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# PREDICTING EFFICACY OF PROTON PUMP INHIBITORS IN REGULATING GASTRIC ACID SECRETION

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Developing drugs to treat gastric acid related illnesses such as ulcers and acid reflux disease is the leading focus of pharmaceutical companies. In fact, expenditure for treating these disorders is highest among all illnesses in the US. Over the last few decades, a class of drugs known as a proton pump inhibitors (PPIs) appeared on the market and are highly effective at abating gastric illnesses by raising stomach pH (reducing gastric acid levels). While much is known about the action of PPIs, there are still open questions regarding their efficacy, dosing and long-term effects. Here we extend a previous gastric acid secretion model developed by our group to incorporate a pharmacodynamic/pharmacokinetic model to study proton pump inhibitor (PPI) action. Model-relevant parameters for specific drugs such as omeprazole (OPZ), lansoprazole (LPZ) and pantoprazole (PPZ) were used from published data, and we conducted simulations to study various aspects of PPI treatment. Clinical data suggests that duration of acid suppression is dependent on proton pump turnover rates and this is supported by our model. We found the order of efficacy of the different PPIs to be OPZ > PPZ > LPZ for clinically recommended dose values, and OPZ > PPZ = LPZ for equal doses. Our results indicate that a breakfast dose for once-daily dosing regimens and a breakfast-lunch dose for twice-daily dosing regimens is recommended. Simulation of other gastric disorders using our model provides atypical applications for the study of drug treatment on homeostatic systems and identification of potential side-effects.

*Keywords*: Omeprazole; lansoprazole; pantoprazole; mathematical modeling; homeostasis; pharmacokinetics; pharmacodynamics.

## 1. Introduction

Monitoring stomach acid levels has long been regarded as a means of verifying gastrointestinal health. A complex network of neural stimuli and effectors interact to provide regulation of gastric acid levels. These interactions involve positive and negative feedback mechanisms that act in concert to maintain a strict pH range of

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1–3 within the stomach (i.e., acid homeostasis). This range is optimal and necessary for activation and catalytic activity of inactive enzyme precursors involved in protein digestion. While an intermittent deviation from this range is permissible, continued hyper- or hypo-acidity can result in gastric dysfunction.

Control of acid secretion by parietal cells in the stomach and the resulting maintenance of stable acid levels is critical for limiting corrosive damage to cellular environments [84]. To protect gastric epithelia from corrosive effects various mechanisms have evolved. These include, but are not limited to

(1) secretion of a mucus layer that maintains a million-fold acid concentration gradient between the stomach lumen and cells lining the surface of the stomach;
(2) cardiac and pyloric sphincters that prevent premature flow of gastric contents into the esophagus and duodenum respectively; and
(3) secretion of bile into the small intestine that serves to neutralize chyme.

The past three decades have seen many advances in the field of gastroenterology and management of associated gastric disorders. Prior to the advent of revolutionary histamine receptor antagonist ($H_2$RA) and proton pump inhibitor (PPI) therapies, acid-related disorders were managed by dietary modifications, antacid administration, or surgical intervention [78]. Although a last resort, surgeries such as highly selective vagotomies proved highly effective at reducing complications from acid hypersecretion. However, an effective but less invasive alternative to surgical intervention was sought.

By the early 1960s, it was apparent that acid secretion is a highly regulated process involving positive and negative feedback mechanisms. Work conducted by Popielski (1920) implicating histamine in stimulating acid secretion together with the development of a class of histamine antagonists by Bouvet (1955) for treating allergies led Black (1972) to propose the use of histamine antagonists to treat acid-related disorders [11, 65, 75]. In 1970, the first gastric selective $H_2$RA (i.e., burimamide) was synthesized. Other $H_2$RAs such as cimetidine, famotidine, ranitidine and nizatidine are now commonly used in the treatment and prevention of ulcers as well as gastroesophageal reflux disease (characterized by reverse flow of acid into the esophagus, commonly known as GERD). Not surprisingly, a reproducible relationship is observed in people suffering from peptic ulcers or acid reflux disease between suppression of acid secretion via treatment, a corresponding elevation of gastric pH, and tissue healing rates [10, 14].

While $H_2$RAs are still commonly used, recent studies consistently observe drug resistance [59] and a return of acid to pre-treatment levels in patients upon administration of $H_2$RAs [24, 62]. Although $H_2$RA inhibition correlates with blood concentration of drug, the effect is short-lived due to reversibility of inhibition. These drawbacks make $H_2$RAs considerably less effective in restoring normal function during extremely debilitating gastric diseases. However, they are still prescribed for treatment of mild hyper-acidity and are available over-the-counter for this purpose [21].

These drawbacks warranted the development of more effective drugs and the last two decades have seen the emergence of a class of potent acid suppressants. This class of drugs lowers acid levels by irreversibly inhibiting proton pumps [30]. Proton pumps are found in the membrane of parietal cells (Fig. 1) and are responsible for secretion of protons into the stomach lumen. These drugs, known as proton pump inhibitors (PPIs), are now the treatment of choice for acid-related disorders. Omeprazole is the most widely used, followed by lansoprazole, pantoprazole, and rabeprazole. Because of irreversible inactivation of proton pumps, the time profile of action of the PPI depends on the cycling rate at which pumps are synthesized, inactivated and degraded and it does not depend on blood concentration [47]. This ensures a long-lasting inhibitory effect during PPI administration as compared with $H_2$RA treatment. Results from several clinical trials and analysis of these studies consistently indicate that PPIs are more effective than $H_2$RAs at suppressing gastric acid levels and providing relief from acid related symptoms [42, 66].

PPIs signify an important advance in treatment of acid related disorders. While their pharmacological properties have been extensively studied, there is still a need to provide conclusive results about various PPIs in context of their efficacy, optimal dosing schedule and long-term effect on gastric health. Several studies describing the effect of single and repeated daily dosing of PPIs on acid levels have been published. Howden *et al.* provided early results on the effects of a single dose and a once-daily dosing regimen of omeprazole −10 mg on 6 healthy volunteers [29]. Chiverton *et al.* found that omeprazole (20 mg) in the morning was significantly better than an evening dose for controlling gastric acid levels [17]. Timmer *et al.* showed that lansoprazole (30 mg) twice daily was more effective at acid suppression than 60 mg once daily [82]. Studies by Landes *et al.* revealed that lansoprazole exhibits an extremely fast onset of action as compared to omeprazole [43]. They also concluded that acid levels returned to normal approximately 7 days after the last administered dose of PPI. Review articles by Stedman *et al.* and Katashima *et al.* list over 50 comparative studies on PPI efficacies and failing to find any consistency, conclude that all PPIs have equivalent potency [37, 79]. While such studies do provide evidence of acid suppression, the effect of PPI treatment on other components of homeostatic mechanisms regulating gastric acid secretion still remains to be determined.

Our work attempts to extend current specifics about the action of PPIs on gastric acid secretion by making predictions regarding the efficacies of PPIs in suppressing acid secretion. To this end, we build on a previously published mathematical model developed by our group describing gastric acid secretion and regulation to develop a treatment model by including the effects of PPI action on acid levels [36]. Our original gastric acid secretion model tracks four cell populations in the stomach considered critical for acid secretion: G, D, ECL and parietal cells, and the effectors secreted by them that regulate acid secretion (gastrin, somatostatin, histamine and hydrochloric acid, respectively) [36] (Fig. 2). The

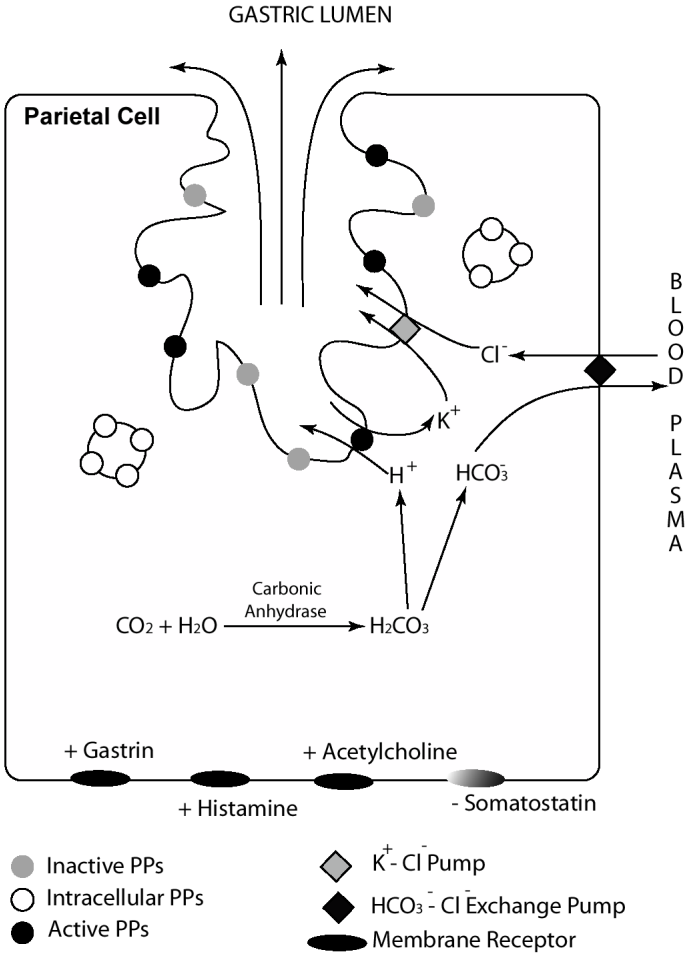



Fig. 1. Schematic of acid secretion by the parietal cell. Carbonic acid ($H_2CO_3$) is synthesized intracellularly by action of carbonic anhydrase, and is broken down to provide protons ($H^+$) that are pumped out by active proton pumps into the gastric lumen in exchange for potassium ($K^+$). Blood chloride ($Cl^-$) is exchanged with bicarbonate ions ($HCO_3^-$) and is then pumped into the gastric lumen in symport with potassium. Note that inactive proton pumps and intracellular vesicle bound proton pumps do not contribute to this process. Also shown are various stimulatory and inhibitory receptors that respectively up- and down-regulate acid secretion.

use of mathematical modeling to study such complex processes provides a unique opportunity to conduct studies not presently possible through clinical or experimental protocols.

### 1.1. *Mathematical modeling*

Several mathematical models describing acid secretion were previously published [19, 20, 45, 46]. de Beus *et al.* [19] developed a model that provided insight into the

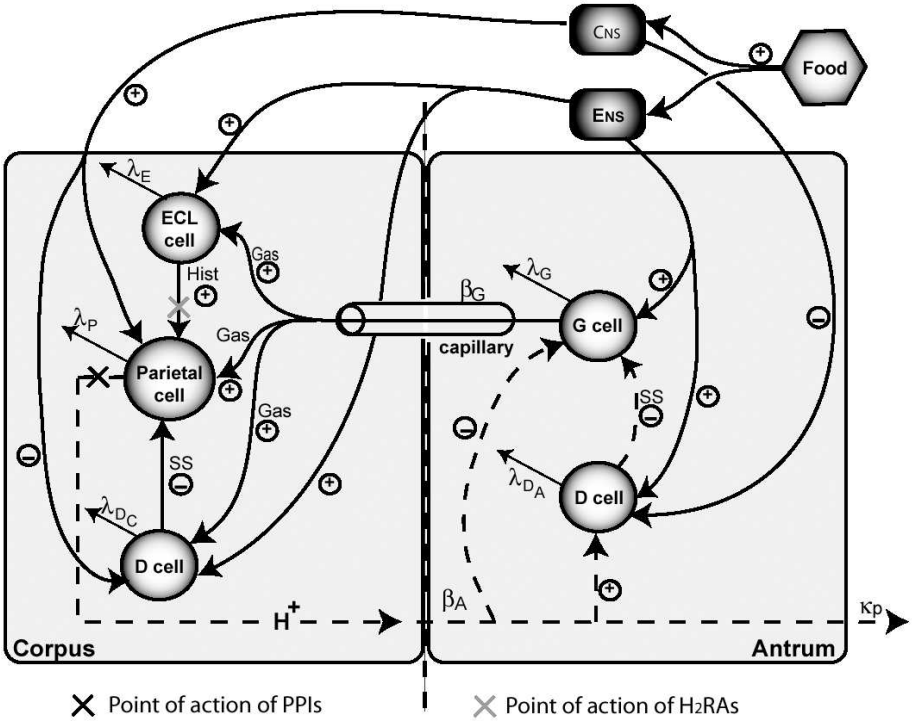



Fig. 2. Shown is a schematic diagram of our model of gastric acid secretion as reported by Joseph *et al.* [36]. This model is altered to reflect the presence of treatment with PPIs. The point of interaction of PPIs within the model is shown above, and $H_2$RA action is also illustrated. Cell populations accounted for include: gastrin (Gas) secreting G cells in the antrum, somatostatin (SS) secreting delta (D) cells in the antrum and corpus, histamine (Hist) secreting enterochromaffin-like (ECL) cells and parietal cells in the corpus.

coupling of gastric acid to bicarbonate secretion. In particular, they analyzed the cascade of molecular and ionic events necessary for acid secretion. Likewise, Licko *et al.* presented an extensive analysis of gastric acid secretion [46] in which they explored mechanics of acid secretion as a sequential two-step process involving the formation of acid that contributes to a storage pool and the subsequent translocation of the stored acid. Both models provided insights into parameters that were not easily estimated experimentally.

We propose a pharmacodynamic/pharmacokinetic model of PPI action and describe how new parameters feed back into the baseline gastric acid secretion model [36]. Pharmacodynamics quantitatively depict effects of a drug on the body, while pharmacokinetics describes effects of physiological processes on a drug over a period of time, such as absorption and clearance. Together, they provide a complete picture of drug-target interaction.

Our goal is to derive useful inferences of therapeutic significance. Specifically, we begin by performing simulations to determine the time course of recovery of

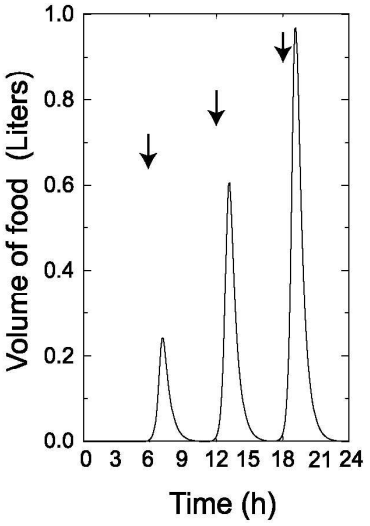



Fig. 3. Food function used in the acid secretion model. Food is administered thrice daily at 7 (breakfast), 14 (lunch) and 19 (dinner) hrs as indicated by the arrows. The phenomenological equation implementing this function is discussed in [52].

acid levels to baseline after administration of a single dose. Also of interest is that recommended PPI dose values that are commonly prescribed by physicians to patients of acid-disorders, differ for each PPI [41]. We thus compare the extent of acid suppression based on recommended dosing regimens for each PPI. In order to compare efficacy, we measure acid levels after setting all PPIs to the same dose value.

We conduct optimization studies based on ability of a drug to lower acid levels to ascertain the best possible dosing time(s) for once-daily and twice-daily regimens. Such experiments yield information on questions about whether differing regimens for the same dose (e.g. 20 mg once daily vs. 10 mg twice a day) have a significant effect on acid levels.

Lastly, we exploit our baseline acid secretion model [36] to study effects of PPI treatment on gastric health measured in terms of proliferation of various gastric cell populations and on variations of effector levels. Maintaining steady state is a special property of complex systems, and this is the first attempt to provide insight into how treatment returns a perturbed system to acid homeostasis.

## 2. The Model

The baseline model of gastric acid secretion [36] is shown in Fig. 2. Food input (Fig. 3) and both central neural system (CNS) and enteric neural system (ENS) provide stimuli. The system is governed by a network of autocrine and paracrine cells and their secreted products. Neural activity elicits a cascade of events charac-

terized first by release of gastrin, a stimulant of gastric acid secretion. At the site of acid secretion (i.e., the stomach corpus region), both gastrin, histamine as well as acetylcholine, a neurotransmitter, synergistically stimulate acid release from parietal cells. Somatostatin, an acid inhibitor, is secreted and inhibits gastrin, histamine and acid release thereby returning acid concentrations to basal levels. The mathematical equations are given in the Appendix [36]. We previously validated this baseline model and performed a number of simulations, predicting new information regarding the roles of cells and their secretory factors [36]. We now incorporate treatment into our gastric acid secretion model by accounting for the effect of PPIs on proton pumps. To this end, we include proton pumps, PPIs and their effects on gastric acid as follows:

### 2.1. *Proton pump categories*

A schematic of the mechanism of acid secretion by parietal cells is provided in Fig. 1. PPIs suppress acid secretion by non-competitive irreversible inhibition of proton pumps that use ATP to actively move protons from the interior of the cell into the gastric lumen in exchange for potassium [30].

The point of PPI interaction with the acid secretion system is shown in Fig. 2. Different categories of proton pumps are shown:

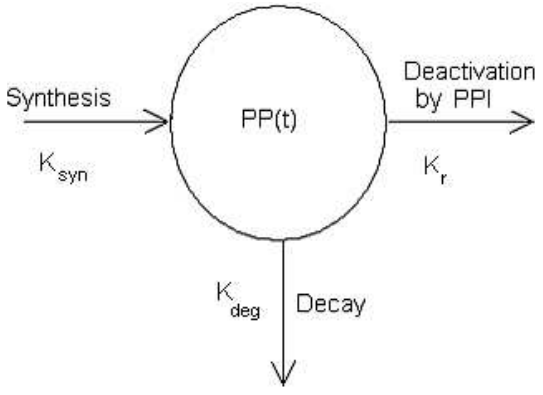
1. *Intracellular*: Intracellular pumps are newly synthesized and are found in the membrane of intracellular vesicles not yet fused with the cell membrane. These pumps are non-functional [74].
2. *Active*: Active pumps are found solely in the cell membrane and are the only proton pumps that contribute to maintenance of acid levels by active proton transport across the membrane [74].
3. *Inactive*: Inactive pumps in the cell membrane are those that have been inhibited by PPI action. Hence, inactive pumps also do not contribute to acid levels [74].

We consider only the active proton pump class and study the effect of PPI treatment on their concentration. Acid levels are slowly restored by cycling of proton pumps, involving degradation of inactive pumps and fusion of vesicles containing non-functional pumps with the cell membrane [1]. We assume that a turnover model for enzyme concentration (Fig. 4) satisfactorily describes this cycling.

## 3. Model Equations

### 3.1. *PPI blood concentration*

The PPI blood concentration is described by a one compartment linear approach. We assume that (1) drug is rapidly and uniformly distributed throughout the body in a single compartment and (2) rate of elimination of drug is proportional to amount of drug in the body [7]. Following administration of a given dose, the




$$\frac{d(PP(t))}{dt} = K_{syn} - K_r \cdot PPI(t) \cdot PP(t) - K_{\deg} \cdot PP(t)$$

Fig. 4. Dynamics of active proton pump concentration. Proton pumps (PP) are synthesized at a rate $K_{syn}$ and deactivated by PPI at a rate $K_r$. They also have a half life with degradation rate $K_{deg}$.

one compartment approach provides an equation for PPI blood concentration as a function of time:

$$PPI(t) = \frac{D}{V*m}\, e^{(-K_{el}*t)}\,, \tag{3.1}$$

where $D$ is the dosage in micrograms, $m$ is the molecular weight of the PPI, $V$ is the volume of distribution, and $K_{el}$ is the elimination constant. The volume of distribution is an apparent volume that relates amount of drug in the body to concentration in the measured compartment, blood in our case. Depending on its chemical nature, a drug may be lipid soluble and consequently have a high $V$, or be lipid insoluble and have a low value for $V$ [49] (see Table 1 for their values for each PPI). It is also important to note here that since elimination constants are derived from fitting to clinical data, they likely include all possible mechanisms of clearance, including renal clearance and metabolism and thus their values are an upper bound on actual values. Absorption time for orally administered PPIs (approx. 30 mins) is much shorter than the time span of their action (almost a week). Hence, for the sake of simplicity, we do not include absorption delays in our model.

We further assume that oral bioavailability of drug is 100%, which is the case if the entire administered dose reaches systemic circulation. This is typically observed with intravenous administration of drug. However, PPIs are usually taken orally and are acid labile [80]. This means that they undergo degradation to some extent when routed through the stomach. In this paper we assume 100% bioavailability. The implications of this assumption are discussed in the Results section. The model can easily be altered to handle less than 100% bioavailability.

### 3.2. *Dosing schedule*

Following its administration PPI blood concentration over time is used to monitor drug blood levels after a single dose. In order to account for daily dosing, we extend this function by superposition to account for possible accumulation of drug in the blood. The blood concentration function conceptually takes the form:

$$PPI(t) = (\text{day } 1)\frac{D}{V^*m}\, e^{(-K_{el}*t1)} + (\text{day } 2)\frac{D}{V^*m}\, e^{(-K_{el}*t1)} + \cdots , \tag{3.2}$$

for a once-daily dosing regimen. We model a standard dosing schedule of once-daily dosing administered every morning with breakfast (7 am). The food function is modeled as a standard American diet of three meals a day (Fig. 3).

By extension, a twice-daily dosing regimen (drug is administered twice a day at times $t_1$ and $t_2$) can be implemented by the following function:

$$\begin{aligned} PPI(t) = {} & (\text{day } 1, \text{dose } 1)\frac{D}{V^*m}\, e^{(-K_{el}*t1)} + (\text{day } 1, \text{dose } 2)\frac{D}{V^*m}\, e^{(-K_{el}*t2)} \\ & + (\text{day } 2, \text{dose } 1)\frac{D}{V^*m}\, e^{(-K_{el}*t1)} + (\text{day } 2, \text{dose } 2)\frac{D}{V^*m}\, e^{(-K_{el}*t2)} + \cdots . \end{aligned} \tag{3.3}$$

In both cases, possible buildup of drug levels in blood is described by adding blood concentration over time for each dose, starting from the first dose (day 1). Using different dosing schedules allows us to study the effects of different dosing times and dosing schemes.

### 3.3. *Proton pump dynamics*

The equations describing active membrane-bound proton pump cycling during treatment is given by (Fig. 4):

$$\frac{d(PP(t))}{dt} = K_{syn} - K_r \cdot PPI(t) \cdot PP(t) - K_{deg} \cdot PP(t)\,, \tag{3.4}$$

where $K_{syn}$ is the zero order *de novo* synthesis/induction rate for the proton pump, $K_{deg}$ is the first order decay rate, and $K_r$ is the bimolecular rate constant of the PPI and the proton pump.

With no treatment, the active proton pump number should remain at an equilibrium value of $PP_0 = K_{syn}/K_{deg}$. This is reasonable, since proton pumps in the membrane are constantly being replaced even in the absence of treatment [30].

$K_{syn}$ is not an observable dynamic, and it is also not reasonable to define *PP(t)* as the number of molecules in the system. However, since pumps are inducted into the membrane due to histamine stimulation [27], synthesis rates should be first order and proportional to histamine concentration, rather than zero order rates. Problems arise due to dearth of such values for humans. The proton pump turnover model has also been developed previously and validated and presented elsewhere [1, 2, 69]. We use this same approach to capture proton pump turnover in our model system.

Dividing Eq. (3.4) by the equilibrium value $PP_0$ yields a normalized value for *PP(t)*:

$$\frac{d(PPn(t))}{dt} = K_{deg} - K_r \cdot PPI(t) \cdot PP_n(t) - K_{deg} \cdot PP_n(t)\,. \tag{3.5}$$

This not only provides us with a relative number, it also eliminates the $K_{syn}$ parameter, and the equation is now defined in terms of parameters that are easily identifiable, and in fact have been extensively studied and recorded in literature [37]. $PP_n(t)$ is now a factor that varies between 0 and 1, and indicates the fraction of pumps in a parietal cell that are uninhibited and still actively secreting acid into the lumen of the stomach.

### 3.4. *Corpus gastric acid dynamics*

The most critical aspect of this work is the coupling between the pharmacodynamic/pharmacokinetic model and our gastric acid secretion model [36] (Fig. 2). To incorporate treatment into the acid secretion model, we assume that (1) acid levels are directly proportional to the number of active proton pumps and (2) inhibition of proton pump activity is independent of secretion. This is reasonable since PPIs inhibit only the last step in acid secretion and have no known direct effect on stimulus receptors on parietal cells. Since PPIs do not interact with any other cell population or their effectors, treatment will only affect the equation representing corpus acid in the gastric acid secretion model [36]. In particular, the product of the $PP_n(t)$ function and the parietal cell number $P(t)$ defines the reduced acid-secretion capacity of the parietal cells in the stomach.

The modified acid secretion equation is given by (where bold shows change to the original equation developed in [36]):

$$\begin{aligned}\frac{d[A_C(t)]}{dt} = \boldsymbol{PP_n(t)} \cdot P \Bigg( & \left( \frac{K_{NA}[N_C(t)]}{([N_C(t)] + \alpha_{NA})\left(1 + \dfrac{[S_C(t)]}{k_{SA}}\right)} \right) \\ & + \left( \frac{[H_C(t)]}{[H_C(t)] + \alpha_H} \right) \left( \frac{K_{GA}[Gtn_C(t)]}{([Gtn_C(t)] + \alpha_{GA})\left(1 + \dfrac{[S_C(t)]}{k_{SA}}\right)} \right) \\ & + \left( \frac{K_{HA}[H_C(t)]}{([H_C(t)] + \alpha_{HA})\left(1 + \dfrac{[S_C(t)]}{k_{SA}}\right)} \right) \Bigg) - hb[A_c][B_c] - \beta_A[A_C(t)]\,.\end{aligned} \tag{3.6}$$

Rate of change of acid is affected by terms that account for (1) increased acid levels due to stimulation of the parietal cells, (2) loss terms due to reaction with

bicarbonate, (3) wash-out [36]. Our work is based on this singular interaction with the acid secretion model and how it then indirectly affects other system components through nonlinear interactions.

## 4. Parameter Estimation

Most PPI-related parameters were obtained from published experimental data on humans. However, *in vivo* rates likely vary with each repeated experiment due to an uncertainty (or intrinsic error) associated with each measurement. We evaluated the effects of uncertainty in values for these rates using C code based on Latin hypercube sampling (LHS) [12, 33, 34]. The LHS method allowed simultaneous, random and evenly distributed sampling of each defined parameter that we varied over a wide range. Having performed uncertainty analyses on the PPI-related parameters we obtained order of magnitude estimates for use in our simulations. Model parameters for the gastric acid secretion model in [36] are presented and discussed therein. We summarize them in Table 2. Given below is a brief outline of new parameters estimated for the proton pump model.

### 4.1. *Elimination constants* ($K_{el}$)

The elimination rates for omeprazole, lansoprazole and pantoprazole were taken from a comparative study and are summarized in Table 1. These values were obtained from single dose studies in humans [37].

Table 1. Pharmacokinetic parameters of the different PPIs.

| | $K_{el}$ ($\text{hr}^{-1}$) | $K_{deg}$ ($\text{hr}^{-1}$) | $K_r$ ($\mu\text{M}^{-1}\text{hr}^{-1}$) | Mol. wt. (Da) $m$ | Vol. of distribution (liters) $V$ | Recommended doses (mg) $D$ |
|---|---|---|---|---|---|---|
| Reference | 17 | 17 | 17 | — | 27 | — |
| Omeprazole (OPZ) | 0.866 | 0.0252 | 1.34 | 345.42 | 43–53 | 20 |
| Lansoprazole (LPZ) | 0.462 | 0.0537 | 0.339 | 369.37 | 43–53 | 30 |
| Pantoprazole (PPZ) | 0.533 | 0.0151 | 0.134 | 432.4 | 43–53 | 40 |

### 4.2. *Volume of distribution* ($V$)

A range of values for volume of distribution was obtained from a study of lansoprazole on 16 healthy male volunteers [69]. Since all PPIs exhibit a largely conserved chemical structure and clinical data indicates a wide range of possible values for $V$, we assume that these values are the same for omeprazole and pantoprazole as well [31, 79, 83].

### 4.3. *Proton pump inactivation ($K_r$) and decay ($K_{deg}$) parameters*

Proton pumps are synthesized (or rather inducted into the membrane and activated) at a zero order rate, and decay at a rate proportional to their number in the membrane (first order). Further, active pumps in the membrane are inactivated by blood PPI at a rate proportional to the blood concentration of the PPI and the active proton pump number, i.e., it is defined by a bimolecular rate constant. The values for these parameters were obtained from published data [37].

At a molecular level, each PPI binds to different sites on the proton pump. While the binding action is assumed to be irreversible, evidence exists for the role of a cellular non-enzymatic reducing agent known as glutathione that is involved in partial recovery of inactivated proton pumps [58]. Hence, we assume that interaction with glutathione and extent of recovery also differs for each of these drugs. To accommodate this, we model $K_{deg}$ as a hybrid parameter accounting for both natural decay of the proton pump (a system constant) and PPI dependent recovery of the proton pump, which differs between different PPIs. This is logical, given that it is not experimentally feasible to discriminate between or quantify these processes separately. Hence, the value of the $K_{deg}$ parameter is variable across different PPIs [37].

## 5. Sensitivity Analysis

The LHS method not only allows us to obtain measures of uncertainty in parameter values but also when used together with partial rank correlation gives a measure of which parameters correlate to changes in the outcome variable (namely gastric acid). We performed 20 simulations (each with a 300 hour timeframe) varying the elimination constant ($K_{el}$) and proton pump inactivation ($K_r$) rates simultaneously. We then combined the resulting uncertainty data with partial rank correlation (PRC) to determine the sensitivity of an outcome variable (i.e., acid levels) to parameter variation. The Student's $t$-test was used to determine the significance of each factor yielding a standard measure of sensitivity. We were also able to evaluate temporal changes in the significance of these parameters to acid levels.

## 6. Methods

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. We use MatLab's ode15s solver for stiff systems (The Math Works, Inc. Natick MA). Simulation results are compared with available experimental data for validation.

### 6.1. *Single dose profile*

The effect of a single dose (administered only once at 7 am on day 2 of the simulation) is studied using a recommended dose value of omeprazole (20 mg). Current

data indicate that normal acid levels are restored approximately a week after the last dose [43], irrespective of the duration of treatment. We perform a 300-hour simulation to verify this.

### 6.2. *Once-daily and twice-daily dose profiles*

The effect of a once-daily dosing regimen (administered once a day, day 4 onwards) and a twice-daily dosing regimen (administered twice a day, day 4 onwards) on acid secretion is studied using a recommended dose value of omeprazole (20 mg). 300-hour simulations are run in both cases. We compare the difference in mean 24-hour gastric acid levels between these two regimens. Once daily dose profiles also allow us to make important inferences about changes in drug bioavailability during the course of treatment, and this is discussed in the Results section.

### 6.3. *Dose comparison simulations*

Of interest in the study of PPIs is the existence of several drugs, and although they all have the same conserved structure and function [79] their pharmacological properties are extremely varied (see Table 1). Further, which of omeprazole, lansoprazole and pantoprazole is the most efficacious in terms of acid suppression is long debated [37, 79]. Another area of study is the recommended dosages of these drugs, which are as described in Table 1. We use our model to compare all three drugs based on recommended dosing, as well as on a per milligram basis. A PPI is considered more efficacious than another if it provides a greater degree of 24-hour acid suppression at clinically tolerable doses. It is considered more potent than another if lower doses are required to achieve a given degree of acid suppression.

To study the comparative efficacies of omeprazole (OPZ), lansoprazole (LPZ), and pantoprazole (PPZ) based on recommended dosing (Table 1), we simulate treatment under wild-type conditions, i.e., for a healthy individual. Treatment is initiated on the third day of simulation with doses of 20 mg for OPZ, 30 mg for LPZ, and 40 mg for PPZ, and a once daily regimen at 7 am.

Comparative efficacy of OPZ, LPZ and PPZ are determined by setting equal dose values for all three PPIs, i.e., we evaluate them on a per-milligram basis. We arbitrarily pick a value of 30 mg for the purpose of presenting our results, although the model yields consistent outcomes for all possible dose values (data not shown). Treatment conditions are similar to previous experiments.

### 6.4. *Optimal dosing schedule and regimen*

Several studies indicate better acid suppression with morning administration of a PPI as compared to evening [17, 67]. We conduct experiments to determine whether this observation is reflected in our model, and if so, to which model parameter is this

schedule most sensitive. An optimal dosing time was defined as one that provides the lowest 24-hour mean acid level as compared to other dosing times.

We vary the dosing time for a once daily-dosing regimen over 24 hours to determine the best dosing schedule for both once daily and twice daily-dosing regimens. For a once daily dosing-regimen, treatment was initiated with OPZ-20 mg once a day, and dose time was varied in 1-hour increments. For each simulation, acid levels are recorded.

For the twice-daily dosing regimen using OPZ-20 mg (10 mg twice a day), the first dose is maintained at the previously determined optimal time for once-daily dosing, and variation in acid levels were recorded with change in timing of the second dose.

### 6.5. *Treatment simulations*

We perform a novel experiment where we examine the use of PPIs in the treatment of gastric disorders. There is a two-fold need for this study: (1) to determine if recommended treatment periods of 4-8 weeks is sufficient for recovery of gastric cell populations and (2) whether PPIs are an appropriate means of treating some common gastric disorders. The definition of disease and recovery is crucial in the context of the model. The acid secretion model has already been used to perform simulations to ascertain critical elements in the acid secretion process [36]. Conditions such as excessive blood gastrin (e.g., hypergastrinemia) can be easily simulated with the model, and thus we are able to study effects of PPI treatment on effector levels and cell populations. Hyper-secretion of acid (hyperchlorhydria) can be similarly modeled. While this logic may be extended to simulate other dysfunctions, we look solely at these two cases and illustrate how by simply exploring a few model interactions a host of useful information may be obtained.

We simulate excess blood gastrin by elevating gastrin stimulation by 10 times its normal value, which is consistent with diagnostic levels for hypergastrinemia [39]. Treatment is initiated after steady state levels have been achieved for all variables in the system (effector levels, cell populations, etc.), and temporal changes in these variables are tracked. Simulations are conducted with a single dose regimen of OPZ-20 mg. A similar experiment is conducted by elevating acid stimulation to simulate excessive acid secretion, a condition known as hyperchlorhydria.

## 7. Results

To predict the efficacy of PPIs, we first simulate the action of PPIs under various conditions and compare with experimental data (Fig. 5). Having tested the model for consistency with published data, we then perform simulations using different criterion (see Methods section) and obtain time profiles for proton pump, $PP_n(t)$ and acid secretion, $A_c(t)$ (Figs. 6–9). All simulations are performed using parameters specified in Tables 1 and 2.

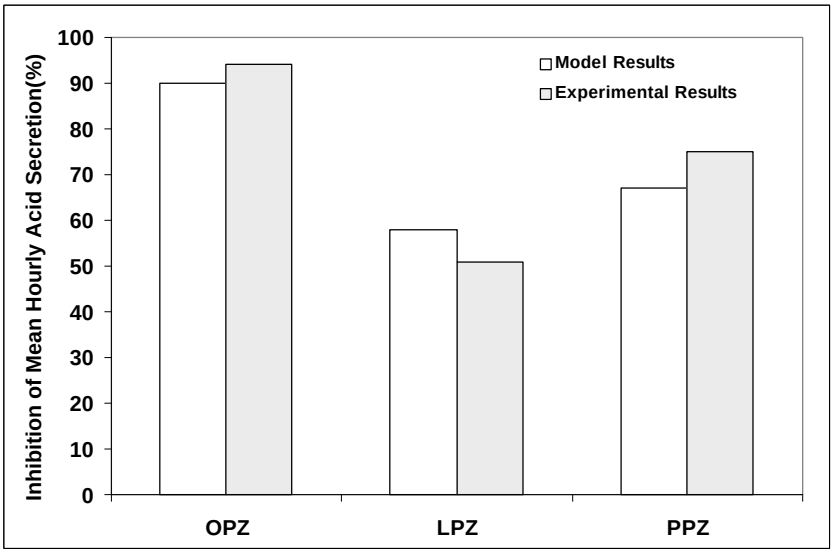



Fig. 5. Comparison between model and experimental results in terms of acid secretion for OPZ-30 mg, LPZ-30 mg, and PPZ-40 mg. Walt *et al.* observe a 94% decline in mean hourly acid secretion with OPZ-30 mg, and this is comparable to our results [87]. We correlate LPZ-30 mg results with baseline and pentagastrin stimulated acid secretion tests conducted by Bell *et al.*, and the mean values from both model and experimental approaches are shown [9]. Model PPZ-40 mg data is corroborated with trials by Metz *et al.* on GERD patients [55].

### 7.1. *Model testing*

We perform simulations to verify our model by replicating experimental conditions and comparing results obtained from published human models. Drug efficacy is normally measured by deviation from baseline, thus we validate our model by studying the extent of suppression of acid secretion by each drug, rather than by absolute acid levels. This is rational, since baseline acid secretion values can differ markedly between individuals. The results for each drug are shown in Fig. 5. The data for omeprazole are acquired from a clinical study of omeprazole — 30 mg on 9 patients with duodenal ulcers and normal acid levels [87]. In another report, Allen *et al.* conducted experiments to study changes in gastrin levels in healthy volunteers with omeprazole 40 mg [3]. They observed an approximate two-fold increase in basal gastrin levels, which is also reflected by our model (data not shown). We validate simulation results for lansoprazole treatment by comparing with a study on healthy male volunteers where pentagastrin (a synthetic polypeptide that mimics the effect of gastrin) infusion is used to stimulate acid secretion, and the ensuing suppression of acid levels using lansoprazole 30 mg is recorded (Fig. 5) [9]. Pentagastrin tests were simulated by maintaining constant gastrin levels. We verify pantoprazole efficacy with a study describing efficacy of pantoprazole to control gastric acid secretion in GERD patients (Fig. 5) [55]. This is again possible since GERD patients exhibit

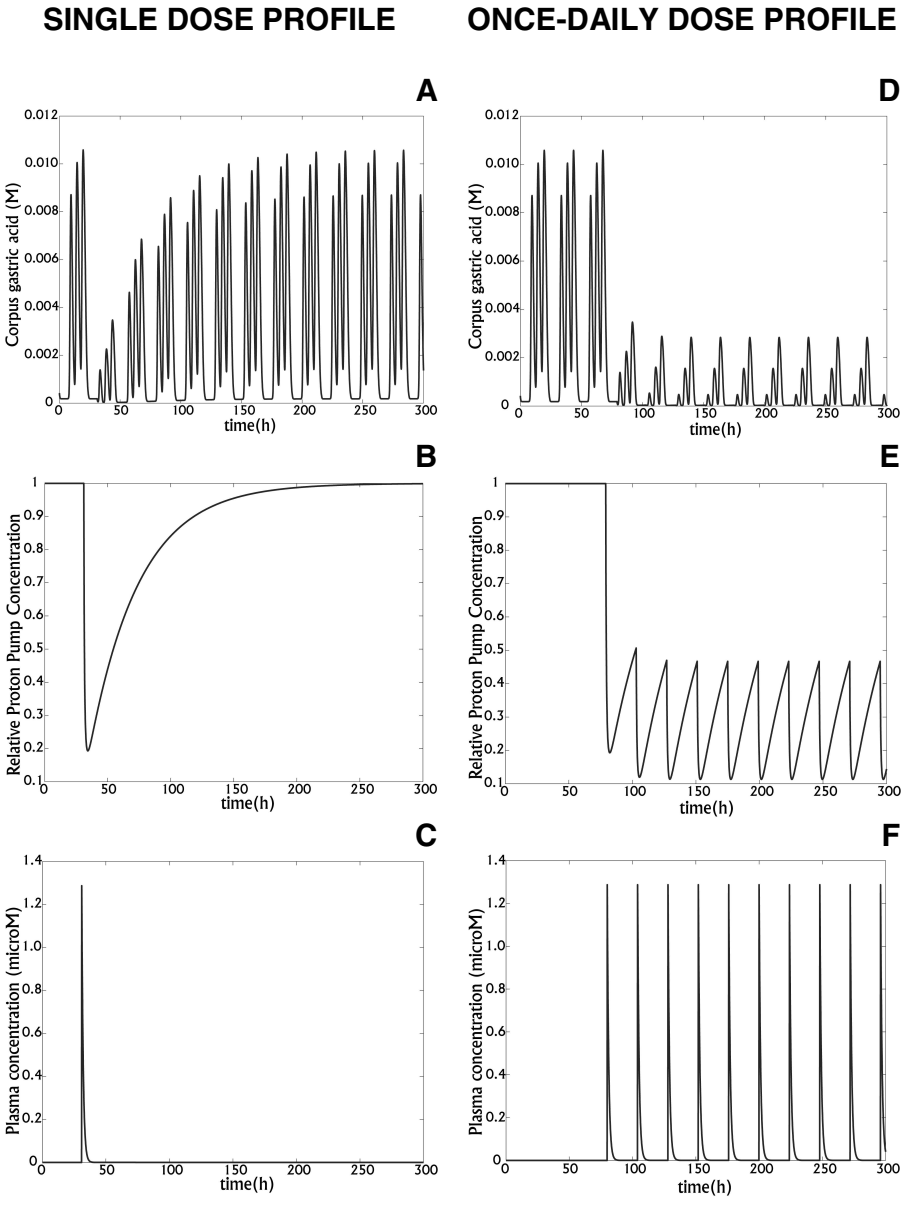



Fig. 6. Panels A, B and C (gastric acid, relative proton pump concentration and PPI blood concentration, respectively) show the effect of a single dose of OPZ-20 mg administered on day 2 of simulation. The acid levels closely follow the active proton pump concentration (Panel B), and return to normal values within 8–10 days. The comparatively shorter blood persistence of the drug reflects the fact that duration of acid suppression is dictated mostly by proton pump cycling. Panels D, E and F similarly indicate the effect of once-daily dosing with OPZ-20 mg daily, simulated from day 4 onwards. Once again, acid levels closely reflect active proton pump concentration. The cumulative effect of drug administration on blood levels is not significant, yet suppressed acid levels are seen to stabilize by the second day of simulated treatment.

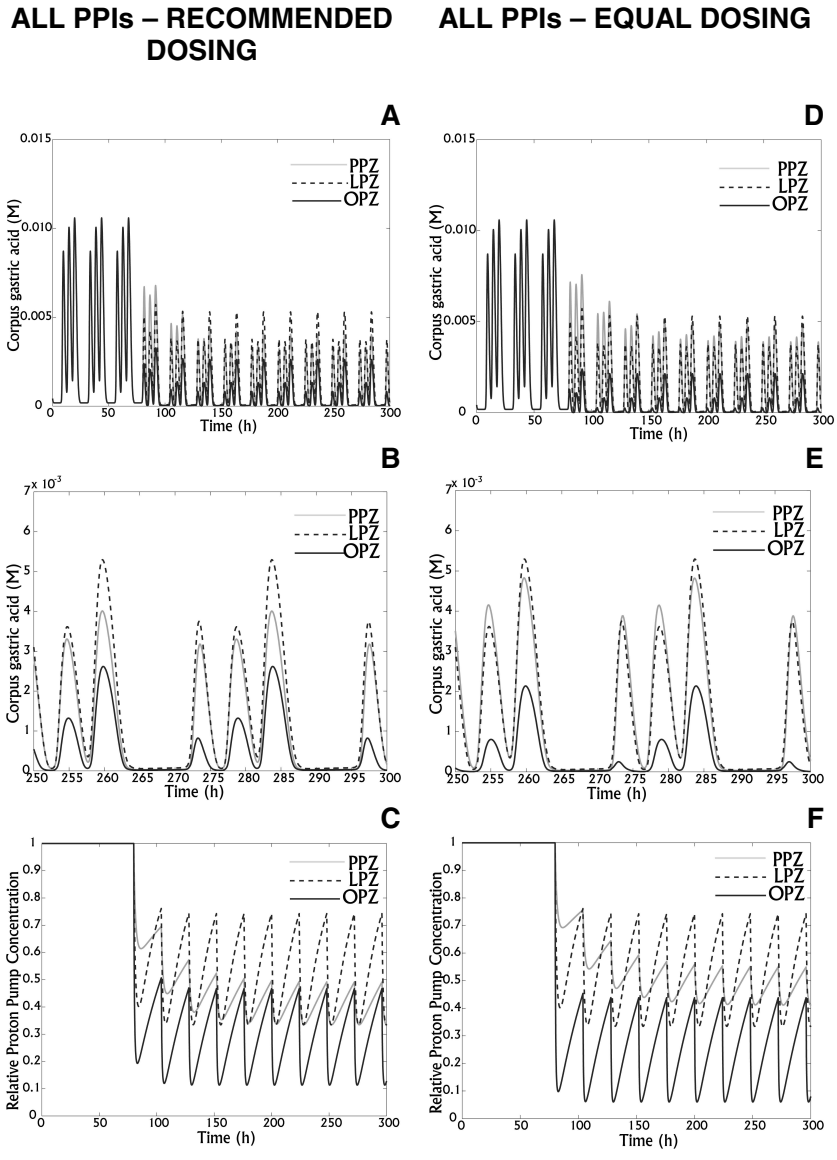



Fig. 7. Panels A, B and C show gastric acid and proton pump dynamics when treatment is simulated with OPZ-20 mg (dark line), LPZ-30 mg (dashed line), and PPZ-40 mg (light line) from day 4 onwards. Steady state acid profiles for all three drugs from 250–300 hours of simulation are magnified for emphasis (Panel B). Increased bioavailability of PPZ over time, as well as sustained bioavailability of LPZ is evident (Panel C). Steady state acid levels indicate drug efficacy (solely based on acid suppression) to be OPZ > PPZ > LPZ. Panels D, E and F illustrate treatment simulated with OPZ (dark line) = LPZ (dashed line) = PPZ (light line) = 30 mg from day 4 onwards. While OPZ is evidently most efficacious, the acid-time profile of LPZ and PPZ is more complicated. Analysis revealed equivalent 24-hour acid levels for both drugs, indicating similar potencies. LPZ provides better control over lunch-stimulated acid levels but is surpassed by PPZ for restraint of acid levels later in the day.

normal acid levels, and gastric homeostasis is oblivious to sphincter malfunctioning. Similar results for pantoprazole are obtained by comparing with data from other studies, including inhibition of pentagastrin-stimulated gastric acid secretion (data not shown) [22], [63].

### 7.2. *Single dose and once-daily dosing study*

The effect of single and once-daily doses on acid secretion is shown using omeprazole, 20 mg. The model predicts that the effect of acid suppression lasts longer than the blood half-life of the drug (Figs. 6A, B, C). The system requires almost 150–200 hours (depending on the drug) to recover to normal acid levels, and this is consistent with clinical trials that also allow a week after the last dose for complete restoration of acid secretion [47]. Figures 6D, E, F provide time profiles for once-daily dosing.

### 7.3. *Comparative efficacy*

Results comparing average 24-hour acid levels upon administration of OPZ-20 mg, LPZ-30 mg and PPZ-40 mg indicates a decreasing order of efficacy of drugs to be OPZ > PPZ > LPZ (Figs. 7A, B, C). Clearly, OPZ is the most efficacious of the drugs tested as shown by the degree of suppression. The need for other drugs, even though they appear less effective, is primarily attributed to a reduction in side effects as compared to OPZ [81]. Clearly, such multiplicity of drugs with identical action provides the physician wider jurisdiction for prescribing a PPI based on other properties such as drug interactions, etc.

An interesting result is seen when all drugs are compared on a per milligram basis (30 mg each); while OPZ is still the most potent, LPZ and PPZ appear to show similar efficacies in terms of 24 hour suppression of acidity (Figs. 7D, E, F). Seemingly, the only added benefit of having multiple drugs with similar potency but marginally different chemical structure is that individuals not responding to one drug can easily be switched to another. Studying relative efficacies in this manner allows us to determine that similar doses must be used to achieve the same effect. This result has also been reported by several clinical studies [35, 41].

### 7.4. *Bioavailability*

Significant observations may also be made regarding bioavailability for these drugs, as compared to clinical observations. In our model, regarding OPZ administration, acid/proton pump levels are seen to stabilize by the second day (Figs. 7B, C), while in actuality, bioavailability of OPZ is seen to increase after repeated administration. Since the only model parameter that accounts for bioavailability is blood drug concentration, our results suggest that OPZ does not accumulate in the blood, but likely undergoes some form of degradation during transport (e.g., in the stomach) or circulation that decreases over time, which is not accounted for in our model. Recent evidence that OPZ is metabolized in the liver by P450 enzymes, while also inhibiting

the same process, provides reasonable substantiation of this fact [54]. OPZ is known to be highly acid labile, and lowering acid levels via prolonged treatment allows progressively larger doses to escape degradation and reach systemic circulation. LPZ levels also stabilize by the second day (Figs. 7B, C), consistent with available data since physiologic processes other than renal clearance do not significantly affect LPZ [25, 43].

Similarly, efficacy of PPZ is seen to increase over time during clinical trials [5, 32]. Our model also indicates that efficacy of PPZ goes up over an extended treatment period of almost a week (Figs. 7B, C) and this can be attributed to low degradability of the PPZ-inhibited proton pump.

### 7.5. *Optimal dosing regimen*

We also performed optimization experiments to study the lowest 24-hour mean acid levels for different dosing times. We observed a consistent pattern, with a peak at 8 am for once-daily regimens, and at 8 am and 1 pm for a twice-daily regimen (Fig. 8). The once-daily regimen reflects clinical observations that PPIs are most effective when taken with the morning meal [17, 57]. A significant difference was seen between the two dosing profiles in terms of efficacy. Acid levels for a twice-daily regimen indicates lesser variation with dosing time as compared to once-daily regimen, although the lowest acid level observed was approximately the same in both

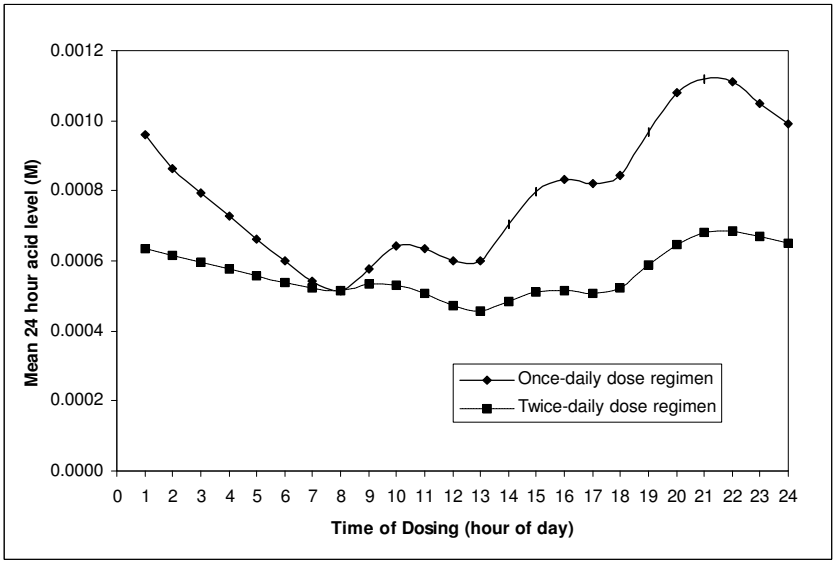



Fig. 8. 24-hour acid levels with single and dual dosing regimens. The plot shows variation in acid levels when dosing time is changed in steps of 1 hour for once-daily (solid line with diamonds) and twice-daily (dotted line with squares) dosing regimens. Maximal 24-hour acid suppression with a single dosing regimen was achieved with an 8 am dose. For dual dosing, the first dose is fixed at 8 am, and the plot indicates change in acid levels with variation in administration of the second dose. The corresponding 24-hour acid level for placebo, i.e., without treatment, is 3.5e–03 M.

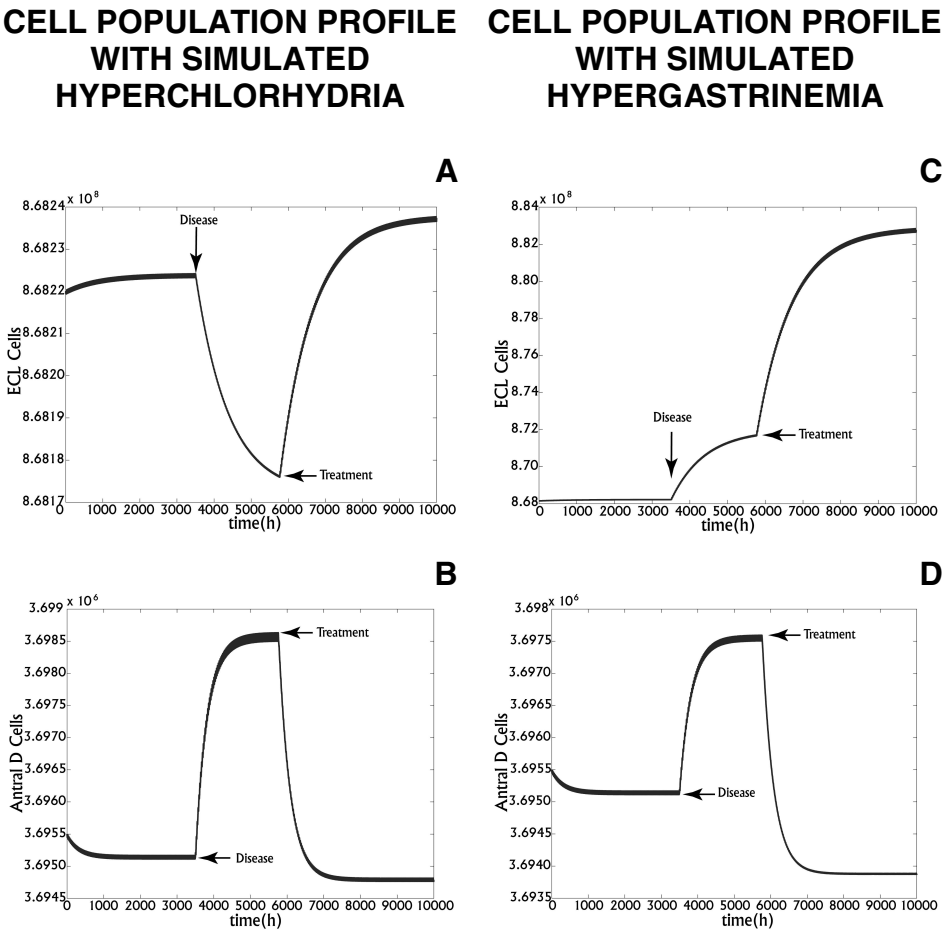



Fig. 9. *Hyperchlorhydria*: Panels A and B indicate ECL and D cell response respectively to elevated acid levels, and subsequent treatment. In both cases cell numbers returned to baseline levels and variation was insignificant. Clearly, PPIs are the treatment of choice for such disorders, since all variables are restored to normal. *Hypergastrinemia*: Panels C and D show ECL and D cell response to elevated gastrin levels, and subsequent treatment. PPI administration led to further increase in ECL numbers, reaching almost 2e+7 above baseline. Variation in D cell numbers in the course of disease and subsequent treatment, while evident and greater than that for other cell populations (G cells, parietal cells), was found to be insignificant.

cases. The dosing pattern was seen to shift in step with the food function, suggesting that optimal dosing time is dependent on daily nutritional routine. Lastly, acid secretion by the model was suppressed in a dose dependent manner [13, 23, 47].

### 7.6. *Disease modeling*

We attempt to study gastric cell populations to determine whether the 4–8 week prescription period recommended by most physicians is adequate for the stom-

ach to return to normal physiological conditions. We simulate hyperchlorhydria by elevating stimulation of acid secretion. After cell populations have stabilized at their new levels, we initiate treatment with OPZ-20 mg once daily for 180 days (Figs. 9A, B). While acid levels return to normal within a day or two, cell populations were seen to stabilize over a period ranging from 700 hours (approx. a month) to 1200 hours (approx. 7 weeks), depending on the cell type under consideration. Specifically, only the ECL population is seen to be significantly affected by treatment. Hence, we also conclude that an 8-week dosing period for minor/single instances of gastric irritation should be sufficient for adequate recovery of the stomach.

Another approach we used was to simulate hypergastrinemia by elevating stimulation for gastrin secretion by approx. 10 times. We observe variations in cell populations after treatment was initiated. Our results indicate that while acid levels decreased, gastrin and histamine levels increased even further, and the ECL population also showed a significant increase (Figs. 9C, D). This indicates that PPIs may not be the best means of treatment of these and other similar disorders.

This method of analysis highlights the importance of how mathematical models can be exploited for clinical diagnostic purposes, particularly when it is not physiologically feasible to distinguish these differences *in vivo* in humans.

### 7.7. *Drug design*

We employ sensitivity analysis (LHS and PRC) to ascertain drug attributes to which the system was most responsive. Our study indicates that while proton pump activity and acid levels both correlated strongly with reaction ($K_r$) and elimination ($K_{el}$) rates of PPIs, $K_{el}$ is the only parameter that significantly affects acid levels ($p < 0.05$). This implies that pervasiveness of the drug in blood has a far greater effect on acid levels than binding affinity of the drug for the proton pump. Such results offer good scope and direction for future drug development, particularly PPIs.

## 8. Discussion/Conclusion

We have previously presented a virtual model for regulation of acid secretion [36]. Using this model, we are able to add proton pump equations to study acid suppression, comparing various acid-inhibitory drugs. We perform simulations under "normal" (or healthy) conditions to compare with clinical trial data derived typically from healthy volunteers. Our findings are in two key areas with respect to dosing schedules and duration of treatment.

Our results indicate that

(1) time period of recovery from PPI treatment does not follow blood concentration of drug, but depends on proton pump cycling rates;

(2) normal acid secretion capacity in parietal cells is restored approximately 1 week after the last dose of PPI;
(3) PPIs may be ordered as OPZ > PPZ > LPZ in terms of efficacy of recommended doses;
(4) when evaluated on a per milligram basis, OPZ is clearly the most potent, while PPZ and LPZ exhibit similar degrees of suppression;
(5) different behaviors occur for OPZ bioavailability when compared to published data, and this is attributed to complex metabolic processes that change over time. Bioavailability of LPZ is reflected in the model, and increased PPZ efficacy over time was ascribed to the persistence of the PPZ-inhibited proton pump in the parietal cell membrane;
(6) a dosing schedule of a once-daily breakfast dose (8 am) or a twice-daily breakfast, lunch dual-dose (8 am, 1 pm) is recommended based on model optimization studies. The twice-daily regimen provided less variation in acid levels with change in dosing time. We also suggested that timing of medication should follow dietary routine rather than discrete time intervals.

Finally, sensitivity analysis yields important information about how gastric acid secretion responds to different aspects of PPI behavior and allows us to propose drug design strategies.

Disease modeling of hypergastrinemia and hyperchlorhydria indicates that only the ECL cell population varies significantly upon treatment. A further increase in ECL populations observed upon treatment of hypergastrinemia points to a possible side effect of PPI administration. The antral D cell population also fluctuates, albeit to a far lesser degree. However, it is easy to see how this variation may be exacerbated under extremely debilitating conditions. Assuming uniform distribution of proliferating cells, an increase in ECL numbers would be localized to the corpus region and to 75% of the gastric glands [36]. Increased ECL numbers would hence be conspicuous histologically, moreso if proliferation is localized. Profound and prolonged elevation of gastrin levels has been demonstrated to cause gastric carcinoids (ECLomas) in rats after life-long omeprazole treatment [18]. While such roles for gastrin are equally contradicted by literature [6, 56, 86], these results are significant to warrant close monitoring to prevent overdosage.

Certain disorders such as duodenal ulcers and GERD involve spatial translocation of acid. Clinical trials that study endoscopic healing with PPI treatment for these patients are comparative in their results and/or provide percentage healing rates for each PPI. These results could possibly be interpreted as the extent to which the site of injury recovers to resemble healthy tissue. Such aspects are not yet feasible for the model, and remain an area of prospective research.

Our work provides a simple means of testing hypotheses about inhibition of gastric acid secretion. We acknowledge that the model is limited by its assumptions, for example in the supposition that pumps are incorporated into the membrane at a zero order rate. We also assume a 100% bioavailability of the drug, whereas

most of these are known to be acid labile and undergo degradation while passing through the stomach. Future work could be used to fine-tune our results, such as the effect of proteins on acid secretion, or by incorporating a spatial description of the localization of PPIs in the internal canaliculus. Modern drug delivery systems could also be accounted for by incorporating sustained release of drug and hence increasing the duration of availability of drug in the blood, ultimately augmenting the area under the blood concentration curve ($AUC_b$). While acid levels are most strongly correlated with dietary routine, a role for circadian rhythm in regulating acid levels is also widely accepted, and provides another workable aspect for prospective research. All these may aid in a better description and understanding of acid secretion and it's therapeutic control.

**Acknowledgements**

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## Appendix

In this section we briefly overview the gastric acid secretion ODE model as presented in [36]. The model assumes that the stomach can be divided into two functionally and histologically distinct regions: the corpus (upper) and antrum (lower). Seven cell populations, CNS and ENS stimuli, bicarbonate, effector hormones, acid and a food function constitute the key elements of the model (Fig. 2). The ODE model is comprised of 18 equations. A list of parameters with definitions is given in Table 2. For further elaboration on the terms and parameter estimation, please refer to Joseph *et al.* [36]

### A.1. *Cell populations dynamics*

Antral stem cells

$$\frac{dA_{sc}(t)}{dt} = (\gamma_{Asc})(A_{sc}(t))(C_{Asc} - A_{sc}(t)) - (p_G(t) + p_{D_A}(t))(\eta_{Asc})(A_{sc}(t))\,. \quad \text{(A.1)}$$

Corpal stem cells

$$\frac{dC_{sc}(t)}{dt} = (\gamma_{Csc})(C_{sc}(t))(C_{Csc} - C_{sc}(t)) + \left(\frac{g_{\max} \cdot [Gtn_C(t)]^2}{[Gtn_C(t)]^2 + \alpha_{\text{csc}}^2}\right) \cdot C_{sc}(t) - (p_E(t) + p_{D_C}(t) + p_P(t))(\eta_{Csc})(C_{sc}(t))\,. \quad \text{(A.2)}$$

Table 2. List of the parameters included in our gastric acid secretion model [36].

| Parameter | Description | Values | References | Unit |
|---|---|---|---|---|
| $K_{NG1}$ | Maximal secretion rate of gastrin due to ENS stimulation per cell | $6.28 \times 10^{-17}$ | [28] [60] [15] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{NG2}$ | Maximal secretion rate of gastrin due to CNS stimulation per cell | $8.75 \times 10^{-17}$ | [53] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{FG}$ | Maximal secretion rate of gastrin due to ENS stimulation per cell | $9.39 \times 10^{-18}$ | LHS | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $\alpha_{NG1}$ | Level of ENS stimulant at which rate of gastrin secretion is 50% | $1.0 \times 10^{-10}$ | [28] | M |
| $\alpha_{NG2}$ | Intensity of the regulator at which rate of gastrin secretion is 50% | $1.0 \times 10^{-10}$ | [28] | M |
| $k_{SG}$ | Dissociation constant of somatostatin from gastrin receptors | $9.0 \times 10^{-11}$ | [73] | M |
| $\kappa_G$ | Clearance rate of gastrin | 11.88 | [26] | $\mathrm{hr}^{-1}$ |
| $\beta_G$ | Transport rate of gastrin from antrum to corpus region | 1.5 | § | $\mathrm{hr}^{-1}$ |
| $K_{AS}$ | Maximal rate of secretion of somatostatin due to stimulation with antrum acid | $8.04 \times 10^{-15}$ | § | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{GS}$ | Maximal rate of secretion of corpal somatostatin due to stimulation with antral gastrin | $2.54 \times 10^{-18}$ | [77] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $\alpha_{AS}$ | Acid concentration at which somatostatin secretion rate is half maximal | 0.05 | [50] | M |
| $\alpha_{GS}$ | Gastrin concentration at which somatostatin secretion rate is half maximal | $5.20 \times 10^{-12}$ | [77] | M |
| $k_{NS}$ | Dissociation constant of GRP from receptors on D cells | $1.0 \times 10^{-9}$ | [76] | M |
| $\kappa_S$ | Clearance rate of somatostatin | 13.86 | § | $\mathrm{hr}^{-1}$ |
| $K_{NS1}$ | Maximal rate of secretion of antral somatostatin due enteric nervous stimulus | $1.14 \times 10^{-15}$ | [76] [28] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{NS2}$ | Maximal rate of secretion of corpal somatostatin due enteric nervous stimulus | $1.5 \times 10^{-17}$ | [76] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $\alpha_{NS1}$ | ENS levels at which antral somatostatin secretion rate is half maximal | $6.28 \times 10^{-7}$ | § | M |
| $\alpha_{NS2}$ | ENS levels at which corpal somatostatin secretion rate is half maximal | $8.98 \times 10^{-11}$ | § | M |
| $k_{SS}$ | Dissociation constant of somatostatin from receptors on D cells | $9.0 \times 10^{-11}$ | [73] | M |

Table 2. (*Continued*)

| Parameter | Description | Values | References | Unit |
|---|---|---|---|---|
| $K_{NH}$ | Maximal rate of histamine secretion due ENS stimulation | $7.59 \times 10^{-16}$ | [64] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{GH}$ | Maximal rate of histamine secretion stimulated by gastrin transported to corpus | $7.77 \times 10^{-16}$ | [4] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $\alpha_{NH}$ | Intensity of regulator at which histamine secretion rate is half maximal | $3.25 \times 10^{-8}$ | [64] | M |
| $\alpha_{GH}$ | Gastrin levels at which histamine secretion rate is half maximal | $3.0 \times 10^{-10}$ | [51] [71] [68] [44] [4] [48] | M |
| $k_{SH}$ | Dissociation constant of somatostatin from receptors on ECL cells | $9.0 \times 10^{-10}$ | [73] | M |
| $\kappa_H$ | Clearance rate of histamine | 11.89 | [8] | $\mathrm{hr}^{-1}$ |
| $K_{NA}$ | Maximal rate of acid secretion due to nervous stimulation mediated through acetylcholine | $2.33 \times 10^{-11}$ | [16] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{GA}$ | Maximal acid secretion rate due to gastrin mediated stimulation | $4.98 \times 10^{-11}$ | [38] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $K_{HA}$ | Maximal acid secretion rate due to histamine mediated stimulation | $7.96 \times 10^{-10}$ | [38] [61] | $\mathrm{M} \cdot \mathrm{hr}^{-1} \cdot \mathrm{cell}^{-1}$ |
| $\alpha_{NA}$ | CNS levels at which acid output rate is half maximal | $5.0 \times 10^{-6}$ | [51, 61] | M |
| $\alpha_{GA}$ | Gastrin levels at which acid output rate is half maximal | $1.8 \times 10^{-10}$ | [70, 72] | M |
| $\alpha_{HA}$ | Histamine levels at which acid output rate is half maximal | $2.0 \times 10^{-8}$ | [51] [61] | M |
| $k_{SA}$ | Dissociation constant of somatostatin from receptors on parietal cells | $9.0 \times 10^{-10}$ | [73] | M |
| $\beta_A$ | Transfer rate of acid from the corpus to antrum | 2.72 | § | $\mathrm{hr}^{-1}$ |
| $\kappa_A$ | Wash out rate of acid | 2.72 | [40] [85] | $\mathrm{hr}^{-1}$ |

(M — molar; hr — hour)

§ denotes mathematically estimated values.

$G$ cells

$$\frac{dG(t)}{dt} = p_G(t) \cdot \eta_{Asc} \cdot A_{sc}(t) + k_{g\max} \cdot \left(1 - \frac{[A_A(t)]^2}{[A_A(t)]^2 + \alpha_{H_A}^2}\right) \cdot G(t) - \lambda_{fd\max} \cdot \left(1 - \frac{(Fd(t))^2}{(Fd(t))^2 + \alpha_{fd}^2}\right) \cdot G(t) - \lambda_{Gc} \cdot G(t)\,. \quad \text{(A.3)}$$

Corpal $D$ cells

$$\frac{dD_C(t)}{dt} = p_{D_C}(t) \cdot \eta_{Asc} \cdot C_{sc}(t) - \lambda_{D_C} \cdot D_C(t)\,. \tag{A.4}$$

Antral $D$ cells

$$\frac{dD_A(t)}{dt} = p_{D_A}(t) \cdot \eta_{Asc} \cdot A_{sc}(t) + \left(\frac{k_{d\max}[A_A(t)]^2}{[A_A(t)]^2 + \alpha_{H_A}^2}\right) \cdot D_A(t) - \lambda_{D_A} \cdot D_A(t) + \lambda_{fd\max} \cdot \left(1 - \frac{(Fd(t))^2}{(Fd(t))^2 + \alpha_{fd}^2}\right) \cdot G(t)\,. \tag{A.5}$$

*ECL* cells

$$\frac{dE(t)}{dt} = p_E(t) \cdot \eta_{Csc} \cdot C_{sc}(t) - \lambda_E \cdot E(t) + \left(\frac{k_{e\max} \cdot [Gtn_c(t)]^2}{[Gtn_c(t)]^2 + \alpha_E^2}\right) \cdot E(t)\,. \tag{A.6}$$

Parietal cells

$$\frac{dP(t)}{dt} = p_P(t) \cdot \eta_{Csc} \cdot C_{sc}(t) - \lambda_P \cdot P(t)\,. \tag{A.7}$$

### A.2. *Hormonal regulation of acid secretion*

Antral gastrin

$$\begin{aligned}\frac{d[Gtn_A(t)]}{dt} = {} & G(t)\left(\frac{K_{NG_1}[N_E(t)]}{([N_E(t)] + \alpha_{NG1})\left(1 + \frac{[S_A(t)]}{k_{SG}}\right)\left(1 + \frac{[A_c(t)]^2}{[A_c(t)]^2 + k_{AG}^2}\right)}\right) \\ & + G(t)\left(\frac{K_{NG_2}[N_C(t)]}{([N_C(t)] + \alpha_{NG_2})\left(1 + \frac{[S_A(t)]}{k_{SG}}\right)\left(1 + \frac{[A_c(t)]^2}{[A_c(t)]^2 + k_{AG}^2}\right)}\right) \\ & + G(t)\left(\frac{K_{FG}[Fd(t)]}{([Fd(t)] + \alpha_{FD})\left(1 + \frac{[S_A(t)]}{k_{SG}}\right)\left(1 + \frac{[A_c(t)]^2}{[A_c(t)]^2 + k_{AG}^2}\right)}\right) \\ & - (k_G + \beta_G)[Gtn_A(t)]\,.\end{aligned} \tag{A.8}$$

Corpal gastrin

$$\frac{d[Gtn_C(t)]}{dt} = \beta_G[Gtn_A(t)] - \kappa_G[Gtn_C(t)]\,. \tag{A.9}$$

Antral somatostatin

$$\frac{d[S_A(t)]}{dt} = D_A(t)\left(\frac{K_{AS}[A_A(t)]}{([A_A(t)]+\alpha_{AS})\left(1+\frac{[S_A(t)]}{k_{SS}}\right)\left(1+\frac{[N_C(t)]}{k_{NS}}\right)}\right) + D_A(t)\left(\frac{K_{NS1}[N_E(t)]}{([N_E(t)]+\alpha_{NS1})\left(1+\frac{[S_A(t)]}{k_{SS}}\right)\left(1+\frac{[N_C(t)]}{k_{NS}}\right)}\right) - \kappa_S[S_A(t)]\,. \tag{A.10}$$

Corpal somatostatin

$$\frac{d[S_C(t)]}{dt} = D_C(t)\left(\left(\frac{K_{NS2}[N_E(t)]}{([N_E(t)]+\alpha_{NS2})\left(1+\frac{[S_C(t)]}{k_{SS}}\right)\left(1+\frac{[N_C(t)]}{k_{NS}}\right)}\right)\right) + D_C(t)\left(\frac{K_{GS}[Gtn_C(t)]}{([Gtn_C(t)]+\alpha_{GS})\left(1+\frac{[S_C(t)]}{k_{SS}}\right)\left(1+\frac{[N_C(t)]}{k_{NS}}\right)}\right) - \kappa_S[S_C(t)]\,. \tag{A.11}$$

Histamine

$$\frac{d[H_C(t)]}{dt} = E(t)\left(\left(\frac{K_{NH}[N_E(t)]}{([N_E(t)]+\alpha_{NH})\left(1+\frac{[S_C(t)]}{k_{SH}}\right)}\right)\right) + E(t)\left(\frac{K_{GH}[Gtn_C(t)]}{([Gtn_C(t)]+\alpha_{GH})\left(1+\frac{[S_C(t)]}{k_SH}\right)}\right) - \kappa_H[H_C(t)]\,. \tag{A.12}$$

### A.3. *Acid and bicarbonate dynamics*

Corpal acid

$$\frac{d[A_C(t)]}{dt} = P\left(\left(\frac{K_{HA}[H_C(t)]}{([H_C(t)]+\alpha_{HA})\left(1+\frac{[S_C(t)]}{k_{SA}}\right)}\right)\right.$$

$$+\left(\frac{[H_C(t)]}{[H_C(t)]+\alpha_H}\right)\left(\frac{K_{GA}[Gtn_C(t)]}{([Gtn_C(t)]+\alpha_{GA})\left(1+\frac{[S_C(t)]}{k_{SA}}\right)}\right)$$
$$+P\left(\frac{K_{NA}[N_C(t)]}{([N_C(t)]+\alpha_{NA})\left(1+\frac{[S_C(t)]}{k_{SA}}\right)}\right)-hb[A_c][B_c]-\beta_A[A_C(t)]\,. \tag{A.13}$$

Antral acid

$$\frac{d[A_A(t)]}{dt}=\beta_A[A_C(t)]-\kappa_A[A_A(t)]\,. \tag{A.14}$$

Corpus bicarbonate

$$\frac{d[B_c(t)]}{dt}=\frac{k_{bc\,\max}[N_c(t)]}{[N_c(t)]+\alpha_{NB}}-hb[A_c(t)][B_c(t)]-\beta_b[B_c(t)]\,. \tag{A.15}$$

Antral bicarbonate

$$\frac{d[B_A(t)]}{dt}=\frac{k_{bA\,\max}[N_c(t)]}{[N_c(t)]+\alpha_{NB}}-hb[A_A(t)][B_A(t)]-\kappa_b[B_A(t)]\,. \tag{A.16}$$

### A.4. *Central and enteric neural stimuli*

Central Neural Stimuli

$$\frac{d[N_c(t)]}{dt}=\left(\frac{N_{\max 1}Fd(t)}{(Fd(t)+k1_{fd})\left(1+\frac{[A_c(t)]^2}{[A_c(t)]^2+k_{AN1}^2}\right)}\right)-\kappa_{N_C}[N_C(t)]+Bas_1\,. \tag{A.17}$$

Enteric Neural Stimuli

$$\frac{d[N_E(t)]}{dt}=\left(\frac{N_{\max 2}Fd(t)}{(Fd(t)+k2_{fd})\left(1+\frac{[A_c(t)]^2}{[A_c(t)]^2+k_{AN_2^2}}\right)}\right)-\kappa_{N_E}[N_E(t)]+Bas_2\,. \tag{A.18}$$

## References


[1] Abelo A., Eriksson U. G., Karlsson M. O., Larsson H. and Gabrielsson J., A turnover model of irreversible inhibition of gastric acid secretion by omeprazole in the dog, *J. Pharmacol. Exp. Ther.* **295** (2000) pp. 662–669.

[2] Abelo A., Gabrielsson J., Holstein B., Eriksson U. G., Holmberg J. and Karlsson M. O., Pharmacodynamic modeling of reversible gastric acid pump inhibition in dog and man, *Eur. J. Pharm. Sci.* **14** (2001) pp. 339–346.

[3] Allen J. M., Adrian T. E., Webster J., Howe A. and Bloom S. R., Effect of single dose of omeprazole on the gastrointestinal peptide response to food, *Hepatogastroenterology* **31** (1984) pp. 44–46.

[4] Andersson N., Rhedin M., Peteri-Brunback B., Andersson K. and Cabero J. L., Gastrin effects on isolated rat enterochromaffin-like cells following long-term hypergastrinaemia *in vivo*, *Biochim. Biophys. Acta* **1451** (1999) pp. 297–304.

[5] Andersson T., Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole, *Clin. Pharmacokinet.* **31** (1996) pp. 9–28.

[6] Arnold R., Frank M., Simon B., Eissele R. and Koop H., Adaptation and renewal of the endocrine stomach, *Scand. J. Gastroenterol. Suppl.* **193** (1992) pp. 20–27.

[7] Balant L. P. and Gex-Fabry M., Physiological pharmacokinetic modeling, *Xenobiotica* **20** (1990) pp. 1241–1257.

[8] Belic A., Grabnar I., Karba R., Mrhar A., Irman-Florjanc T. and Primozic S., Interdependence of histamine and methylhistamine kinetics: Modeling and simulation approach, *Comput. Biol. Med.* **29** (1999) pp. 361–375.

[9] Bell N., Karol M. D., Sachs G., Greski-Rose P., Jennings D. E. and Hunt R. H., Duration of effect of lansoprazole on gastric pH and acid secretion in normal male volunteers, *Aliment. Pharmacol. Ther.* **15** (2001) pp. 105–113.

[10] Bell N. J., Burget D., Howden C. W., Wilkinson J. and Hunt R. H., Appropriate acid suppression for the management of gastro-oesophageal reflux disease, *Digestion* **51** (1992) pp. 59–67.

[11] Black J. W., Duncan W. A., Durant C. J., Ganellin C. R. and Parsons E. M., Definition and antagonism of histamine $H_2$-receptors, *Nature* **236** (1972) pp. 385–390.

[12] Blower S. M. and Dowlatabadi H., Sensitivity and uncertainty analysis of complex models of disease transmission: An HIV model, as an example, *Int. Stat. Rev.* **62** (1994) pp. 229–243.

[13] Blum R. A., Hunt R. H., Kidd S. L., Shi H., Jennings D. E. and Greski-Rose P. A., Dose-response relationship of lansoprazole to gastric acid antisecretory effects, *Aliment. Pharmacol. Ther.* **12** (1998) pp. 321–327.

[14] Burget D. W., Chiverton S. G. and Hunt R. H., Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression, *Gastroenterology* **99** (1990) pp. 345–351.

[15] Campos R. V., Buchan A. M., Meloche R. M., Pederson R. A., Kwok Y. N. and Coy D. H., Gastrin secretion from human antral G cells in culture, *Gastroenterology* **99** (1990) pp. 36–44.

[16] Cantor P., Petersen M. B., Christiansen J. and Rehfeld J. F., Does sulfation of gastrin influence gastric acid secretion in man? *Scand. J. Gastroenterol.* **25** (1990) pp. 739–745.

[17] Chiverton S. G., Howden C. W., Burget D. W. and Hunt R. H., Omeprazole (20 mg) daily given in the morning or evening: A comparison of effects on gastric acidity, and

plasma gastrin and omeprazole concentration, *Aliment. Pharmacol. Ther.* **6** (1992) pp. 103–111.

[18] Creutzfeldt W. and Lamberts R., Is hypergastrinaemia dangerous to man? *Scand. J. Gastroenterol. Suppl.* **180** (1991) pp. 179–191.

[19] de Beus A. M., Fabry T. L. and Lacker H. M., A gastric acid secretion model, *Biophys. J.* **65** (1993) pp. 362–378.

[20] Engel E., Peskoff A., Kauffman G. L., Jr. and Grossman M. I., Analysis of hydrogen ion concentration in the gastric gel mucus layer, *Am. J. Physiol.* **247** (1984) pp. G321–338.

[21] Feldman M., Comparison of the effects of over-the-counter famotidine and calcium carbonate antacid on postprandial gastric acid. A randomized controlled trial, *JAMA* **275** (1996) pp. 1428–1431.

[22] Ferron G. M., McKeand W. and Mayer P. R., Pharmacodynamic modeling of pantoprazole's irreversible effect on gastric acid secretion in humans and rats, *J. Clin. Pharmacol.* **41** (2001) pp. 149–156.

[23] Fitton A. and Wiseman L., Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders, *Drugs* **51** (1996) pp. 460–482.

[24] Fullarton G. M., McLauchlan G., Macdonald A., Crean G. P. and McColl K. E., Rebound nocturnal hypersecretion after four weeks treatment with an $H_2$ receptor antagonist, *Gut* **30** (1989) pp. 449–454.

[25] Gerloff J., Mignot A., Barth H. and Heintze K., Pharmacokinetics and absolute bioavailability of lansoprazole, *Eur. J. Clin. Pharmacol.* **50** (1996) pp. 293–297.

[26] Hansen C. P., Stadil F., Yucun L. and Rehfeld J. F., Pharmacokinetics and organ metabolism of carboxyamidated and glycine-extended gastrins in pigs, *Am. J. Physiol.* **271** (1996) pp. G156–163.

[27] Hirschowitz B. I., Keeling D., Lewin M., Okabe S., Parsons M., Sewing K., Wallmark B. and Sachs G., Pharmacological aspects of acid secretion, *Dig. Dis. Sci.* **40** (1995) pp. 3S–23S.

[28] Holst J. J., Knuhtsen S., Orskov C., Skak-Nielsen T., Poulsen S. S. and Nielsen O. V., GRP-producing nerves control antral somatostatin and gastrin secretion in pigs, *Am. J. Physiol.* **253** (1987) pp. G767–774.

[29] Howden C. W., Forrest J. A., Meredith P. A. and Reid J. L., Antisecretory effect and oral pharmacokinetics following low dose omeprazole in man, *Br. J. Clin. Pharmacol.* **20** (1985) pp. 137–139.

[30] Huang J. Q. and Hunt R. H., Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician, *Best Pract. Res. Clin. Gastroenterol.* **15** (2001) pp. 355–370.

[31] Huber R., Hartmann M., Bliesath H., Luhmann R., Steinijans V. W. and Zech K., Pharmacokinetics of pantoprazole in man, *Int. J. Clin. Pharmacol. Ther.* **34** (1996) pp. S7–16.

[32] Huber R., Kohl B., Sachs G., Senn-Bilfinger J., Simon W. A. and Sturm E., Review article: The continuing development of proton pump inhibitors with particular reference to pantoprazole, *Aliment. Pharmacol. Ther.* **9** (1995) pp. 363–378.

[33] Iman R. L., Helton J. C. and Campbell J. E., An approach to sensistivity analysis of computer models: Part 1 — Introduction, input variable selection and preliminary variable assessment., *J. Qual. Technol.* **13** (1981) pp. 174–183.

[34] Iman R. L., Helton J. C. and Campbell J. E., An approach to sensistivity analysis of computer models. Part II: Ranking of input variables, response surface validation, distribution effect and technique synopsis., *J. Qual. Technol.* **13** (1981) pp. 232–240.

[35] Jaspersen D., Diehl K. L., Schoeppner H., Geyer P. and Martens E., A comparison

of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis, *Aliment. Pharmacol. Ther.* **12** (1998) pp. 49–52.

[36] Joseph I. M., Zavros Y., Merchant J. L. and Kirschner D., A model for integrative study of human gastric acid secretion, *J. Appl. Physiol.* **94** (2003) pp. 1602–1618.

[37] Katashima M., Yamamoto K., Tokuma Y., Hata T., Sawada Y. and Iga T., Comparative pharmacokinetic/pharmacodynamic analysis of proton pump inhibitors omeprazole, lansoprazole and pantoprazole, in humans, *Eur. J. Drug Metab. Pharmacokinet.* **23** (1998) pp. 19–26.

[38] Kleveland P. M., Waldum H. L. and Larsson H., Gastric acid secretion in the totally isolated, vascularly perfused rat stomach. A selective muscarinic-1 agent does, whereas gastrin does not, augment maximal histamine-stimulated acid secretion, *Scand. J. Gastroenterol.* **22** (1987) pp. 705–713.

[39] Konturek S. J., Konturek P. C., Bielanski W., Lorens K., Sito E., Konturek J. W., Kwiecien S., Bobrzynski A., Pawlik T., Karcz D., Areny H. and Stachura T., Case presentation of gastrinoma combined with gastric carcinoid with the longest survival record — Zollinger-Ellison syndrome: Pathophysiology, diagnosis and therapy, *Med. Sci. Monit.* **8** (2002) pp. CS43–59.

[40] Kreiss C., Schwizer W., Borovicka J., Jansen J. B., Bouloux C., Pignol R., Bischof Delaloye A. and Fried M., Effect of lintitript, a new CCK-A receptor antagonist, on gastric emptying of a solid-liquid meal in humans, *Regul. Pept.* **74** (1998) pp. 143–149.

[41] Kromer W., Horbach S. and Luhmann R., Relative efficacies of gastric proton pump inhibitors: Their clinical and pharmacological basis, *Pharmacology* **59** (1999) pp. 57–77.

[42] Labenz J., Peitz U., Leusing C., Tillenburg B., Blum A. L. and Borsch G., Efficacy of primed infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: A prospective randomised controlled study, *Gut* **40** (1997) pp. 36–41.

[43] Landes B. D., Petite J. P. and Flouvat B., Clinical pharmacokinetics of lansoprazole, *Clin. Pharmacokinet.* **28** (1995) pp. 458–470.

[44] Lawton G. P., Tang L. H., Miu K., Gilligan C. J., Absood A. and Modlin I. M., Adrenergic and cromolyn sodium modulation of ECL cell histamine secretion, *J. Surg. Res.* **58** (1995) pp. 96–104.

[45] Licko V. and Ekblad E. B., Dynamics of a metabolic system: What single-action agents reveal about acid secretion, *Am. J. Physiol.* **262** (1992) pp. G581–592.

[46] Licko V. and Ekblad E. B., What dual-action agents reveal about acid secretion: A combined experimental and modeling analysis, *Biochim. Biophys. Acta.* **1137** (1992) pp. 19–28.

[47] Lind T., Cederberg C., Forssell H., Olausson M. and Olbe L., Relationship between reduction of gastric acid secretion and plasma gastrin concentration during omeprazole treatment, *Scand. J. Gastroenterol.* **23** (1988) pp. 1259–1266.

[48] Lindstrom E. and Hakanson R., Neurohormonal regulation of secretion from isolated rat stomach ECL cells: A critical reappraisal, *Regul. Pept.* **97** (2001) pp. 169–180.

[49] Mahmood I., Allometric issues in drug development, *J. Pharm. Sci.* **88** (1999) pp. 1101–1106.

[50] Makhlouf G. M. and Schubert M. L., Gastric somatostatin: A paracrine regulator of acid secretion, *Metabolism* **39** (1990) pp. 138–142.

[51] Mardh S., Norberg L., Ljungstrom M., Wollert S., Nyren O. and Gustavsson S., A method for *in vitro* studies on acid formation in human parietal cells. Stimulation by histamine, pentagastrin and carbachol, *Acta. Physiol. Scand.* **123** (1985) pp. 349–354.

[52] Marino S., Ganguli S., Joseph I. M. P. and Kirschner D., Comparison of ordinary and delay differential equation models for human gastric acid secretion, *Bulletin of Mathematical Biology* (in press) (2003).

[53] Matsuno M., Matsui T., Iwasaki A. and Arakawa Y., Role of acetylcholine and gastrin-releasing peptide (GRP) in gastrin secretion, *J. Gastroenterol.* **32** (1997) pp. 579–586.

[54] McColl K. E. and Kennerley P., Proton pump inhibitors — differences emerge in hepatic metabolism, *Dig. Liver. Dis.* **34** (2002) pp. 461–467.

[55] Metz D. C., Pratha V., Martin P., Paul J., Maton P. N., Lew E. and Pisegna J. R., Oral and intravenous dosage forms of pantoprazole are equivalent in their ability to suppress gastric acid secretion in patients with gastroesophageal reflux disease, *Am. J. Gastroenterol.* **95** (2000) pp. 626–633.

[56] Modlin I. M., Kumar R., Nangia A., Soroka C. J., Pasikhov D. and Goldenring J. R., Gastrin-dependent inhibitory effects of octreotide on the genesis of gastric ECLomas, *Surgery* **112** (1992) pp. 1048-1056; discussion 1056–1048.

[57] Mussig S., Witzel L., Luhmann R. and Schneider A., Morning and evening administration of pantoprazole: A study to compare the effect on 24-hour intragastric pH, *Eur. J. Gastroenterol. Hepatol.* **9** (1997) pp. 599–602.

[58] Nagaya H., Satoh H. and Maki Y., Possible mechanism for the inhibition of acid formation by the proton pump inhibitor AG-1749 in isolated canine parietal cells, *J. Pharmacol. Exp. Ther.* **252** (1990) pp. 1289–1295.

[59] Netzer P., Gaia C., Sandoz M., Huluk T., Gut A., Halter F., Husler J. and Inauen W., Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours, *Am. J. Gastroenterol.* **94** (1999) pp. 351–357.

[60] Nishi S., Seino Y., Takemura J., Ishida H., Seno M., Chiba T., Yanaihara C., Yanaihara N. and Imura H., Vagal regulation of GRP, gastric somatostatin, and gastrin secretion *in vitro*, *Am. J. Physiol.* **248** (1985) pp. E425–431.

[61] Norberg L., Ljungstrom M., Vega F. V. and Mardh S., Stimulation of acid formation by histamine, carbachol and pentagastrin in isolated pig parietal cells, *Acta. Physiol. Scand.* **126** (1986) pp. 385–390.

[62] Nwokolo C. U., Smith J. T., Sawyerr A. M. and Pounder R. E., Rebound intragastric hyperacidity after abrupt withdrawal of histamine $H_2$ receptor blockade, *Gut* **32** (1991) pp. 1455–1460.

[63] Pisegna J. R., Martin P., McKeand W., Ohning G., Walsh J. H. and Paul J., Inhibition of pentagastrin-induced gastric acid secretion by intravenous pantoprazole: A dose-response study, *Am. J. Gastroenterol.* **94** (1999) pp. 2874–2880.

[64] Pisegna J. R., Ohning G. V., Athmann C., Zeng N., Walsh J. H. and Sachs G., Role of PACAP1 receptor in regulation of ECL cells and gastric acid secretion by pituitary adenylate cyclase activating peptide, *Ann. N. Y. Acad. Sci.* **921** (2000) pp. 233–241.

[65] Popielski L., $\beta$-imidazolylethylamin und die orgunextrakte. Erst Teil: $\beta$-imidazolylethylamin also machtiger Erreger der Masendrusen, *Pfluger. Arch. ges. Physiol.* **178** (1920) pp. 214–238.

[66] Prewett E. J., Hudson M., Nwokolo C. U., Sawyerr A. M. and Pounder R. E., Nocturnal intragastric acidity during and after a period of dosing with either ranitidine or omeprazole, *Gastroenterology* **100** (1991) pp. 873–877.

[67] Prichard P. J., Yeomans N. D., Mihaly G. W., Jones D. B., Buckle P. J., Smallwood R. A. and Louis W. J., Omeprazole: A study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage, *Gastroenterology* **88** (1985) pp. 64–69.

[68] Prinz C., Scott D. R., Hurwitz D., Helander H. F. and Sachs G., Gastrin effects on isolated rat enterochromaffin-like cells in primary culture, *Am. J. Physiol.* **267** (1994) pp. G663–675.

[69] Puchalski T. A., Krzyzanski W., Blum R. A. and Jusko W. J., Pharmacodynamic modeling of lansoprazole using an indirect irreversible response model, *J. Clin. Pharmacol.* **41** (2001) pp. 251–258.

[70] Roche S., Gusdinar T., Bali J. P. and Magous R., Biphasic kinetics of inositol 1,4,5-trisphosphate accumulation in gastrin-stimulated parietal cells. Effects of pertussis toxin and extracellular calcium, *F.E.B.S. Lett.* **282** (1991) pp. 147–151.

[71] Roche S., Gusdinar T., Bali J. P. and Magous R., "Gastrin" and "CCK" receptors on histamine- and somatostatin-containing cells from rabbit fundic mucosa-II. Characterization by means of selective antagonists (L-364,718 and L-365,260), *Biochem. Pharmacol.* **42** (1991) pp. 771–776.

[72] Roche S., Gusdinar T., Bali J. P. and Magous R., Relationship between inositol 1,4,5-trisphosphate mass level and [14C] aminopyrine uptake in gastrin-stimulated parietal cells, *Mol. Cell Endocrinol.* **77** (1991) pp. 109–113.

[73] Rocheville M., Lange D. C., Kumar U., Sasi R., Patel R. C. and Patel Y. C., Subtypes of the somatostatin receptor assemble as functional homo- and heterodimers, *J. Biol. Chem.* **275** (2000) pp. 7862–7869.

[74] Sachs G., Proton pump inhibitors and acid-related diseases, *Pharmacotherapy* **17** (1997) pp. 22–37.

[75] Sachs G., Shin J. M., Vagin O., Munson K., Weeks D., Scott D. R. and Voland P., Current trends in the treatment of upper gastrointestinal disease, *Best Pract. Res. Clin. Gastroenterol.* **16** (2002) pp. 835–849.

[76] Schaffer K., Herrmuth H., Mueller J., Coy D. H., Wong H. C., Walsh J. H., Classen M., Schusdziarra V. and Schepp W., Bombesin-like peptides stimulate somatostatin release from rat fundic D cells in primary culture, *Am. J. Physiol.* **273** (1997) pp. G686–695.

[77] Schubert M. L., Edwards N. F., Arimura A. and Makhlouf G. M., Paracrine regulation of gastric acid secretion by fundic somatostatin, *Am. J. Physiol.* **252** (1987) pp. G485–490.

[78] Smoot D. T., Go M. F. and Cryer B., Peptic ulcer disease, *Prim. Care* **28** (2001) pp. 487–503, v.

[79] Stedman C. A. and Barclay M. L., Review article: Comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors, *Aliment. Pharmacol. Ther.* **14** (2000) pp. 963–978.

[80] Termanini B., Gibril F., Stewart C. A., Weber H. C. and Jensen R. T., A prospective study of the effectiveness of low dose omeprazole as initial therapy in Zollinger–Ellison syndrome, *Aliment. Pharmacol. Ther.* **10** (1996) pp. 61–71.

[81] Thomson A. B., Are the orally administered proton pump inhibitors equivalent? A comparison of lansoprazole, omeprazole, pantoprazole, and rabeprazole, *Curr. Gastroenterol. Rep.* **2** (2000) pp. 482–493.

[82] Timmer W., Ripke H., Kleist P., Ehrlich A., Wieckhorst G., Lucker P. W. and Fuder H., Effect of four lansoprazole dose levels and one dosage regimen of omeprazole on 24-hour intragastric pH in healthy subjects, *Methods Find. Exp. Clin. Pharmacol.* **17** (1995) pp. 489–495.

[83] Tran A., Rey E., Pons G., Pariente-Khayat A., D'Athis P., Sallerin V. and Dupont C., Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children, *Clin. Pharmacol. Ther.* **71** (2002) pp. 359–367.

[84] Turnberg L. A., Gastric mucosal defence mechanisms, *Scand. J. Gastroenterol. Suppl.* **110** (1985) pp. 37–40.

[85] Van Duijn B., Ypey D. L., de Goede J., Verveen A. A. and Hekkens W., A model study of the regulation of gastric acid secretion, *Am. J. Physiol.* **257** (1989) pp. G157–168.

[86] Waldum H. L., Haugen O. A., Isaksen C., Mecsei R. and Sandvik A. K., Enterochromaffin-like tumor cells in the diffuse but not the intestinal type of gastric carcinomas, *Scand. J. Gastroenterol. Suppl.* **180** (1991) pp. 165–169.

[87] Walt R. P., Gomes M. D., Wood E. C., Logan L. H. and Pounder R. E., Effect of daily oral omeprazole on 24 hour intragastric acidity, *Br. Med. J.* (*Clin. Res. Ed.*) **287** (1983) pp. 12–14.