A model for integrative study of human gastric acid secretion
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Running Title
Modeling human acid secretion

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**ABSTRACT**

We developed a unique virtual human model of gastric acid secretion and its regulation in which food provides a driving force. Food stimulus triggers both neural activity in central and enteric nervous systems and G cells to release gastrin, a critical stimulatory hormone. Gastrin stimulates ECL cells to release histamine that together with acetylcholine stimulates acid secretion from parietal cells. Secretion of somatostatin from antral and corpus D cells comprises a negative feedback loop. We demonstrate that while acid levels are most sensitive to food and nervous system inputs, somatostatin-associated interactions are also important in governing acidity. The importance of gastrin on acid secretion is exemplified greatest at the level of transport between the antral and corpus regions. Our model can be applied to study conditions not yet experimentally reproducible. For example, we are able to preferentially deplete either antral or corpus somatostatin. Depletion of antral somatostatin exhibits a more significant elevation of acid release as compared to corpus somatostatin depletion. This increase in acid release is likely due to elevated gastrin levels. Prolonged hypergastrinemia has significant effects in the long term (5 days) by promoting ECL cell overgrowth. Our results may be useful in the design of therapeutic strategies for acid secretory dysfunctions such as hyper- and hypo-chlorhydria.

**Keywords:** gastrin, gastric acid secretion, stomach, mathematical model
**INTRODUCTION**

Acid secretion from parietal cells in the stomach is a highly regulated, complex and dynamic process optimized to facilitate food digestion. Not only are there interactions between the central (CNS) and enteric (ENS) nervous systems but a complex network of paracrine and endocrine cells is also involved. The overall goal is maintenance of stomach luminal pH within a strict range (i.e., pH homeostasis); food consumption and other deviations altering this range invoke either increased or decreased acid release.

Four cell populations and their secreted products form the core acid secretory process in humans. These four cell populations are gastrin (G) and somatostatin (D) secreting cells, enterochromaffin-like (ECL) and parietal cells. Both G and ECL cell products stimulate acid secretion (positive feedback), whereas D cell inhibits acid release (negative feedback). Inconsistencies in the way that the feedback loops are integrated still exist and may be due to species-specific differences. For example, the ability of gastrin to directly stimulate acid release in some species is in dispute (1, 2). Other inconsistencies involving effector and acid regulation may relate to the experimental approach such as *in vitro* vs. *in vivo* studies. The basic requirement for acid secretion, however, appears to be conserved among the species (3, 4). The need for an integrative approach to study gastric acid secretion is clear. Mathematical modeling is a powerful tool that allows for exploration of both the integrated system and its components in a systematic fashion. Further, mathematical modeling is immune to inconsistencies that often arise from comparison of in vivo and in vitro studies.

Mathematical models based on acid secretion have appeared in literature (5-8). DeBeus *et al.* explored the coupling of gastric acid release to bicarbonate secretion through extensive mathematical analyses of the cascade of molecular and ionic events constituting acid secretion.
Licko et al., focused on gastric acid as a two-step, sequential process. They modeled formation of acid that contributes to an acid storage pool and translocation of stored acid into the lumen of the stomach. Both models provide insight but do not address regulation of acid secretion.

In this paper we describe the complex system of gastric acid regulation using a novel mathematical model. Our model is unique because we consider regulatory processes that have been identified experimentally as essential for proper maintenance of acid secretion. Our two main goals are to validate the model and perform new experiments. Validation involves comparing simulations during healthy and depletion situations with experimental data. The model can then be used to perform studies not yet experimentally reproducible. For example, we are able to preferentially deplete either antral or corpus somatostatin.

**METHODS**

The stomach is comprised of many histologically distinct regions (Fig. 1A), however, we simplify by describing two main compartments, the antrum and corpus regions (Fig 1B). The relevant biological processes affecting acid secretion occur here and include dynamic changes in cell populations, secretion of effectors, neurotransmitters and acid, and the release of gastric protective factors. Below we outline the components of the model and our assumptions; the mathematical details are described in the Appendix.

**THE MODEL**

**Cellular elements:** The key cells involved are found in gastric glands of the antrum and corpus (Fig. 2). Several studies were conducted outlining gastric paracrine, endocrine and exocrine cell development (9-16). These electron microscopy studies show that the lineage of these differentiated cells can be traced to undifferentiated stem cells abundant in the isthmus of gastric glands (15).
Cells arising from stem cells are terminally differentiated and, with the exception of ECL cells, do not undergo mitosis (17, 18). We monitor seven cell populations in our model (Fig 3): antral and corpus stem cells; antral G cells; antral and corpus D cells; ECL cells and corpus parietal cells.

Although cell fluctuations are minimal in the short term (24 hrs), they have been observed in the long term (5 days). For example, during prolonged hypergastrinemia ECL cell overgrowth occurs and results in increased acid secretion. We use a five-day period and show that it is sufficient to detect significant cell changes. These changes may ultimately affect gastric function; and therefore, it is necessary to track cell dynamics in our model (19, 20). Under normal conditions, we assume that stem cell differentiation balances the loss of differentiated cells resulting in cell homeostasis. We also assume that differentiation is not a random event but is governed by feedback mechanisms. Without these mechanisms differentiation would be uncontrolled leading to exacerbated G, D, ECL and parietal cell populations. Although feedback mechanisms controlling stem cell differentiation have not been characterized in the stomach, their existence has been demonstrated in non-gastric systems (21). In addition to feedback mechanisms, other factors may also influence stem cell differentiation such as long-term presence or absence of food and prolonged occurrence of neutral pH conditions in the stomach such as during chronic hypochlorhdria (22-25). Standard loss of G, D, ECL and parietal cells occurs through apoptosis, sloughing of mucosal lining or engulfment by neighboring cells (10, 13, 14, 26). We assume that cells in the same region (antrum or corpus) have equivalent loss rates.

**Feeding function:** We model a standard American diet of three meals a day (0600h, 1200h and 1800h) using a sinusoidal function to describe the volume of food consumed (Fig. 4). The volume of food increases with each successive meal during the day and ranges between 0.0 L and 1.0 L; 1.5L being the maximal capacity of the stomach. We rigorously test the model with other feeding
functions where the feeding intervals are varied (data not shown). The response is appropriate: there is strong correlation between the modality pattern of the feeding function and the effector, bicarbonate and acid responses. This is critical for optimal food digestion.

Food also buffers acid and increases luminal pH. We assume that buffering of acid is dependent on food volume. We assume that there is an upper limit on the buffering capacity of food. Michaelis-Menten dynamics adequately describe this effect.

**Neural elements**: ENS and CNS neurotransmitters are secreted in response to food volume. There is a lack of kinetic data describing the influence of food volume on neural activity; we assume that neural activity increases in a Michaelis-Menten manner with food volume. Neuropeptides are metabolically degraded and this degradation is governed by first order kinetics (see Appendix). Food stimulates CNS activity that is conducted via the vagus nerve to the ENS of the stomach resulting in both acid and gastrin release (27). Indirect action of the CNS on acid secretion has also been demonstrated; cholinergic neurotransmitters inhibit somatostatin secretion promoting acid release (27-29). The physical (degree of distention) and biochemical (pH, neural and effector concentrations) states of the stomach then feedback to the CNS modulating its response (30, 31) (Fig. 1B).

How the CNS controls the ENS is not fully understood (32); however, for modeling purposes we assume that the two are independent. This does not have any qualitative effect on our results (data not shown).

**Effector regulation of acid secretion**: When food is received in the lumen, alterations in stomach pH and volume together with neural stimulation induce events leading to acid secretion. G cells within the antrum secrete gastrin that is released into antral blood capillaries and diffuses into the corpus (Fig. 1B). In the corpus, gastrin both directly stimulates parietal cells to secrete gastric acid
(33) and stimulates ECL cells to release histamine in conjunction with ENS neurotransmitters (20, 34). Histamine acts in a paracrine manner in conjunction with gastrin and acetylcholine, enhancing acid secretion (27, 35) and also potentiates gastrin stimulation of parietal cells (1). To down-regulate these processes in both the antrum and corpus, D cells secrete somatostatin, a negative effector of gastric acid secretion (36-38). Gastrin, somatostatin and histamine are released in a dose-dependent manner upon appropriate stimulation (39-41). In addition to effectors described above, gastric acid secretion by parietal cells can also be directly stimulated by CNS activity in response to food, although not to the same magnitude (42).

Antral D cells are morphologically and functionally dissimilar to their counterparts in the corpus (43). Antral D cells possess apical projections that sense luminal pH and release somatostatin when pH falls below 2 (44). Corpus D cells lack these projections and are insensitive to luminal pH changes (43). Both ENS neuropeptides and gastrin must stimulate D cells in the corpus to secrete somatostatin, which acts in a paracrine manner to inhibit both ECL and parietal cell activity (45, 46).

**Gastric protection:** Gastric acid is corrosive to host cells, thus to protect epithelia, bicarbonate ions are released into the mucus layer. Bicarbonate ions buffer secreted acid and increase pH at the mucus-epithelial interface to tolerable pH conditions (47). Although gastric protection is important, we do not thoroughly describe gastric protection in our model except to correct for acid levels buffered by bicarbonate ions. Details on how we modeled gastric protection are presented in the *Appendix.*

**EXPERIMENTS**

*Parameter estimation:* Once the model is developed and before simulations are performed, rates of each of the processes outlined in Figs. 1B and 3 must be estimated. Rate
parameters are estimated from published experimental data and are presented in Table 1. Human-derived experimental data are used in estimations when possible. Animal data are used when no human data are available to derive magnitude estimates. In the absence of data, mathematical estimation is used. All parameters are evaluated using uncertainty analyses performed with C code based on Latin hypercube sampling (LHS; (48-50)). To estimate cell population numbers, we perform immunohistochemistry on representative cross-section samples of human stomach mucosa (discussed below). The details of the parameter estimation are further outlined in the Appendix.

Estimation of model parameters using animal data is hampered by species differences. For example, it is reported that there are significantly more ECL cells in rats than in humans (43), and that rat ECL cells comprise 66% of the endocrine cell population in the corpus (43) while they make up 30% of the population in humans (51). These species differences are not limited to cells but are also observed at the level of effectors. Even given these difficulties, we find that estimating ranges for some parameters based on order of magnitude estimates from animal studies yields results that are biologically feasible.

Uncertainty and sensitivity analyses: There are variances in many of the parameter values due to extensive variability in data. This requires an evaluation of the uncertainty in the system. We employ the LHS method to assess effects of uncertainties in our parameter estimation on model outcomes. LHS allows for simultaneous random, evenly distributed, sampling of each parameter within a defined range. A matrix is generated, comprised of \( m \) columns corresponding to the number of varied parameters and \( n \) rows for the number of simulations performed. \( n \) solutions are generated that show uncertainty in model outcomes due to parameter variations. For our uncertainty analyses, we run 20 short-term simulations (18 degrees of freedom; 24 hours) varying a
given parameter by a factor of 1000. This is repeated for each parameter in the system individually and in combination.

Combining the uncertainty analyses outlined above with partial rank correlation (PRC), we are able to assess the sensitivity of our outcome variable (acid secretion) to parameter variation. This allows us to identify and quantify critical parameters (both neural and non-neural) that dramatically affect the outcome when varied. In each case a student t-test is used.

**Immunohistochemistry:** We obtained archived cross-sectional, biopsy or surgical specimens of human stomach mucosa from individuals participating in a study on *Helicobacter pylori* colonization (IRBMED#: 1999-0708). Biopsies are taken from healthy regions of the stomach and samples are fixed in 4% paraformaldehyde/PBS and then embedded in paraffin. Sections are deparaffinized through an alcohol series and permeabilized in 3% H2O2 and 100% ethanol. Non-specific binding sites are blocked with 20% goat serum/PBS, and 0.1% Triton X-100 for 30 min before a 2-hour incubation with either a 1:200 dilution of rabbit anti-GRPr antibodies specific for G cells or mouse anti-H+,K+-ATPase β-subunit antibodies (Medical and Biological Laboratories, Japan) specific for parietal cells. We incubated in a 1:500 dilution of secondary anti-rabbit or anti-mouse IgG antibodies for 30 minutes to conjugate seconday antibodies and visualization is achieved in avidin-biotin complexes using the Vectastain Elite ABC Kit and diaminobenzidine (DAB) for substrate (Vector Laboratories, Inc. Burlingame, CA). Sections are also counterstained with hematoxylin and eosin (H&E). The stained cross-sections are morphometrically analyzed by randomly selecting fields from which averages of each gastric cell type per gland could be assessed.

We estimate cell population using morphometry and use the 3-dimensional nature of the gastric gland to extrapolate the numbers of each cell type. Fig. 2B shows the result of one of these studies. The number of parietal cells per cross-sectional gland range from 4 to 8 cells (n=5). Corpus
glands have a depth of about 0.1mm (52), and parietal cells are observed to occupy approximately two-thirds of the glands with an apical height of about 10 µm per cell. Given this dimensional data, we multiply the number of parietal cells per cross-sectional gland by a factor of 6. We estimate that there are between 25 to 50 parietal cells per gland. In addition, there are between 14 to 35x10^6 glands in the whole stomach of which 75% are found in the corpus (52, 53). Therefore we estimate the number of parietal cells in the whole stomach ranges from 2.6x10^8 to 1.32x10^9 cells and this is consistent with published morphometric data (Table 2). The number of D cells in the corpus is estimated using similar methods.

We used a different procedure to estimate the number of antral G and D cells. From microscopic analysis of the antrum, we estimate that there are an average of 3.9 G cells (n = 9 glands) and 1.6 D cells (n = 9 glands) per antral gland. The G/D cell ratio obtained from our immunohistochemistry analysis is similar to reported G/D cell ratios (54). Experimental evidence suggests that there are fewer than 10 of each endocrine cell type per gastric gland (54, 55); therefore, the 3-dimensional analysis used to estimate corpus D and parietal cells is not needed to estimate the numbers of antral cells. To deduce the number of G and D cells in the antrum, we assume that the antrum comprises 25% of the stomach and given the total number of gastric glands in the stomach (52), we calculate the number of each of the antral cell type (Table 1).

**Computer simulations:** Once we define the model and estimate parameters, we solve the system of ordinary differential equations to obtain temporal dynamics for each variable in our model. To this end, we use appropriate numerical methods for solving the system of ODEs over periods of 24 hours (short term) and 5 days (long term). We use MatLab’s ode15s solver for stiff systems (The Math Works, Inc. Natick MA) and compare results with those generated from a numerical
algorithm using C code of a stiff adaptive solver based on the Rosenbrock Method for consistency (56). Simulation results are also compared with similar experimental data.

**Virtual depletions:** To further validate our model we perform virtual depletion experiments of different effectors of gastric acid secretion. We define our simulations as depletion experiments because we set the appropriate variables (effectors) to be depleted to zero over a specific time frame. The system begins in steady state with wild-type conditions prior to depletion. An example of a depletion experiment involves neutralization of somatostatin. In contrast, in deletion experiments a gene is disrupted or deleted, thus the system starts in a condition different from wild-type. Virtual depletions are performed for gastrin, histamine and somatostatin using numerical methods and initial conditions as described above. We compare our results with published experimental depletion and deletion data. We then demonstrate the application of the model to address questions not easily performed experimentally. For example, we independently deplete somatostatin in the corpus and antrum regions. Student t-tests are used to evaluate significant differences between our virtual depletion simulations and appropriate controls.

**Virtual ECL cell proliferation:** To assess the role of gastrin in ECL cell proliferation, we induce prolonged hypergastrinemia (5 days) by increasing the maximal gastrin secretion rate due to CNS stimulation ($K_{NG}$). The three curves were each fitted to a generic quadratic form ($y = c + a_1t + a_2t^2$, where $y$ represents the number of ECL cells; $c$ and $t$ are the initial number of ECL cells and time, respectively; and $a_1$ and $a_2$ are parameters that we estimate). Since the confidence intervals for the three curves do not overlap, their trajectories are significantly different.
RESULTS

We perform simulations that can be divided into two categories: (1) those designed to validate the model, and (2) those that assess the importance of gastrin. We conduct simulations under normal conditions and these serve as controls for subsequent simulated experiments. Simulations are performed over both short term (24 hours) and long term (5 days) time-scales. Unless otherwise specified (in the legend) we use the parameter values listed in Table 1. We first present baseline simulations comparing our results with published data and subsequently perform a series of virtual depletion experiments. Our simulation results represent effector levels in the extracellular spaces of the stomach mucosa. Experimentally, effector levels are typically determined from blood plasma measurements. Thus, in some cases, our simulation values are larger than those we compare with from published data and are accounted for by compartmental differences.

Baseline conditions: Under normal conditions, we observe increases in neural and effector activity with food intake, which is consistent with experimental data (Fig 5). The trimodal pattern of the feeding function (see Fig. 4) is strongly correlated with neural and effector activity (Fig. 5). Food ingestion promotes release of gastrin, which is transported to the corpus. This transport implies a delay exists between the release of gastrin and its stimulatory effects. We are able to observe this delay between gastrin and histamine release using this model (data not shown), and we have developed a separate study exploring this delay (57). In addition, the model also reproduces a characteristic reciprocal behavior of gastrin and antral somatostatin that is observed in both in vivo and in vitro systems (Fig 5J; c.f. (58)). This highlights the antagonistic relationship between the two effectors: gastrin release occurs first followed by somatostatin activity which down-regulates gastrin secretion.
Cell population sizes remain in steady state over 24 hours (Fig. 6) and this is consistent with biological evidence (59). While cell numbers are in homeostasis during the short-term, we capture changes in cell numbers in the long term (data not shown), and we show below cell dynamics under altered conditions.

**Virtual depletion experiments:** To further validate the model as well as identify key effectors, we perform several depletion studies and compare results with experimental data. In each virtual depletion experiment, the depleted variable remains at zero during the 24-hour simulation.

**Gastrin depletion:** Consistent with published data, we show a significant reduction of both basal and stimulated acid secretion ($p<0.001$; (60-62); Fig. 7). We suggest that this reduction is due to a decline in the secretion of downstream effectors (Fig. 7). In the long term, we also observe a decline in ECL cell populations that is consistent with similar experimental observations ((62); data not shown). This indicates a critical role for gastrin in maintenance of cell homeostasis.

**Histamine depletion:** During histamine depletion, we observe a significant reduction in acid levels ($p<0.001$; Fig 8) in agreement with experimental data (63). This reduced output is less dramatic than that observed during gastrin depletion (see Fig 7). Basal acid levels are unaffected which is also consistent with data ((63); Fig 8). Gastrin is significantly elevated by 25% over wild-type conditions ($p<0.001$). This is not as significant as the 300% increase in gastrin reported in mice with a dysfunctional histamine receptors (63); however, this discrepancy is likely due to species-specific differences. In mice with deleted histamine receptors, acid secretion stimulated by gastrin is eliminated (63). On the contrary, in human studies using histamine antagonists, gastrin is still able to stimulate parietal cells to release acid (64). Hypergastrinemia continues during the duration of histamine depletion resulting in a slow ECL cell overgrowth (data not shown).
**Somatostatin depletion**: During somatostatin depletion simulated basal effector levels are higher when compared to control simulations ($p<0.001$; data not shown). This is in agreement with data demonstrating the inhibitory role of somatostatin in regulating intragastric acidity using somatostatin receptor subtype-2 (sst-2) deficient mice (65). We also observe increases in stimulated secretion of effectors inhibited by somatostatin. Histamine levels significantly increase by 15% ($p<0.001$; data not shown), and gastrin levels are slightly elevated by 2.5%.

**Antral vs. corpus somatostatin depletion**: Of key interest is the difference in contribution of somatostatin from the antral and corpus regions. Using our human model of gastric acid secretion, we are able to preferentially deplete somatostatin in either region; an experiment that is presently impossible to perform. Given the known dissimilarities between antral and corpus D cells as described above, we expect the impact of antral and corpus somatostatin on system dynamics to differ significantly. Gastrin is significantly elevated by 15% during antral somatostatin depletion ($p<0.05$), whereas it is unchanged during corpus somatostatin depletion (Fig. 9). Histamine levels are significantly increased (900%) during antral somatostatin depletion when compared to corpus somatostatin depletion (7%). Our results indicate that antral somatostatin depletion has a much greater effect on acid output than somatostatin produced in the corpus.

**Effect of food**: Comparing the feeding function (Fig. 4) to effector and acid levels (Fig. 5) there is a clear correlation between the two. To study this dependence, we supply various feeding functions where we vary the intervals between meals, the volume of food consumed and the number of meals administered each day. In each case, the system response is directly correlated with the pattern of the feeding function. A stability analysis reveals stable limit cycles whose period corresponds to the modality of the feeding function (data not shown, see (57) for more details).
The importance of the CNS: Using uncertainty and sensitivity analyses we are able to assess the importance of each parameter, both individually and in combination, on the dynamics of acid secretion. Rates governing CNS activity has the greatest effects on the system when varied (Fig. 10 A & B). Variations in CNS activity due to food stimulation have dramatic effects on our outcome variable, gastric acid (PRCC = 0.94; \( p << 0.001 \)). This is not surprising given the direct proportionality between CNS activity and food stimulus. We also observe that variations in food input propagate via the CNS throughout the system (data not shown; see above). Surprisingly, variations in the maximal gastrin secretion rate due to CNS stimulation (range of \( 6.28 \times 10^{-20} \) to \( 6.28 \times 10^{-17} \) M hr\(^{-1}\) cell\(^{-1}\)) do not have significant effects on acid levels (\( p > 0.5 \)). We observe reductions in acid secretion when the maximal rate of gastrin secretion due to CNS stimulation is significantly increased (Fig. 10 C & D).

The importance of neural-independent parameters: We also observe independent of neural activity that have significant effects on gastric acidity. Variations in the transport rate of gastrin between the antral and corpus regions exerts the strongest effect on acid levels (PRCC = 0.80, \( p << 0.001 \)). This is not unexpected given evidence for increased mucosal blood flow during feeding (66-68). We suggest that increasing blood flow increases the availability of gastrin in the corpus thereby enhancing acid release. While gastrin is important in acid secretion, we cannot omit the significance of the negative feedback of somatostatin. Not surprising, we observe a variety of somatostatin-associated parameters that also exert significant effects on acid release. These parameters include dissociation constants of somatostatin from G and ECL cell receptors (\( p << 0.001 \) for both parameters) as well as the maximal somatostatin secretion rate stimulated by luminal acid (\( p < 0.05 \)). In the case of dissociation constants, somatostatin dissociation from receptors on G cells exerts a stronger effect than its dissociation from ECL cell receptors. This agrees with our comparison of
antral and corpus somatostatin depletion (Fig. 9) where we show the stronger effect of antral somatostatin on acid release when compared to corpus somatostatin.

**The effect of gastrin on ECL cell growth:** Using our mathematical model we investigate the role of gastrin in ECL cell proliferation (Fig. 10E). When we increase gastrin levels by increasing the maximal gastrin secretion rate due to CNS stimulation (Fig. 10 C&D), ECL cell proliferation increases (Fig. 10E) while other cells do not (Fig. 10F). We use nonlinear parameter estimation of a generic quadratic form to assess the significance of each ECL cell increase and demonstrate that their respective 95% confidence intervals do not overlap (data not shown). This suggests that induced ECL cell proliferation is significant. Our results are consistent in vivo data where only long-term administration of proton pump inhibitors (69) or blockade of histamine 2 receptors (70) promotes ECL cell overgrowth.

**DISCUSSION**

We present a model of human gastric acid secretion using a system of 18 nonlinear ODEs together with a food function. In this system, positive and negative effectors strictly maintain acid homeostasis, the degree of which depends on food input. We show that the model is valid by demonstrating consistency with experimental results under normal and depletion conditions. The key modulators of the system are both food and neural input. We also demonstrate the significance of gastrin through depletion studies. This is further substantiated using sensitivity analyses and together this suggests that gastrin is an important signal transducer relaying information from the CNS to parietal cells. We also demonstrate that while gastrin is important, somatostatin activity is a key regulator of gastric acidity.
Maintenance of gastric acid levels is important for optimal function of the stomach (71). Both food digestion and sterilization of the lumen require strict control of acid levels implying that the system return quickly to equilibrium if disturbed. We find that our model satisfies this requirement thereby suggesting that the gastric system is stable. While redundancies ensure that gastric acid release continues if one pathway is lost, these redundancies cannot fully explain gastric stability. Maintenance of stability requires extensive feedback mechanisms that act to achieve homeostasis during disturbances. We show that compensatory mechanisms are likely invoked to stabilize acid secretion during altered conditions, such as effector depletion.

During virtual depletion of histamine, we observe a compensatory mechanism at work whereby the D cell population declines promoting elevation of gastrin levels by reducing somatostatin production. When gastrin levels rise, gastric acid secretion is stimulated. This may account for the higher acid levels observed during histamine depletion (Fig. 8D) when compared to levels during gastrin depletion (Fig. 7D). During virtual gastrin depletion, gastric acid secretion is reduced. We argue that by boosting ECL cell numbers, histamine levels would increase thereby restoring acid levels. On the contrary, this is not observed in gastrin knockout mice (60, 61). We therefore suggest that gastrin, and not histamine, plays a pivotal compensatory role. Further, we suggest that gastrin levels may be useful as indicators of gastric health status.

We also demonstrate the significance of the negative feedback loop involving somatostatin on acid release. Therefore, intact negative regulation is critical for proper function of the gastric system. We demonstrate that acid levels are sensitive to variations in somatostatin dissociation from G and ECL cells. Variations in these parameters may have dramatic and even detrimental effects on acid secretion given the prominence of somatostatin in inhibition of acid release. This may partially explain why these parameters do not vary significantly unless manipulated experimentally (72).
While somatostatin is important in inhibition of acid, it may also play a compensatory role controlling gastrin levels thereby modulating acid secretion. During long-term absence of somatostatin, higher gastrin levels may promote ECL cell overgrowth. On the other hand, chronic elevations in somatostatin levels lower gastrin levels and may lead to loss of mucosal integrity. Therefore, we suggest that somatostatin levels are strictly controlled to maintain both acid and cell homeostasis.

We demonstrate a technique for exploring gastric acid secretion and its regulation by gastric effectors. Mathematical models are not only tractable to long and short-term studies but they allow for rapid assessment of global effects. We are able to quickly assess critical elements in the system using virtual depletion/deletion analyses. Although our model is a simplification of human gastric acid secretion and its regulation, we include cells and effectors that are conserved among different species. Species-specific differences do not significantly affect our results because we capture qualitatively and, to some extent, quantitatively the dynamical behavior of the human system.

Our model is a powerful tool for analyzing gastric effector and acid secretion, but there are limits to its potential. One of our immediate goals is to model acid secretion to assess important effectors in the system. To do this, we neglect many of the complex cellular events that contribute to the secretion of effectors and acid. Therefore, we cannot precisely reproduce some of the dynamical behaviors in secretion that are observed experimentally. For example, the secretion of somatostatin is biphasic and this may be due to intracellular calcium release, which is intimately coupled to somatostatin release (73). We also observe differences in some of the cell dynamics when compared to in vivo and in vitro data. We attribute these discrepancies, such as the elevation of immature cell populations, to model simplifications. In the case of cell dynamics, we do not account for intermediate cell stages observed during stem cell differentiation. While cell and signal
transduction dynamics are not modeled rigorously, this does not detract from the qualitative significance of our results. In fact, inclusion of some of these events may render the model too complex for study.

While the main purpose of the stomach is food digestion, pathogens can be ingested with food. Many of these pathogens are acid intolerant and thus acid secretion mechanisms help maintain a sterile environment. However, *Helicobacter pylori* has adapted to persist in this hostile environment. Most infections are asymptomatic and persist for the lifetime of the host while other outcomes such as peptic ulcer, gastric carcinomas occur less often. One key application of this model is to study colonization by this pathogen. For example, one effect of bacterial colonization is a significant elevation of gastrin levels (74, 75), the significance of which is not fully understood. Recent studies in mice demonstrate that this response in not specific to *H. pylori* but is mounted towards mixed flora that colonize the mouse stomach (75). It is therefore possible that elevated gastrin levels during colonization may be host induced and may represent an effort toward bacterial clearance by increasing gastric acidity. With this model, we have another tool for exploring not only host-bacterial interactions but also the potential importance of compensatory mechanisms in bacterial persistence.

Another model application is designing therapeutic strategies to diminish effects of gastric ailments associated with *H. pylori*. A recent study has suggested that prolonged use of proton pump inhibitors (PPIs) by individuals infected with CagA positive *H. pylori* strains accelerated progression of gastric mucosal atrophy (76). Further, while effective in reducing acid output, long-term administration of PPIs may predispose individuals with gastrinomas to ECL cell overgrowth (77). Our model could be used to identify targets for reducing acid secretion without harmful side effects.
**APPENDIX**

*Lifespans of gastric cells:* Lifespans of gastric cells vary from species to species, and data on lifespans of cells is scarce, so we use murine data (10-14). Units for growth, differentiation and death rates are reported per day, and we convert them to units of per hour. We find the model to be robust in that parameters within the range of a factor of 1000 did not dramatically affect the outcomes.

*Parameters for factors that influence growth, differentiation and death of cells:* We assume that gastrin-mediated proliferation of cells follows Michaelis-Menten kinetics, thus we estimate maximal growth rates and half-maximal proliferation using uncertainty analyses. Kinetic studies regarding influences of prolonged starvation on stomach physiology are not available; therefore, we estimate these parameters using sensitivity analyses. We assume that loss of cells due to starvation also occurs via Michaelis-Menten kinetics. We estimate the maximal loss of cells due to starvation, $K_{f_{max}}$, and a threshold at which cell loss is half-maximal, $\alpha_f$.

*Effector and acid parameters:* Effector release dynamics can be described by Michaelis-Menten kinetics. In the absence of stimulus, effector secretion remains at basal levels; however, effector secretion is enhanced upon stimulation at a rate that is approximately proportional to stimulus intensity. Subsequently, as stimulus intensity increases, a maximal rate of effector secretion is achieved. Again we estimate maximal rates and half-maximal constants of effector and acid secretion upon stimulation.

The parameters described above constitute parameters in the positive terms of the differential equations. For loss terms, degradation and transfer are incorporated. Degradation rates are estimated from the half-life of each effector. Formula (1.1) is employed in the derivation of these degradation rates.
\[ \kappa = \ln 2 / \text{Half-life} \] (1.1)

Flow rates between corpus and antrum are estimated from experimental data. We assume the flow of acid from the lumen of the corpus to the antrum (\( \beta_A \)) to be in equilibrium with the washout rate of stomach contents (\( \kappa_A \)) into the duodenum. Gastric content washout can be described by exponential decay kinetics. We obtain the half-life of gastric contents and we use it to estimate the washout rate.

**Model equations:** Stem cells in the antrum undergo differentiation, at rate \( T_{Asc} \), to terminally developed G and D cells (Fig. 3A). Similar terminology describes the cell differentiation of stem cells in the corpus region. In both regions, loss of stem cells occurs only through differentiation. We assume that the antral and corpus stem cells divide at rates \( \gamma_{Asc} \) and \( \gamma_{Csc} \), respectively and model division of stem cell populations using logistic growth with defined carrying capacities. We also account for the effect gastrin may have on corpus stem cell differentiation by including the term \( (g_{max} [Gtn_c(t)]^2) / ([Gtn_c(t)]^2 + \alpha_{CSC}^2) \) into differential equation 1.3. Below are the differential equations describing stem cell population dynamics.

**Antral stem cells:**

\[ \frac{dA_{sc}(t)}{dt} = (\gamma_{Asc})(A_{sc}(t))(C_{Asc} - A_{sc}(t)) - (p_{G}(t) + p_{D}(t))(\eta_{Asc})(A_{sc}(t)) \] (1.2)

**Corpus stem cells:**

\[ \frac{dC_{sc}(t)}{dt} = (\gamma_{Csc})(C_{sc}(t))(C_{Csc} - C_{sc}(t)) + \left( \frac{g_{max} [Gtn_c(t)]^2}{[Gtn_c(t)]^2 + \alpha_{CSC}^2} \right) \cdot C_{sc}(t) - (p_{G}(t) + p_{D}(t) + p_{E}(t))(\eta_{Csc})(C_{sc}(t)) \] (1.3)
We adopt the exponential term described by Sato for describing feedback mechanisms that modulate stem cell differentiation (78). In equation (1.2) and (1.3), the feedback mechanisms are given by $p_{Gc}(t), p_{DA}(t), p_{E}(t), p_{DC}(t)$, and $p_{P}(t)$ and have the general form:

$$p_{N_i}(t) = e^{-\frac{f_{N_i(t)}^2}{N^{**}}}$$

where $N$ represents the specific terminally differentiated cell type $G, D_A, D_C, E$ or $P$.

Stem cells differentiate to a specific cell type when the cell population size falls below a critical value $N^*$; however, as the cell population size increases above this critical value, differentiation ceases.

Paracrine, endocrine and parietal cells emerge from stem cells in their appropriate compartments. These cells undergo death at a rate $\lambda$ specific to the cell type under study completing the dynamic process. Death rates are exclusive of periodic sloughing of surface cells that is known to occur every 3 days (79-81).

Starvation also affects a decrease in $G$ cell numbers (25). We incorporate this feature into the model in the form of $\lambda_{\text{gmax}}(1 - (Fd(t))^2/((Fd(t))^2 + \alpha_{g}^2)))$. As food intake is reduced the rate of loss of $G$ cells increases towards $\lambda_{\text{gmax}}$. In contrast, high acid levels decrease $G$-cell growth while promoting antral $D$-cell growth (82). In the case of $G$ cells, we use: $k_{\text{gmax}}(1 - ([A_c(t)]^2/([A_c(t)]^2 + \alpha_{A}^2)))$. For antral $D$ cells, we include the positive term $((k_{\text{dmax}}[A_c(t)]^2)/([A_c(t)]^2 + \alpha_{A}^2))$ to capture the effect of acid on $D$ cell growth.

We model the dynamics of paracrine, endocrine and exocrine cells as follows:

**G cells:**

$$\frac{dG(t)}{dt} = p_G(t) \cdot \eta_{ac} \cdot A_c(t) + k_{\text{max}} \cdot \left(1 - \frac{[A_c(t)]^2}{[A_c(t)]^2 + \alpha_A^2}\right) \cdot G(t) - \lambda_{\text{dmax}} \cdot \left(1 - \frac{(Fd(t))^2}{(Fd(t))^2 + \alpha_{\lambda}^2}\right) \cdot G(t) - \lambda_{ac} \cdot G(t)$$  (1.4)
Antral D cells:

\[
\frac{dD_A(t)}{dt} = p_{DA}(t) \cdot \eta_{sw} \cdot A_v(t) \cdot \left( \frac{k_{max} \cdot A_v(t)}{[A_v(t)] + \alpha_{DA}} \right) \cdot D(t) - \lambda_{DA} \cdot D_A(t) + \lambda_{D_{max}} \cdot \left( 1 - \frac{(Fd(t))^2}{(Fd(t))^2 + \alpha_{D}} \right) \cdot D_A(t) 
\]  

(1.5)

Corpus D cells:

\[
\frac{dD_C(t)}{dt} = p_{DC}(t) \cdot \eta_{sw} \cdot C_v(t) - \lambda_{DC} \cdot D_C(t) 
\]  

(1.6)

ECL cells:

\[
\frac{dE(t)}{dt} = p_E(t) \cdot \eta_{sw} \cdot C_v(t) - \lambda_{EC} \cdot E(t) + \left( \frac{k_{max} \cdot [Gtn_e(t)]^2}{[Gtn_e(t)]^2 + \alpha_{E}} \right) \cdot E(t) 
\]  

(1.7)

Parietal cells:

\[
\frac{dP(t)}{dt} = p_P(t) \cdot \eta_{sw} \cdot C_v(t) - \lambda_p \cdot P(t) 
\]  

(1.8)

**Effector regulation of acid secretion:** We use Michaelis-Menten kinetics to describe effector secretion in response to stimuli. For example, gastrin secretion is dependent on CNS, ENS and food stimuli in a dose-dependent manner. On the other hand, somatostatin, acts in a non-competitive manner (36). This result is incorporated into the Michaelis-Menten terms since the non-competitive inhibition of enzyme catalyzed reactions have been extensively explored (36). Therefore, we include an inhibitory term of the general form \((1 + [I]/k)\). If two inhibitors exist, as in the case of inhibition of somatostatin secretion by both somatostatin and the CNS neurotransmitter acetylcholine, we assume that the product of the inhibitory terms \((1 + [S(t)]/k_S)(1 + [N(t)]/k_N)\) captures the desired inhibitory dynamics.

We propose that loss of gastrin from the antrum occurs via two mechanisms: transport and degradation. In both circumstances, we hypothesize that this loss is directly proportional to the gastrin concentration \([Gtn_A]\) in the antrum at time \(t\). We do not account for any other molecular mechanisms such as active transport that may affect gastrin transport into the blood circulatory system.
network of the stomach nor do we account for metabolic degradation. We suggest from our results that exclusion of these mechanisms, if they do exist, does not detract greatly from the qualitative outcome (data not shown).

The dynamics for effectors are defined using the following equations:

**Antral gastrin**

\[
\frac{d[Gm_\text{a}(t)]}{dt} = G(t) \left( \frac{K_{NG}[N_{K}(t)]}{\left(1 + \frac{[S(t)]}{K_{SG}}\right)\left(1 + \frac{[A(t)]}{k_{AG}^2}\right)} \right) + \frac{K_{NG2}[N_{C}(t)]}{\left(1 + \frac{[A(t)]}{k_{AG}^2}\right)} + \frac{K_{FG}[F(d(t))]}{\left(1 + \frac{[A(t)]}{k_{AG}^2}\right)} - (\kappa_G + \beta_G)[Gm_\text{a}(t)]
\]  

**Corporal gastrin**

\[
\frac{d[Gm_\text{c}(t)]}{dt} = \beta_c[Gm_\text{c}(t)] - \kappa_c[Gm_\text{c}(t)]
\]  

**Antral somatostatin**

\[
\frac{d[S_\text{a}(t)]}{dt} = D(t) \left( \frac{K_{sa}[A(t)]}{\left(1 + \frac{[S(t)]}{k_{ss}}\right)\left(1 + \frac{[N_{sa}(t)]}{k_{sa}}\right)} + \frac{K_{sa}[N_{sa}(t)]}{\left(1 + \frac{[N_{sa}(t)]}{k_{sa}}\right)} - \kappa_c[S_\text{a}(t)] \right)
\]

**Corpus somatostatin**

\[
\frac{d[S_\text{c}(t)]}{dt} = D(t) \left( \frac{K_{sc}[N_{sc}(t)]}{\left(1 + \frac{[S(t)]}{k_{ss}}\right)\left(1 + \frac{[N_{sc}(t)]}{k_{sc}}\right)} + \frac{K_{sc}[Gm_\text{c}(t)]}{\left(1 + \frac{[Gm_\text{c}(t)]}{k_{sc}}\right)} - \kappa_c[S_\text{c}(t)] \right)
\]

**Histamine**

\[
\frac{d[H_\text{c}(t)]}{dt} = E(t) \left( \frac{K_{sh}[N_{sh}(t)]}{\left(1 + \frac{[S(t)]}{k_{sh}}\right)\left(1 + \frac{[N_{sh}(t)]}{k_{sh}}\right)} + \frac{K_{sh}[Gm_\text{c}(t)]}{\left(1 + \frac{[Gm_\text{c}(t)]}{k_{sh}}\right)} - \kappa_h[H_\text{c}(t)] \right)
\]
Gastrin, histamine and central neural stimuli elicit the secretion of acid from parietal cells. Again we employ Michaelis-Menten kinetics to describe stimulated acid secretion. Somatostatin acts non-competitively to inhibit acid secretion. Loss of gastric acid from the corpus region occurs at a rate $\beta_A$. This acid passively diffuses to the antral region where it reappears as the source term of the differential equation describing antral gastric acid (Equation 1.15). Bicarbonate buffering of acid leads to further loss of acid. This is represented by a mass action term, $hb[A_c(t)][B_c(t)]$. In addition, we also describe the potentiation of histamine on gastrin-mediated gastric acid secretion using the term $(\frac{[H_c(t)]}{[H_c(t)]+\alpha_d})$. This term multiplies the Michaelis-Menten term describing gastrin-stimulated acid secretion by parietal cells. Acid is lost through transportation, buffering or washout. The equations for the rate of change of gastric acid in the corpus and the antrum are found below.

**Corpus gastric acid**

$$\frac{d[A_c(t)]}{dt} = \rho \left[ \frac{K_{aa}[N_c(t)]}{([N_c(t)]+\alpha_d)\left(1+\frac{[S_c(t)]}{k_{ss}}\right)} \right] \left[ \frac{[H_c(t)]}{[N_c(t)+\alpha_d]} \right] \left[ \frac{K_{aa}[G_m(t)]}{([G_m(t)]+\alpha_d)\left(1+\frac{[S_c(t)]}{k_{ss}}\right)} \right] + \frac{K_{aa}[H_c(t)]}{([H_c(t)]+\alpha_d)\left(1+\frac{[S_c(t)]}{k_{ss}}\right)}}$$

$$-hb[A_c(t)]\left[\frac{k_{fca}F_d(t)}{F_d(t)+\alpha_{fa}}\right] - \beta_A[A_c(t)]$$

(1.14)

**Antral gastric acid**

$$\frac{d[A_c(t)]}{dt} = \beta_A[A_c(t)] - \kappa_A[A_c(t)]$$

(1.15)

Bicarbonate secretion follows Michaelis-Menten kinetics with the CNS stimulating secretion. This secretion therefore reaches a maximum at CNS stimulus intensity considerably greater than the
half-maximal threshold. Loss of free bicarbonate from the system occurs via buffering of acid, transport to the antrum from the corpus or from washout from the antrum to the intestines. Differential equations describing the change in bicarbonate concentration in the corpus and antrum are given by:

**Corpus bicarbonate**

\[
\frac{d[B_c(t)]}{dt} = \frac{k_{bc max}[N_c(t)]}{[N_c(t)] + \alpha_{NB}} - hb[A_c(t)][B_c(t)] - \beta_b[B_c(t)]
\]  \hspace{1cm} (1.16)

**Antral bicarbonate**

\[
\frac{d[B_a(t)]}{dt} = \frac{k_{ba max}[N_c(t)]}{[N_c(t)] + \alpha_{NB}} - hb[A_a(t)][B_a(t)] - \kappa_b[B_a(t)]
\]  \hspace{1cm} (1.17)

The central and enteric neural stimuli, \([N_c(t)]\) and \([N_e(t)]\) respectively, are evoked by food \(Fd(t)\) stimulus. We assume that the qualitative behavior is adequately described by Michaelis-Menten kinetics; hence the following differential equations define central and enteric neural activity respectively.

\[
\frac{d[N_c(t)]}{dt} = \frac{N_{max}Fd(t)}{(Fd(t) + k1_{1b}) \left(1 + \frac{[A_c(t)]^2}{[A_c(t)]^2 + k_{en1}}\right)} - \kappa_{nc}[N_c(t)] + Bas_1
\]  \hspace{1cm} (1.18)

\[
\frac{d[N_e(t)]}{dt} = \frac{N_{max}Fd(t)}{(Fd(t) + k2_{2b}) \left(1 + \frac{[A_c(t)]^2}{[A_c(t)]^2 + k_{en2}}\right)} - \kappa_{ne}[N_e(t)] + Bas_2
\]  \hspace{1cm} (1.19)
Feedback from the luminal acidic environment is accomplished by non-competitively inhibiting neural activity and is represented by \(1 + (\frac{[\mathcal{A}(t)]^2}{([\mathcal{A}(t)]^2 + k_{\text{AN}}^2)})\). In addition, we account for basal neural activity in the CNS and ENS in the form of \(\text{Bas}_1\) and \(\text{Bas}_2\) respectively.
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REFERENCES


65. **Martinez V, Curi AP, Torkian B, Schaeffer JM, Wilkinson HA, Walsh JH and Tache Y.**


FIGURE LEGENDS

Fig. 1. (A) Histology of the stomach. (B) Model diagram of effector regulation of gastric acid secretion. The model includes positive and negative effector feedback systems. Cells are assigned to their respective compartments. G cells found in the antrum secrete gastrin (Gtn), an effector of gastric acid secretion. Gtn, not only stimulates histamine release from ECL cells (EC) and gastric acid (H+) secretion from parietal cells (PC) but also stimulates somatostatin (SS) secretion. The Greek symbols represent rates at which events occur. β represents a transport rate. λ symbolizes death rates of given cell types as specified by the subscript. κA corresponds to the washout rate of acid with gastric emptying. Also shown are central and enteric neural stimuli (CNS and ENS) supplied to the physiological system upon feeding. (Solid arrows represent positive stimuli whereas dashed arrows represent negative stimuli. The weight of the arrows indicates the relative intensity of the stimulus)

Fig 2. A cross sectional and schematic longitudinal section of a gastric gland. (A) Stained parietal cells in the corpus region of a human stomach. The ellipse highlights a cross-sectional view of a typical corpus gland. (B) The cross sectional view fails to capture the 3-D nature of the gland. Shown here is a schematic view of longitudinal section of a gastric gland. The assumption is that the human gland is long and tubular. However, species-specific variations in the arrangements of glands do occur.

Fig. 3. Ontogeny of G, D, ECL and parietal cells from underlying antral (Ae) and corpus (Cc) stem cells. (A) shows differentiation within the antrum and (B) presents differentiation in the corpus region. The dashed lines represent feedback control of stem cell differentiation (p(t)). The alphanumeric and Greek symbols represent the rates at which the respective processes occur. γ and λ represent growth and death rates of the respective cells. T represents differentiation of the respective stem cells.
Fig. 4. **The food input supplied to the virtual human gastric system.** B, L, and D represent breakfast (7h00), lunch (13h00), and dinner (19h 00) respectively. The amplitude of the peak at each meal represents the volume of food intake.

Fig. 5. **Baseline simulations of effectors and gastric acid.** (A) Simulation of CNS activity. (B) Simulation of ENS activity. (C) Virtual simulation of changes in plasma gastrin concentration due release of gastrin by G cells. (D) Simulated gastrin release is in agreement with published plasma data (83). Upper and lower bounds of gastrin concentration are shown. (E) Simulated total somatostatin released by antral and corpus D cells. (F) This is consistent with experimental results (84). (G) Simulated histamine release from ECL cells. No human data on histamine diurnal changes have been reported to date. (H) Simulated gastric acid in the corpus is consistent with (I) experimental data from Feldman and Richardson showing upper and lower bounds of gastric acid (85). (J) Reciprocal behavior of gastrin and somatostatin (B, Ln, and D represent breakfast (7h00), lunch (13h00), and dinner (19h 00), respectively).

Fig. 6. **Simulated cell populations.** Cell population numbers remain in homeostasis over the 24-hour time course. (A) Stem cells in the corpus and antrum. (B) Antral endocrine cells include G and D cells. (C) Cells found in the corpus include D, ECL and parietal cells.

Fig. 7. **Virtual depletion of gastrin.** (A) Simulated gastrin. (B) During gastrin depletion, somatostatin levels are lowered. (C) Histamine levels are reduced due to the lack of gastrin stimulation as well as (D) gastric acid levels. (Controls are represented by dashed lines; histamine depletions by solid lines; * represents $p < 0.05$; and ** represent $p < 0.001$).

Fig. 8. **Virtual histamine depletion.** (A) During histamine depletion, gastrin is elevated and (B) somatostatin concentration is significantly reduced. (C) Simulated histamine levels. (D) Lack of histamine significantly reduces gastric acid levels although to a lesser extent than during gastrin depletion. (Controls are represented by dashed lines; histamine depletions by solid lines; * represents $p < 0.05$; and ** represent $p < 0.001$).
**Fig. 9.** Virtual depletion of somatostatin in the antrum (A-D) and the corpus (E-F). Antral somatostatin depletion has a more dramatic effect on the gastric system than does corpus somatostatin depletion. (Breakfast, lunch, and dinner were administered at 7h00, 13h00 and 19h00 respectively. Controls are represented by dashed lines; histamine depletions by solid lines; * represents $p < 0.05$; and ** represent $p < 0.001$).

**Fig. 10. The effect of variation of CNS parameters.** The effects of variation of maximal CNS activity due to food stimulation ($N_{\text{max}}$) on (A) simulated gastrin and (B) gastric acid and the effects of variation of the maximal gastrin secretion rate due to CNS stimulation ($K_{\text{NG1}}$) on (C) simulated antral gastrin and (D) gastric acid. (E) The long-term effects of gastrin on ECL overgrowth during 1200 hours (5 days). Gastrin levels are elevated following increases in the maximal gastrin secretion rate due to CNS stimulation ($K_{\text{NG1}}$). (F) The long-term effects of gastrin on G cells during 1200 hours (5 days). There is no change in G cell populations as $K_{\text{NG1}}$ increases. (* represents $p < 0.05$; and ** represent $p < 0.001$)
**Table 1. Parameters included in our model analysis.** (§ indicates use of uncertainty analysis for parameter estimation).

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<td>$K_{NG1}$</td>
<td>Maximal secretion rate of gastrin due to ENS stimulation per cell</td>
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<td>(86), (28), (87)</td>
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<td>$1.0 \times 10^{-10}$</td>
<td>(86)</td>
<td>M</td>
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<tr>
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<td>$1.0 \times 10^{-10}$</td>
<td>(86)</td>
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<td>$k_{SG}$</td>
<td>Dissociation constant of somatostatin from somatostatin receptor</td>
<td>$9.0 \times 10^{-11}$</td>
<td>(89)</td>
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<td>$\kappa_G$</td>
<td>Clearance rate of gastrin</td>
<td>$11.88$</td>
<td>(90)</td>
<td>hr$^{-1}$</td>
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<td>$\beta_G$</td>
<td>Transport rate of gastrin from the antrum to corpus regions</td>
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somatostatin due to stimulation with antrum acid

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<td>(38)</td>
<td>$\text{M} \cdot \text{hr}^{-1} \cdot \text{cell}^{-1}$</td>
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<td>$\text{M}$</td>
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<td>Gastrin concentration at which the rate of somatostatin secretion is half maximal</td>
<td>$5.20 \times 10^{-12}$</td>
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<td>Dissociation constant of GRP from receptors on D cells</td>
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<td>$\kappa$</td>
<td>Clearance rate of somatostatin</td>
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<td>(91)</td>
<td>$\text{hr}^{-1}$</td>
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<td>$K_{NS1}$</td>
<td>Maximal rate of secretion of antral somatostatin due enteric nervous stimulus</td>
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<td>(45)</td>
<td>$\text{M} \cdot \text{hr}^{-1} \cdot \text{cell}^{-1}$</td>
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<td>$\alpha_{NS}$</td>
<td>Concentration of the ENS stimulant at which the rate of corpal somatostatin secretion is half maximal</td>
<td>$8.98 \times 10^{-11}$</td>
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<td>Dissociation constant of somatostatin from somatostatin receptors on D cells</td>
<td>$9.0 \times 10^{-11}$</td>
<td>M</td>
<td>(89)</td>
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<td>$K_{NH}$</td>
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<td>$7.59 \times 10^{-16}$</td>
<td>M/hr•cell</td>
<td>(92)</td>
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<td>Maximal rate of histamine secretion stimulated by gastrin transported to the corpal region</td>
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<td>(19)</td>
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<td>(93), (94), (95), (96), (19), (97)</td>
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<td>$k_{SS}$</td>
<td>Dissociation constant of somatostatin from somatostatin</td>
<td>$9.0 \times 10^{-10}$</td>
<td>M</td>
<td>(89)</td>
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</table>
receptors on ECL cells

\[ \kappa_H \]
Clearance rate of histamine 11.89 (98) hr\(^{-1}\)

\[ K_{NA} \]
Maximal rate of acid secretion due to nervous stimulation mediated through acetylcholine $2.33 \times 10^{-11}$ (99) M\(\cdot\)hr\(^{-1}\)\(\cdot\)cell\(^{-1}\)

\[ K_{GA} \]
Maximal rate of acid secretion due to gastrin mediated stimulation $4.98 \times 10^{-11}$ (100) M\(\cdot\)hr\(^{-1}\)\(\cdot\)cell\(^{-1}\)

\[ K_{HA} \]
Maximal rate of acid secretion due to histamine mediated stimulation $7.96 \times 10^{-10}$ (100), (101) M\(\cdot\)hr\(^{-1}\)\(\cdot\)cell\(^{-1}\)

\[ \alpha_{NA} \]
Concentration of CNS stimulant at which the rate of acid output is half maximal $5.0 \times 10^{-6}$ (93), (101) M

\[ \alpha_{GA} \]
Gastrin concentration at which the rate of acid output is half maximal $1.8 \times 10^{-10}$ (102), (103) M

\[ \alpha_{HA} \]
Histamine concentration at which the rate of acid output is half maximal $2.0 \times 10^{-8}$ (93), (101) M

\[ k_{SA} \]
Dissociation constant of somatostatin from somatostatin receptors on parietal cells $9.0 \times 10^{-10}$ (89) M
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<tr>
<td>$\kappa_A$</td>
<td>Wash out rate of acid</td>
<td>2.72</td>
<td>(104), (105)</td>
<td>hr$^{-1}$</td>
</tr>
</tbody>
</table>
Table 2. Comparison of results obtained through immunohistochemical experiments and published data. (NA = not assessed).

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Steady state simulated cell numbers</th>
<th>Immunohistochemistry estimates (cells/stomach)</th>
<th>Published data</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>G</em> cells</td>
<td>8.75x10^6</td>
<td>23.82 x10^6±14.44x10^6</td>
<td>8.0 – 15x10^6 (106)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15.5x10^6 (dogs) (107)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.6x10^6 (dogs) (108)</td>
</tr>
<tr>
<td>Antral <em>D</em> cells</td>
<td>3.70x10^6</td>
<td>9.53x10^6±5.77 x10^6</td>
<td>G/D cells ratio of 2:1 (109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11x10^6 (dogs) (107)</td>
</tr>
<tr>
<td><em>ECL</em> cells</td>
<td>8.68x10^8</td>
<td>NA</td>
<td>30% total endocrine cell population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(humans) (110), (51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35% (111)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.81x10^6 (rats)</td>
</tr>
<tr>
<td>Corpus <em>D</em> cell</td>
<td>2.69x10^8</td>
<td>2.61x10^8±0.83 x10^8</td>
<td>4x10^6 (dogs) (107)</td>
</tr>
<tr>
<td>Parietal cells</td>
<td>1.00x10^8</td>
<td>1.09x10^9±2.4 x10^8</td>
<td>1.005x10^9 (humans)(112)</td>
</tr>
</tbody>
</table>
Figure 1
Figure 2

A

B
gastric pit
isthmus
neck
base
Figure 3

[Diagram of stem cell differentiation and acid secretion pathways]
Figure 4
Figure 5

A. Central neural activity (μM) vs. Time (h)

B. Enteric neural activity (nM) vs. Time (h)

C. Simulated antral gastrin (pM) vs. Time (h)

D. Plasma gastrin data (pM) vs. Time (h)

E. Simulated total somatostatin (pM) vs. Time (h)

F. Plasma somatostatin data (pM) vs. Time (h)

G. Simulated corpus histamine (nM) vs. Time (h)

H. Simulated corpus gastric acid (mM) vs. Time (h)

I. Gastric acid concentration (mM) vs. Time (h)

J. Simulated antral gastrin (pM) vs. Time (h)

Simulated antral somatostatin (pM) vs. Time (h)
Figure 6

A

Stem cell populations (x10^7)

- Corpus Stem Cells
- Antral Stem Cells

Time (h)

0  6  12  18  24

B

Antral glandular cells (x10^6)

- D Cells
- ECL Cells
- Parietal Cells

Time (h)

0  6  12  18  24

C

Corpus glandular cells (x10^8)

- D Cells
- ECL Cells
- Parietal Cells

Time (h)

0  6  12  18  24
Figure 7

![Graphs showing simulated gastric and somatostatin levels over time.](image-url)
Figure 8

(A) Simulated antral gastrin (pM) over time (h) showing peaks at specific intervals.

(B) Simulated total somatostatin (pM) over time (h) with peaks indicated.

(C) Simulated corpus histamine (nM) over time (h) with peaks marked.

(D) Simulated corpus gastric acid (mM) over time (h) with peaks indicated.
Figure 9

A

Simulated antral gastrin (pM)

B

Simulated total somatostatin (pM)

C

Simulated corpus histamine (nM)

D

Simulated corpus gastric acid (nM)

E

Simulated antral gastrin (pM)

F

Simulated total somatostatin (pM)

G

Simulated corpus histamine (nM)

H

Simulated corpus gastric acid (nM)
Figure 10

A

Simulated antral gastrin (pM)

- $N_{\text{max}1} = 6.28 \times 10^{-17}$
- $N_{\text{max}1} = 4.26 \times 10^{-15}$
- $N_{\text{max}1} = 5.28 \times 10^{-15}$

Time (h)

B

Simulated corpus gastrin acid (mM)

**

Time (h)

C

Simulated antral gastrin (nM)

- $K_{NG1} = 5.28 \times 10^{-17}$
- $K_{NG1} = 4.26 \times 10^{-15}$
- $K_{NG1} = 6.28 \times 10^{-15}$

Time (h)

D

Simulated corpus gastrin acid (mM)

**

Time (h)

E

ECL cell population size ($x10^{6}$)

- $K_{NG1} = 6.28 \times 10^{-15}$
- $K_{NG1} = 4.26 \times 10^{-15}$
- $K_{NG1} = 6.28 \times 10^{-17}$

Time (h)

F

G cell population size ($x10^{6}$)

Time (h)