by a reversion process of the pathogenic bacteria. More precisely, a bacterium containing a plasmid may revert to a bacterium without a plasmid, the so-called reversion process [22]. On

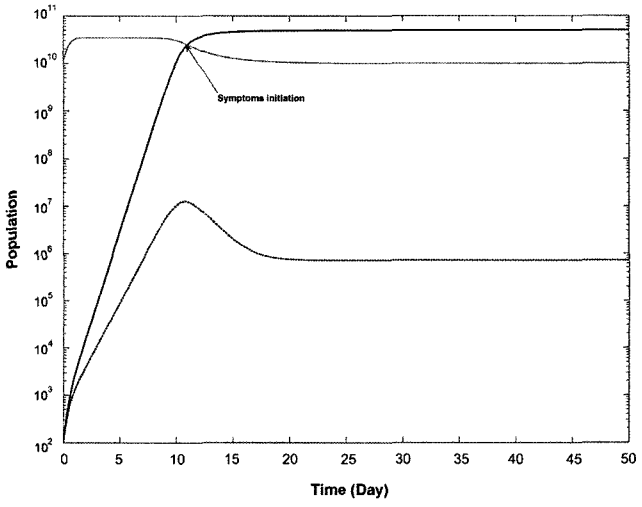

Fig. 5. Behavior of normal flora (dotted line), and nonresistant (dashed line) and resistant (straight line) bacteria during acute infection.

The parameters are β_{nm}=5 ln(2), β^+=9 ln(2), β^-=8 ln(2), τ=0.001, γ=0.00001, ε=1.3, δ=0.5, and all $\kappa=10^{10}$. The initial population of the normal flora was 10^{10} and of the two pathogens 100 each. Resistant bacteria overcame normal flora, and became the dominant species.

the other hand, when a bacterium with a plasmid combines with a bacterium not carrying the plasmid, both of the bacteria can have the plasmid, which is called a recombination process [22]. Therefore, although an infiltrated pathogen vanishes for various reasons, it can emerge again as a result of a reversion or recombination process of the same species that has not vanished. The reversion rate used in this study was 0.00001, which means that 0.001% of the total resistant bacteria can lose their R-plasmid and become nonresistant. Moreover, the recombination rate is higher than the reversion rate because the acquiring process of R-plasmid is a survival problem to the bacteria under the antibiotic treatment condition. Hence, the reversion rate used in this study was lower than the recombination rate by 100 times (τ=0.001).

Fig. 5 shows that the proliferation rate of resistant bacteria is higher than that of the normal flora. Thus, infiltrating resistant bacteria are destined to overcome the dominant normal flora within a host. After 20 days, the population of the resistant bacteria reaches their carrying capacity, and resistant bacteria have or induce deleterious effects to the host. The end result may be disease. This is known as the active infectious status, and antibiotic treatments are required at this time to prevent the pathogen from becoming the dominant species in a host.

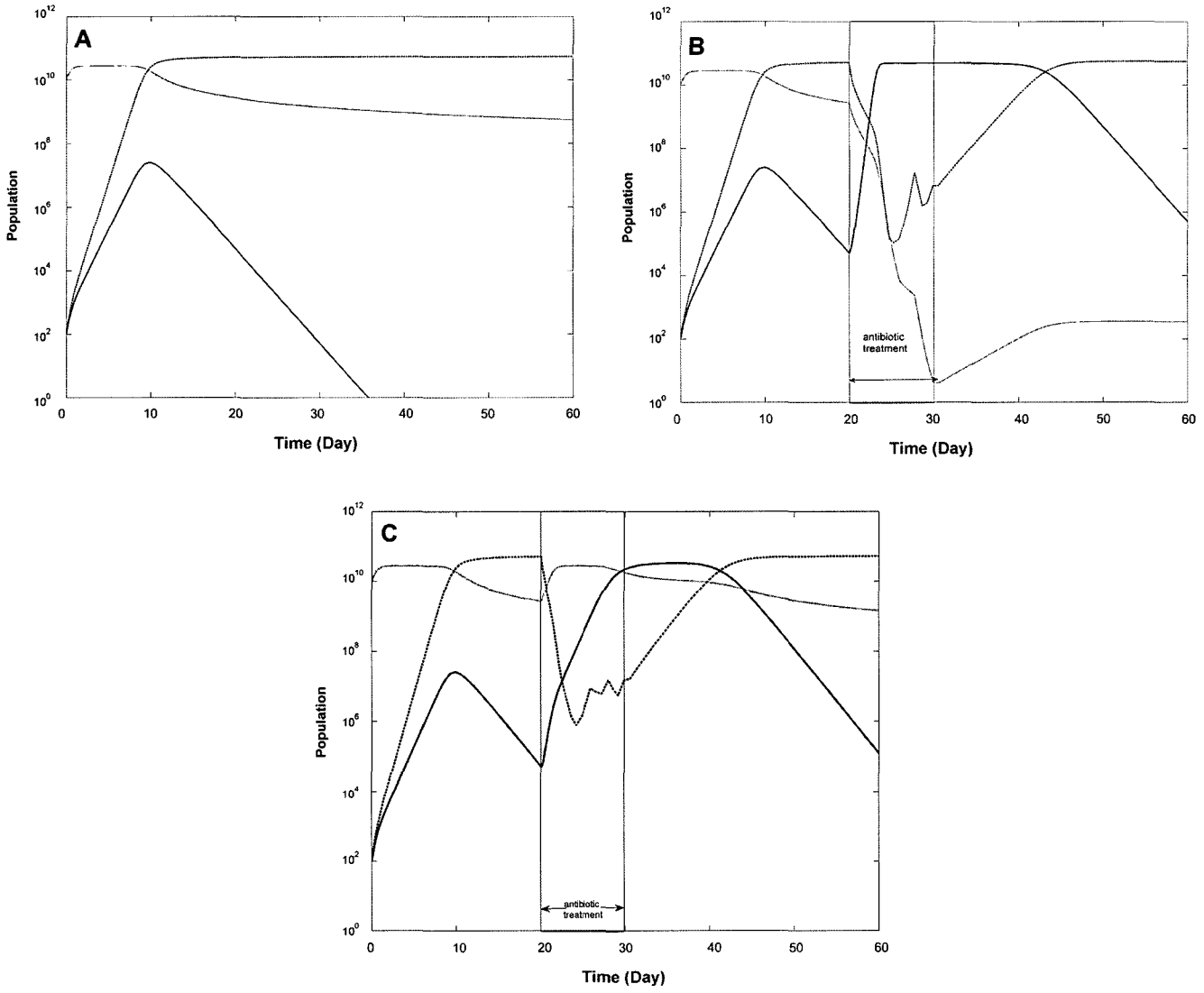

Fig. 6. Various patterns of bacterial behavior according to disease status. Acute infection status before antibiotic treatment (**A**), bacterial behavior when broad-spectrum antibiotics are administered (**B**), and narrow-spectrum antibiotic effect (**C**).
Antibiotic treatment was started on day 20 and lasted 30 days. The parameters are β_{nm}=4 ln(2), β^{+}=7 ln(2), β^{-}=8 ln(2), τ=0.001, γ=0.00001, ε=1.3, δ=0.5, and all $\kappa=10^{10}$. In **B**, normal flora (dotted line) showed a tendency to be reduced by broad-spectrum antibiotics during the treatment period. After antibiotic treatment (after 30 days), normal flora may not be the dominant species. For narrow-spectrum antibiotic treatment, in **C**, normal flora were not affected by antibiotics and maintained their population level. However, normal flora did not recover to normal dominant species, and instead showed a decreasing tendency because of the nonresistant bacteria (dashed line) and resistant bacteria (straight line), after treatment.

Antibiotic Treatment Strategies

In the previous section, the competition and growth behavior of normal flora and pathogens in the absence of antibiotic treatment was investigated. Pathogenic bacteria were either eliminated or controlled by the normal flora. An antibiotic treatment is required when a beneficial human microorganism is depressed by an infiltrating pathogen and results in an active infectious status. In order for an antibiotic treatment to be successful, it must kill or inhibit the pathogen while producing little or no damage to the host. If antibiotics were treated to the host with extreme dosage, then not only pathogen but also normal flora can be damaged. This is why the concept of cutoff value was used, as this prevents the re-emergence of eliminated bacteria, and the concept of normal flora is used to prevent the overuse of antibiotics. Antibiotics were classified into two categories: narrow- and broad-spectrum. Narrow-spectrum drugs are effective only against a limited variety of pathogens, whereas broad-spectrum drugs attack many different types of pathogens. In addition, similarities between pathogen types also need to be considered when treating infections with antibiotics. For example, if the normal flora and pathogen are of the same species, the antibiotics are likely to affect both equally. On the other hand, a broad-spectrum drug can affect both even when the normal flora and pathogen belong to different species. In order to avoid confusion, we assumed that the normal flora and the infiltrating pathogen are of different species. Fig. 6 shows the effect of an antibiotic treatment, and Fig. 6A shows active infectious status before antibiotic treatment. After 10 days, resistant bacteria caused disease, while the nonresistant bacteria vanished in backgrounds of normal flora and nonresistant bacteria. Broad- and narrow-spectrum drugs were also examined to compare the effects of antibiotic ranges. Figs. 6B and 6C show the effect of a broad-spectrum drug and narrow-spectrum drug, respectively, on infectious status. The broad-spectrum drug affected both the normal flora and nonresistant bacteria. However, because the normal flora has a lower rate of proliferation than nonresistant bacteria, the nonresistant bacteria predominates after treatment (Fig. 6B).

Fig. 6C shows that narrow-spectrum drug administration affected the pathogen without affecting the normal flora. As shown in Fig. 6C, the growth of the normal flora actually increased slightly during treatment because of the effects of antibiotics on nonresistant bacteria. However, after treatment, normal flora were re-depressed because of competition.

Recovery of Normal Flora After Treatment

The previous section showed the effects of a range of antibiotics. However, after treatment with either a narrow- or broad-spectrum drug, nonresistant bacteria became the dominant species. This means that a permanent cyclic antibiotic treatment is required, because nonresistant bacteria can emerge again periodically after treatment. Such a phenomenon may appear to be unrealistic. For example, normal healthy people, can overcome disease caused by an infiltrating pathogen via their own immune systems and proper medical treatment. However, it explains what can occur if host immunity has been depressed by some congenital or acquired factor. Nevertheless, it is not appropriate to expand this generally to those infected with a pathogen for a short time. In general, most healthy people maintain a high proliferation rate and population of normal flora (healthy status; Fig. 3). A pathogen can proliferate when the immune system is weakened; *i.e.*, when the proliferation rate of normal flora is depressed. Therefore, the proliferation rate of normal flora may aid recovery to the healthy state if antibiotics block the pathogen. Fig. 7 shows a successful treatment that eliminated a pathogen because of the proliferation rate recovery of the normal flora after antibiotic treatment. Unlike Fig. 6C, Fig. 7 shows that the population of the normal flora recovered to carrying capacity after antibiotic treatment, and both pathogens had vanished as a result.

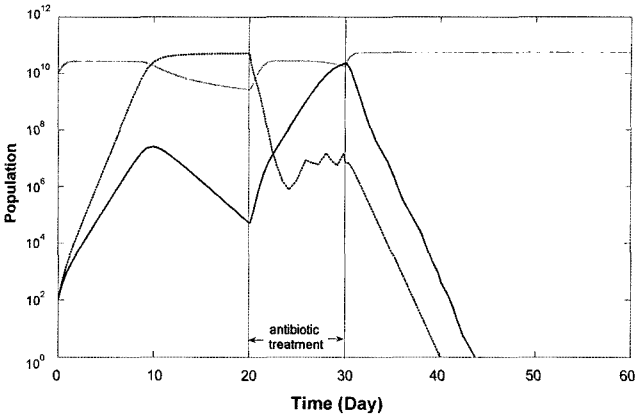

Fig. 7. The normal flora recovery process after antibiotic treatment.
The parameters used were β_{nm}=4 ln(2), β^{+}=7 ln(2), β^{-}=8 ln(2), τ=0.001, γ=0.00001, ε=1.3, δ=0.5, and all $\kappa=10^{10}$. Note that proliferation rate recovery was set to $\beta_{nm,\,after}$=8 ln(2). Unlike the growth patterns shown by normal flora (dotted line) in Fig. 6C, its population recovered to carrying capacity, and resistant (straight line) and nonresistant (dashed line) bacteria were eliminated by this recovery.

In this study, we developed a simple within-host dynamic simulation model to investigate competition between the normal flora and an infiltrating pathogen in the presence of antibiotic. The described competition model between the normal flora and a pathogen was based on Gause's competitive exclusion principle. The main advantage of this approach is that it allows the intuitive and realistic behavior of bacterial species in an infected host to be

modeled. Simulation results showed that the normal flora can be depressed by antibiotics and other pathogens, and suggest that the normal flora should be considered when devising optimal antibiotic treatment strategies. Some errors in the previous simulation models can lead to the incorrect modeling of bacterial behavior. Therefore, a cutoff value was applied in the present study to the re-emergence of previously eliminated bacteria.

Three categories, normal, latent infection, and active infection, were used to investigate bacterial behavior under different health conditions. It was assumed that a pathogen can proliferate when the immune system is weakened, and thus, these classifications describe more realistically bacterial infections in the host. After antibiotic treatment, some pathogenic bacteria may persist or even become dominant species. This phenomenon was shown in some cases of bacterial infection models [1–3, 9, 22]. The recovery of the proliferation rate of normal flora was introduced into the model in consideration of the human health recovery mechanism in population dynamics. As a result, infiltrated pathogens were successfully removed, owing to the recovery of the proliferation rate of the normal flora. Unlike previous models, the described model can be used to describe not only bacterial interactions within the human body but also the spread of antibiotic-resistant microorganisms in the community, because of the introduction of the normal flora concept. Thus, we suggest that the normal flora should be considered in the fields of host population dynamics and pharmacodynamics.

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