J. theor. Biol. (1995) **176,** 281–290

The Dynamics of *Helicobacter pylori* Infection of The Human Stomach

DENISE E. KIRSCHNER†‡ AND MARTIN J. BLASER‡§

† *Department of Mathematics, Texas A&M University, College Station, TX* 77843-3368
and ‡ *Departments of Medicine and Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN* 37232, *U.S.A.*

(*Received on* 12 *January* 1995; *Accepted on* 2 *May* 1995)

Helicobacter pylori is a bacterial pathogen of the gastrointestinal tract of humans causing chronic superficial gastritis which persists for decades. The mechanism by which *H. pylori* is able to persist, despite environmental constraints, remains unknown. Therefore, a model is proposed describing the interactions of *H. pylori* with its host, involving an autoregulatory network in which inflammation leads to nutrient release. A determinist mathematical model examining the interactions necessary to maintain chronic infection indicates that this proposed autoregulatory network can produce steady-state solutions, and the model is robust in encompassing biological variations.

Introduction

Mucosal surfaces in vertebrates may be considered as internal structures in communication with the external environment. Bacteria that are introduced to these locales (such as the mammalian gastrointestinal tract) often face three major constraints limiting their numbers: peristalsis, microbial competition and specific immune effectors. Not surprisingly, for most exogenous organisms, colonization is transient.

In contrast, *Helicobacter pylori* is an acquired bacterial pathogen of the gastrointestinal tract that persists for decades (Blaser & Parsonnet, 1994). *H. pylori* induces chronic gastric inflammation, which results in peptic ulcer disease or gastric neoplasia in a subset of infected persons; as such, it is an important human pathogen (Nomura *et al.*, 1991; Hentschel *et al.*, 1993). *H. pylori* is able to flourish in the acid-rich stomach where there is essentially no microbial competition, and the immune response, although universally present (Dooley *et al.*, 1989), appears to be ineffective (Crabtree *et al.*, 1991). Colonization provides a model to study the ability of bacterial populations to persist despite the physical constraint of peristalsis. This *in vivo* result parallels those encountered in classical chemostat models, where in the presence of a nutrient source, a microbe persists (*cf.* Edelstein-Keshet, 1987; Gause, 1969; Rubinow, 1975).

Auto-regulatory feedback is proposed as the mechanism for the ability of *H. pylori* to persist. A mathematical model created to explore the theoretical construct indicates that the proposed feedback network produces the observed steady-state solutions.

Even for *H. pylori*, however, persistence may not be simple. Bacterial adherence is a strategy for resisting peristalsis, since the mucus layer in which most *H. pylori* reside is washed away due to peristalsis. The epithelial cells also are sloughed, although at a slower rate (Lipkin *et al.*, 1963). Since adherence to the epithelial cells is thus beneficial, *H. pylori* migrates from the mucus to adhere to these cells. Since the adherent *H. pylori* divide, and the carrying capacity of the tissue is most likely near saturation, most daughter cells must migrate into the mucus layer. Thus, bi-directional migration is assumed.

Although most *H. pylori* cells are free-living and highly motile in the mucus layer over-laying the gastric epithelium, a small proportion (approximately 1–5%)

§ Author to whom correspondence should be addressed at: Division of Infectious Disease, A3310 Medical Center North, Vanderbilt University School of Medicine, Nashville, TN 37232, U.S.A.

attach to epithelial cells, forming adherence pedestals (Hessey *et al*., 1990; Thomsen *et al*., 1990). Although estimates of binding vary between studies, it is clear that only a small minority of *H. pylori* are bound to epithelial cells. Hence, we assume that the free-living *H. pylori*, referred to as mucus (M) population, and those living on the epithelial cells, the adherent (A) population, represent 98% and 2% of the *H. pylori* cells, respectively. This high $M{:}A$ ratio, although characteristic, is not necessary for persistence, as low concentrations of *H. pylori* may be present during the course of infection. Therefore, we hypothesize that it is the A population which serves to sustain the infection, and the M population is present to replenish A and for transmission to new hosts.

The existence of two populations (adherent and non-adherent) with different survival characteristics, and the likelihood that there is interaction between these two populations, indicates that the characteristics of *H. pylori* infection are mathematically complex.

To explain how *H. pylori* derives its nutrition from the host, a model has been proposed in which these colonizing (non-invasive) organisms adaptively induce an inflammatory response in the host (Fig. 1). In this model, bacteria elaborate pro-inflammatory effectors provoking host responses leading to tissue damage with consequent nutrient release; in isolation, this is a positive-feedback cycle that appears favorable for *H. pylori* (Fig. 1). Inflammation, while advantageous to the host for microbes that can be eliminated, may be deleterious when infection cannot be eradicated, since it leads to impairment of tissue structure and function. Thus, the ability of hosts to curtail inflammatory responses during persistent infections may be adaptive, and natural selection may have enriched for populations that down-regulate inflammation (Blaser, 1993). Not surprisingly, the cellular response to *H. pylori* infection appears to be suppressed (Karttunen, 1991; Sharma *et al*. 1994). In the long-term, uncontrolled inflammation may be deleterious for *H. pylori* as well, since its niche would be lost (Ihamaki *et al*., 1985; Karnes *et al*., 1991); thus it may also be adaptive for *H. pylori* to down-regulate inflammation (Blaser and Parsonnet, 1994; Nomura *et al*., 1991; Hentschel *et al*. 1993). Consistent with this view is the observation that important *H. pylori* surface molecules, such as the lipopolysaccharide, have low pro-inflammatory activity (Muotiala *et al*., 1992).

Thus, *H. pylori* may be constrained both to continue replicating to maintain population and to preserve its environment to ensure long-term survival. Multiplicity of goals can be best handled by regulatory pathways; systems involving environmental sensors and regulatory activators are highly conserved in bacteria (Parkinson, 1993). Released host nutrients may activate *H. pylori* signal transduction pathways that

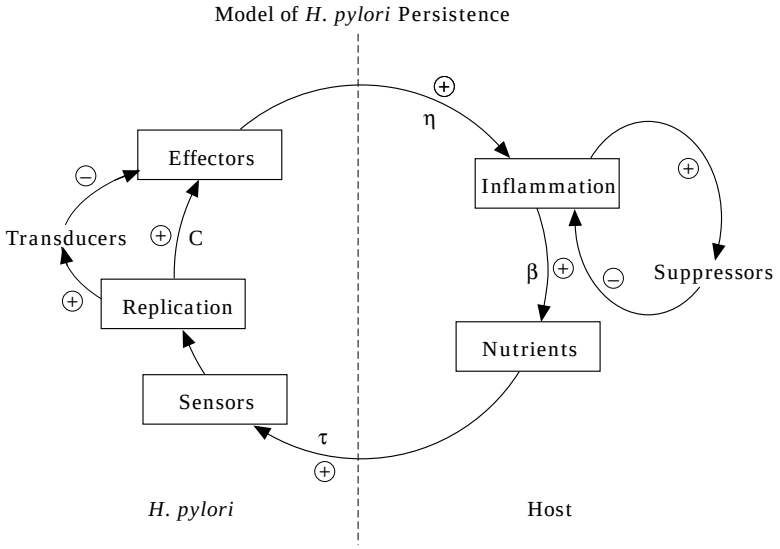

FIG. 1. Feedback model. A model proposed to describe the interactions of *H. pylori* with the host incorporating positive and negative feedback systems. Effectors (E) released by *H. pylori* cells are adsorbed into the mucosa and induce inflammation. Inflammation leads to release of nutrients which are taken up by *H. pylori* cells allowing replication and further release of effectors. The relationships within this cycle are governed by the parameters τ, c, β and η. It is postulated that in the steady state, the host suppresses inflammation, which limits the nutrient release produced by any level of effectors, and that *H. pylori* curtails signal transduction, which limits the number of effectors that a given level of nutrients will induce.

repress synthesis of bacterial pro-inflammatory effectors (Blaser & Parsonnet, 1994); nitrogen repression (Cussac *et al*., 1992) of cloned *H. pylori* urease is consistent with this hypothesis, since urease and its products have important pro-inflammatory activities (Mai *et al*., 1992; Suzuki *et al*., 1992). The monitoring of host-derived nutrients by *H. pylori* would permit modulation of inflammation and bacterial numbers at the lowest level necessary for prolonged carriage of the population. Using the proposed feedback model for *H. pylori* infection (Fig. 1), we sought to create a mathematical model that elaborates these interactions, and to describe the ranges of values for key parameters permitting steady-state solutions.

The Model

Four populations are defined and their interactions are formulated using differential equations describing their rates of change, where $M(t)$ is the concentration of *H. pylori* in the mucus layer at any time, and $A(t)$ is the concentration of *H. pylori* adherent to the epithelial cells. Let $N(t)$ represent the nutrients and $E(t)$ the effectors.

THE MICROBE POPULATIONS

$$\frac{dM}{dt} = g_M \cdot r \cdot N(t)M(t) - \mu_M M(t) - aM(t)(K - A(t)) + \delta A(t). \quad (1)$$

In this equation, the change in population M is marked by a growth term which is a function of nutrient; a loss term, at rate μ_M, due to shedding of the mucus; a migration (loss) term, at rate a, for the M population which can become the A population when the population of A is below the carrying capacity of the epithelium, K; and a gain term from the migration of adherent *H. pylori* to the mucus, at rate δ, due to their replication.

$$\frac{dA}{dt} = g_A \cdot r \cdot N(t)A(t) - \mu_A A(t) + aM(t)(K - A(t)) - \delta A(t). \quad (2)$$

In this equation, the change in population A is marked by a growth term which is a function of nutrient, a loss term, at rate μ_A, due to sloughing of epithelial cells; a gain term from the mucus organisms (M), at rate a, when the A population is less than the carrying capacity; and a loss term, at rate δ, representing the migration of replicating adherent bacteria to the mucus layer. Although a linear growth term is used here to represent bacterial growth, many choices are plausible. For example, a Michaelis–Menten-type growth term ($g_M rN(t)/(K+N(t))$) also was considered, and the results were similar with the linear growth term, so the simpler was chosen for the model.

Each growth term is a function of the nutrient, and since the nutrient is growth-limiting, the total amount is consumed by populations $M + A$ in proportions g_M, g_A, respectively, such that $g_M + g_A = 1$.

THE POSITIVE AND NEGATIVE FEEDBACK SYSTEMS

$$\frac{dN}{dt} = \beta E(t) - g_M rN(t)M(t) g_A rN(t)A(t). \quad (3)$$

This equation represents the change in nutrient concentration, which depends solely on the presence of the other populations. The growth term for the nutrient population is governed by the effectors, and the loss is dependent on the mucus and adherent populations of *H. pylori* which consume it:

$$\frac{dE}{dt} = [c - g(N)]S(t) - \eta E(t), \quad (4)$$

This equation represents the change in the effector concentration, where the total *H. pylori* population, $S(t) = M(t) + A(t)$, and was derived as follows. Since effector production is governed by the $S(t)$ population through the amount of nutrient present, $S(t)$ must be scaled by this limiting factor. The term $c - g(N)$ represents the amount of effector production per unit of $S(t)$ as a function of N. This equals 0 when $g(N) = c$ (maximal effector production), and this has value c when no nutrient is present. (This implies that $g(0) = 0$, and $g(\infty) = c$.) A function $g(N)$ that achieves these mathematical results is of the form $g(N) = cN(t)/(\tau + N(t))$; therefore, $c - g(N) = c\tau/(\tau + N(t))$. The constant τ governs the production of effectors in the presence of a low nutrient concentration. The equation also includes a loss term $-\eta E(t)$ from the interaction of effectors with the host epithelial cells, i.e. loss through absorption and utilization.

Analytical Results

To analyze eqns (1)–(4), the steady-state system that occurs when all the derivatives are equal to zero was examined, permitting each of the equations to be solved for the respective populations. Due to the nonlinear nature of the equations, it is not possible to solve explicitly for the respective populations in terms of the parameters alone. However, it is possible to solve for population M as a function of the

parameters and population A (see Appendix). Therefore, given a value for the adherent population A, a value for population M as well as the nutrient and effector populations can be calculated. This is plausible, since bi-directional migration permits the adherent population to maintain the mucus population. Thus, for any value of A, a steady state can be achieved for the system.

Parameter Estimation

Before considering numerical results, we first must estimate the parameters in (1)–(4), as summarized in Table 1. We choose the units for volume of population concentrations to be in milliliters, and time to be measured in days. Based on the available biological data, the values for the following parameters are estimated. (Table 1). There are approximately 10^5 *H. pylori* per mg in the mucus (Khulusi *et al*., 1993). Population A comprises approximately 2% of the total population (Lipkin *et al*., 1963; Hessey *et al*., 1990), hence $A(0) = 2000$. The initial amounts for the nutrient and effector populations are chosen as multiples of these populations. Since nutrient is growth-limiting, it is chosen as a small percentage of the populations, for example $N(0) = 10^{-2}$. Since epithelial cells slough every 2–3 days (Lipkin *et al*., 1963), on a daily basis $\mu_A = 0.3$. Estimating that the mucus sheds at a rate at least two to three times that of the epithelial cells, $\mu_M = 0.85$. The amount of nutrient used by each of the respective populations M and A are in proportion, namely $g_M = 0.98$ and $g_A = 0.02$; however, the model can incorporate variability in these percentages. Although we assume that all populations are in log-phase growth, this is not necessary for the model to yield steady state, and a variable growth rate is equally feasible. The growth of *H. pylori* can be determined from the doubling time based on logistic growth. If the *in vivo* doubling time (D) is 20 min, (0.0125 day) then the formula for the growth rate ($r = ln2/D$) yields a value of 55.45 per day; for $D = 2$ hr, $r = 8.32$. Therefore, the model should be accurate for the range of growth rates between 8 and 55. For initial calculations, a doubling time of 1 hr ($D = 0.0416$ day) will be assumed. Since the adherent population is replicating, we assume the carrying capacity of the epithelium for these organisms approaches saturation. For $A(0) = 2000$, a carrying

TABLE 1
Variables and parameters

		Values
Dependent Variables		
M	Population of *H. pylori* living in the mucus	10^5 ml^{-3}
A	Population of *H. pylori* adherent to mucosal epithelial cells	2000 ml^{-3}
N	Concentration of nutrients	10^{-2} ml^{-3}
E	Concentration of effectors	10^6 ml^{-3}
S	Total *H. pylori* population $= M + A$	102000 ml^{-3}
Parameters and constants		
μ_M	= rate *H. pylori* is lost due to shedding of mucus layer	0.85 day^{-1}
μ_A	= rate *H. pylori* is lost due to sloughing of epithelial cells	0.33 day^{-1}
g_M	= proportionate amount of nutrient to M	0.98
g_A	= proportionate amount of nutrient to A	0.02
a	= rate (proportion) that M migrates to A	0.001 day^{-1}
δ	= migration of A to M	0.5 ml^{-3} day^{-1}
α	= growth yield constant between N and *H. pylori*	1
K	= carrying capacity of the A population	2100 ml^{-3}
r	= growth rate of *H. pylori* population	16.66 day^{-1}
c	= maximal production of effectors by *H. pylori*	1.007 day^{-1}
β	= proportion of N produced based on effectors	0.1 ml^{-3}
τ	= monitors presence of nutrient	50 ml^{-3} day^{-1}
η	= rate effectors are depleted by epithelial cell interaction	0.1199 ml^{-3} day^{-1}
Derived quantities		
ϵ	$= c\tau$	50 ml^{-3} day^{-1}
r_1	$= g_M r$	16.32 day^{-1}
r_2	$= g_A r$	0.3332 day^{-1}
c_1	$= \delta + \mu_A$	0.833 day^{-1}
c_2	$= \frac{-\tau}{2}$	-25 ml^{-3} day^{-1}
c_3	$= \frac{\epsilon\beta}{\eta}$	41.67 ml^{-3} day^{-1}

capacity $K=2100$ was selected; 95% saturation accounts for time delays between the introduction of new sites and the ability of the mucus bacterial population to migrate to fill them. Because the carrying capacity is nearly full, when the A population divides, essentially all the offspring migrate and become M. Therefore, $\delta = Dx24/\text{day}$. Since we assume that approximately 5% of the adherent positions on the epithelial cells are available, only a small portion of M are able to migrate to A; thus the rate, a is 0.001. The remainder of the parameters (c, β, τ, η) relate to the interactions of effectors and nutrients (Fig. 1). Actual values for these four parameters are not presently known; however, through numerical studies, ranges of values can be predicted.

Numerical Results

The system (1)–(4) was solved using a MATHEMATICA package (Wolfram, 1988) for systems of differential equations. Using the parameter values from Table 1, Fig. 2(a) was generated. Changes in parameter values may lead to any of the three major dynamics that are possible results for the system: *steady state* occurs when the behavior of the system is unchanged after a prolonged time (e.g. >1000 days) [Fig. 2(a)]; *washout* occurs when the bacterial populations go to zero, usually by exponential decay [Fig. 2(b)]; *unbounded growth* occurs when one or more of the populations grow to infinity [Fig. 2(c)]. Changing experimental values from those shown in Table 1 elucidated the boundaries of the system and enabled the identification of bifurcation parameters (Table 2).

Competition

Both phenotypic and genotypic variation in *H. pylori* occur; however, the present model is sufficient for this heterogeneity and for the polymorphism of the human hosts. Since multiple *H. pylori* strains have been recognized in a single host (Akopyanz *et al*., 1992; Fujimoto *et al*., 1994; Cover *et al*., 1994), consideration of a model exhibiting balanced competition between two different strains is relevant. Two strains of *H. pylori* (H1 and H2) give rise to two different free-living mucus and adherent populations, $M1(t)$, and $A1(t)$ and $M2(t)$ and $A2(t)$. Let us assume that the strains differ in that H1 is more motile than H2, but H2 uses nutrient more efficiently than H1. Since it is beneficial to adhere, and the number of sites is limited by the carrying capacity, K, there is competition between the respective populations of the two strains for adherence sites. Populations $N(t)$ and $E(t)$ are as

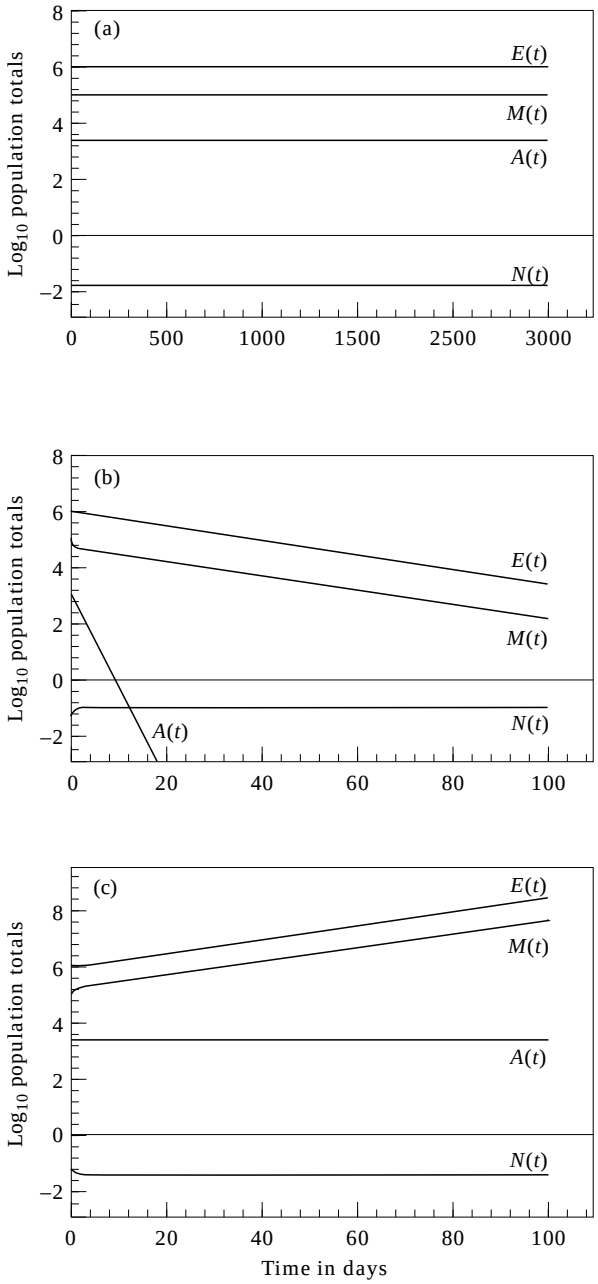

FIG. 2. Model dynamics. For the system (1)–(4), (a) represents equilibrium, with steady state values for the four populations over 3000 days using the parameter values from Table 1. (b) represents exponential decay. Parameter values are the same as in Table 1 except now $a=0$; note that decay occurs within 100 days. (c) represents exponential growth. Parameter values are the same as in Table 1 except now $\mu_M = 0.55$; note that population M grows from 10^5 to 10^7 over 100 days.

before. The competition model is analogous to equations (1)–(4):

$$\frac{dM1}{dt} = g_{M1} rN(t)M1(t) - \mu_{M1} M1(t) - a_1 M1(t)(K - (A1(t) + A2(t))) + \delta_1 A1(t), \quad (5)$$

$$\frac{dM2}{dt} = g_{M2} rN(t)M2(t) - \mu_{M2} M2(t) - a_2 M2(t)(K - (A1(t) + A2(t))) + \delta_2 A2(t), \quad (6)$$

$$\frac{dA1}{dt} = g_{A1} rN(t)A1(t) - \mu_{A1} A1(t) + a_1 M1(t)(K - (A1(t) + A2(t))) - \delta_1 A1(t), \quad (7)$$

$$\frac{dA2}{dt} = g_{A2} rN(t)A2(t) - \mu_{A2} A2(t) + a_2 M2(t)(K - (A1(t) + A2(t))) - \delta_2 A2(t), \quad (8)$$

$$\frac{dN}{dt} = \beta E(t) - rN(t)(g_{M1} M1(t) + g_{M2} M2(t)) - rN(t)(g_{A2} A2(t) + g_{A1} A1(t)), \quad (9)$$

$$\frac{dE}{dt} = \frac{c\tau}{\tau + N(t)} [M1(t) + M2(t) + A1(t) + A2(t)] - \eta E(t), \quad (10)$$

with $g_{A1} + g_{A2} + g_{M1} + g_{M2} = 1$.

Balanced competition is possible, in which all populations exist in non-zero steady state [Fig. 3(a)]. After one strain has achieved steady state, introduction of a second strain can lead to steady state for both competing organisms [Fig. 3(b)]. In contrast, for particular parameter values, the model permits competitive exclusion [Fig. 3(c)].

Biological Variations

Biological variation during the course of a decades-long infection also should be considered. First, exogenous stimuli such as aspirin intake or smoking may alter the epithelial cells and hence change the carrying capacity. These phenomena are illustrated through a transient increase in carrying capacity; for each condition, steady state occurs [Fig. 4(a)]. To mimic effects of periodic, rather than constant, mucus shedding, the parameter μ_M is changed to a periodic function of time, $\mu_M(t)$ [Fig. 4(b)] to incorporate diurnal variability. Nevertheless, the system (1)–(4) [Fig. 4(c)], can maintain values similar to those previously shown (Fig. 2).

Can A Simpler Model Work?

What if the feedback cycle were not necessary to induce chronic infection?

A scenario in which the food consumed by the host is the single (limiting) source of nutrient for *H. pylori* would reduce eqns (1)–(4) to only two equations; (1) and (2). The growth rate of *H. pylori* then can be redefined as a time-dependent rate, $r(t)$, reflecting a sinusoidal fluctuation in the availability of host food. For example, $r(t)$ could be a function that peaks three

TABLE 2

Parameter dynamics—Affect on system by change in default parameter value†

Parameter	Increase	Decrease	Comment
μ_M	$\to 0$‡	$\to \infty$	Biologically significant, since population size is sensitive to peristaltic washout rate
μ_A*	$\to 0$	$\to \infty$	Biologically significant, since population size is sensitive to peristaltic washout rate
g_M, g_A	$\to SS$	$\to SS$	Change affects the steady-state population size only
K§	$\to \infty$	$\to SS$	The size of K governs A, which is central to model
a*§	$\to SS$	$\to 0$	Replenishment of A is necessary for persistence
r§	$\to \infty$	$\to 0$	Biologically significant, since population size is sensitive to growth rate
δ§	$\to SS$	$\to 0$	Peristalsis diminishes effect of δ increase, but if $M \to 0$, then $A \to 0$
c§‖	$\to SS$	$\to 0$	Effectors are necessary for persistence
β§‖	$\to \infty$	$\to 0$	Nutrient is necessary for persistence
η§‖	$\to 0$	$\to \infty$	Depletion of effectors dampens the system
τ‖	$\to SS$	$\to SS$	Change affects the steady-state population size only

† Default values shown in Table 1.

‡ KEY $\to 0$: washout; $\to \infty$: unbounded growth; $\to SS$: remains in steady state.

§ Bifurcation parameter.

‖ Parameter that plays a significant role in the dynamics of this system, although at present it is not experimentally measurable.

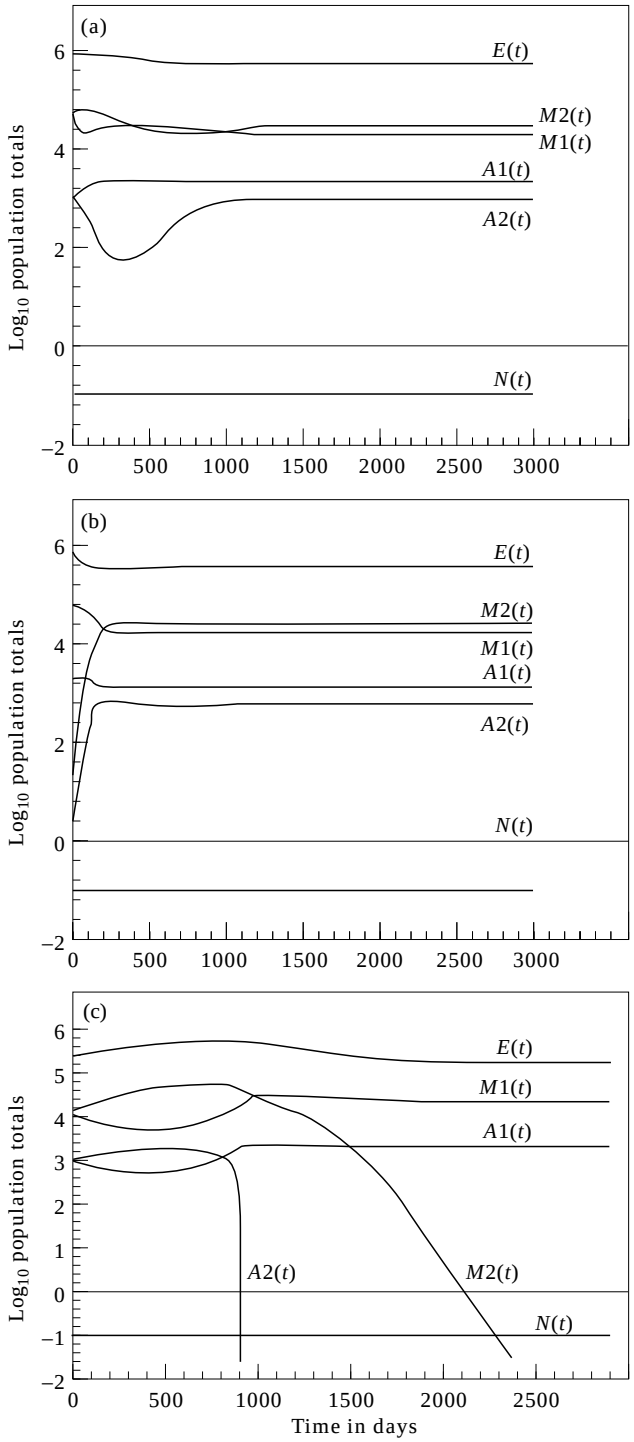

FIG. 3. Competition. (a) represents two competing strains (1 and 2) of *H. pylori* present in the stomach. Strain 1 is more motile than strain 2, but strain 2 uses nutrient more efficiently. To incorporate this in the model, parameter values shown in Table 1 are used except that the values for μ_{M1} and μ_{M2} are 0.89 and 0.85, respectively, and $g_{M1} = 0.49$ and $g_{M2} = 0.51$. To include competition effects for adherent positions, a_1 is chosen larger ($= 0.001$) than a_2 ($= 0.0009$), since strain 1 is more motile. (b) represents strain 2 being introduced after strain 1 had reached a steady state value (initial conditions: M1 = 97,000, M2 = 10; A1 = 2000, A2 = 1). (c) represents the case of competitive exclusion, in which strain H1 is able to gain total control under certain parameter values.

times a day (every 8 hr) when meals are ingested, and decays until the next meal, If the shedding rate is defined as μ, it can be easily shown that if $\mu > r(t)$, for any t, the population goes to zero, and if $\mu < r(t)$ for any t, the population grows without bound. However, if $\mu = \max(r(t))$, then a steady state can be reached; however, it is unlikely to occur. In the host, there exists variability in mucus shedding (e.g. in relation to meals), but for steady state, the variability in growth rate ($r(t)$) must match. However, it is unlikely that *H. pylori* can alter its growth rate $r(t)$ to exactly match μ as required for steady state. Furthermore, given the ranges for expected values for the washout rate μ (0.5–1.0), a corresponding equal value of max ($r(t)$) would imply a range of 16–33 hr doubling times. *In vitro*, we can observe colonies (containing 10^6 cfu) within 24 hr, implying a doubling time of < 72 min. Since the intrinsic *in vitro* doubling time is less than 72 min, it is unlikely that the *in vivo* doubling time is any greater. Therefore, the steady state cannot be reached *in vivo* in this scenario. With this possible exception conformance to the feedback cycles is required for persistent infection.

Discussion

Organisms that have evolved a lifestyle based on persistent parasitism face different constraints than transient or opportunistic invaders. The goals of the parasite are to maintain a stable niche that allows transmission to other hosts. Stability is an elusive goal in the face of a host seeking the elimination of a parasite, and a parasite whose survival coincides with the longevity of the host (Anderson, 1994). Simple mathematical systems cannot accurately depict such a relationship; greater complexity, involving a regulated interaction, is required. For *H. pylori*, a persistent colonizer, both analytic and numerical results indicate that a steady state can occur when a regulated model with interlocking feedback loops is used. Other analyses demonstrate that a simple model can not exist under the known biologic parameters between the microbe and the host. The regulated model (Fig. 1) is robust in that it can incorporate host variability in clearance of the microbe, the effects of transient perturbations (Fig. 4), and competition between organisms (Fig. 3). Analysis of the model further indicates the central role of adherent organisms for maintenance of colonization (Boren *et al*. 1993). Development of this model may have utility in designing the therapeutic approaches to *H. pylori* infection that affect such parameters as adherence efficiency or bacterial growth rate. Such a model also may be useful in modeling other chronic infectious

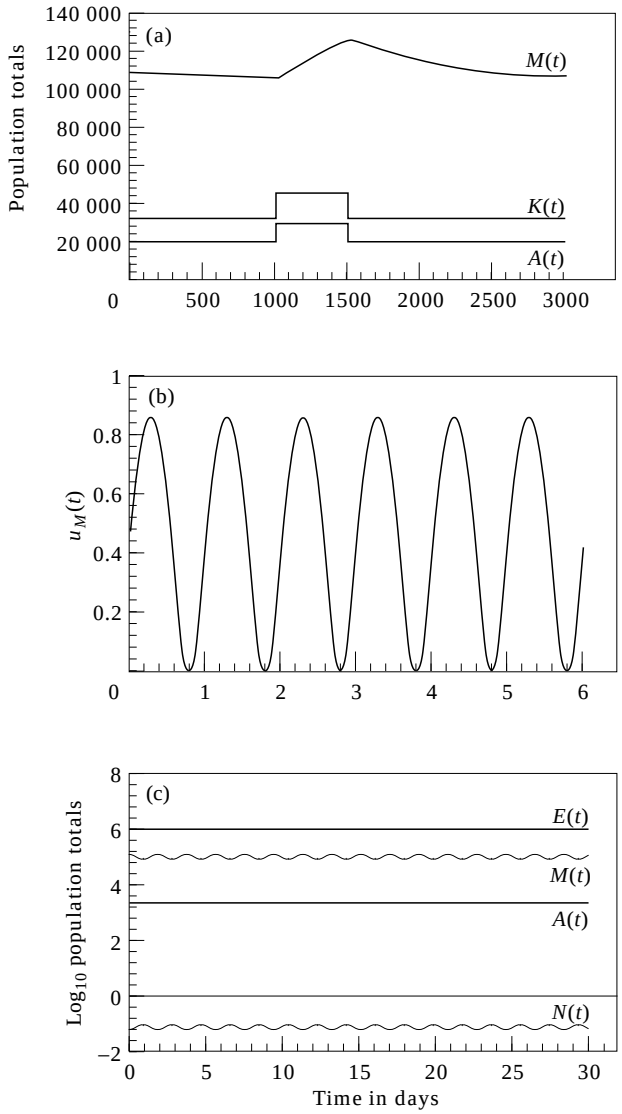

FIG. 4. Biological variations. The carrying capacity of the epithelial cells may change due to independent events such as aspirin intake or smoking. This is modeled as a time-dependent change in the carrying capacity, $K(t)$. With a temporary increase in carrying capacity, system (1)–(4) shows (a), a temporary (500 days) increase in the M and A populations before gradually returning to baseline. $A(t)$ and $K(t)$ are scaled by ten times and 15 times, respectively, for ease of presentation. The function $\mu_M(t)$ incorporates diurnal variability to mimic effects of periodic rather than constant mucus shedding (b). (c) represents the system (1)–(4) incorporating this periodic shedding, $\mu_M(t)$.

diseases, especially those that occur at mucosal surfaces, including *Pseudomonas aeruginosa* infection in patients with cystic fibrosis, or intestinal carriage of *Entamoeba histolytica*.

This system was designed to model the steady-state condition, which exists for the majority of *H. pylori*'s residence in the human stomach. During this period, there is immune recognition of *H. pylori* by the host as evidenced by a humoral response (Dooley *et al*., 1989; Crabtree *et al*., 1991). However, we do not characterize the initial events in which a presumably small inoculum is introduced into a non-immune host, nor do we consider the long-term decline in bacterial numbers that occurs when atrophy develops in the stomach and the niche is gradually lost (Blaser & Parsonnet, 1994; Nomura *et al*., 1991; Blaser, 1993; Karttunen, 1991). The characteristics of these stages of the infection are beyond the scope of this report, although presumably they can be modeled by a modified version of eqns (1)–(4). It may be presumed that η, the term describing the ability of bacterial effectors to generate inflammation, is not static, but changes in relation to host immunity, particularly down-regulation. Finally, four parameters derived from the feedback system (Fig. 1) play a key role in the dynamics of the system (1)–(4). Except for the parameter τ, which appears in ratio in eqn (4), the other three are bifurcation parameters, in which varying the values of each slightly causes great change in the resulting dynamics (Table 2). This is not surprising, since a fine-tuned feedback system may be crucial for the unprecedented survival of *H. pylori* in the human stomach.

We thank Douglas Berg, Alan Perelson, Philip Russell, Glenn Webb and Mary Ballyk for helpful discussions and comments. Part of this work was supported by grant R01CA58834 from the National Cancer Institute, and by the Medical Research Service of the Department of Veterans Affairs.

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APPENDIX

Steady State Analysis

In one steady state, $A=M=E=0$, $N=N_0$ where N_0 is the value of N when the other populations all are zero. This zero steady state is feasible, but trivial, so we examine further. There also is the case in which any one of the populations may grow without bounds (i.e. to "infinity"). Although this is not a steady state, it is mathematically but not biologically feasible. Since E is calculated in terms of all three of the other parameters in eqn (4), in the main text, once expressions for those are known, E can be solved. To simplify notation, let $r_1=g_M r$, $r_2=g_A r$ and $\epsilon=c\tau$. Substituting the expression for $E=0$, from (4) leaves three equations and three unknowns:

$$M=\frac{-\delta A}{r_1 N-\mu M-a(K-A)}, \tag{A.1}$$

$$A=\frac{aKM}{(\delta-r_2 N+\mu_A+aM)}, \tag{A.2}$$

$$N=\frac{\beta\epsilon(M+A)}{(\tau+N)\eta(r_1 M+r_2 A)}. \tag{A.3}$$

Solving (A.3) for N using the quadratic formula, the one positive root for this equation is obtained (the negative root has no biological significance):

$$N=\frac{-\tau}{2}+\sqrt{\frac{\tau^2}{4}+\frac{\epsilon\beta}{\eta}\frac{(M+A)}{(r_1 M+r_2 A)}}. \tag{A.4}$$

Now that N is expressed in terms of M and A, it can be substituted into eqns (A.1) and (A.2) to reduce the system to two equations in two unknowns. For simplification, let

$$c_1=\delta+\mu_A, \quad c_2=\frac{-\tau}{2}, \quad c_3=\frac{\beta\epsilon}{\eta}.$$

This yields the nonlinear system:

$$aMK+A\left[c_1+aM-r_2\left(c_2+\sqrt{c_2^2+c_3\frac{(M+A)}{(r_1 M+r_2 A)}}\right)\right]=0,$$

$$\delta A+M\left[r_1\left(c_2+\sqrt{c_2^2+c_3\frac{(M+A)}{(r_1 M+r_2 A)}}\right)-\mu_M-a(K-A)\right]=0. \tag{A.5}$$

If each equation is expanded and the powers of M collected, there now are two cubic equations in the variable M. Algebraic calculation reduces the two cubics to a single quadratic equation for M, of the form $\bar{a}M^2+\bar{b}M+\bar{c}$, where the coefficients are expressions of the parameters and the variable A. Using this single equation, there are a maximum of two roots for M from the polynomial formula, each of which will depend on A. Therefore, for a given value of A, the non-zero steady state values for M can be found. For every case, except when $\bar{a}>0$, $\bar{b}<0$ and $\bar{b}^2-4\bar{a}\bar{c}>0$, there is at most one positive real root to this quadratic equation. In that special case when there are two positive roots, it can be shown numerically that it only occurs outside biologically achievable parameters.