

Abstract

YOKLEY, KAREN ALYSE Physiologically Based Model Development and Parameter Estimation: Benzene Dosimetry in Humans and Respiratory Irritation Response in Rodents. (Under the direction of Professor H.T. Tran).

One can form mathematical equations based on a combination of chemistry, physics, and biological information to represent a physiological system. Once a model is formulated based on the physiological system, we must make sure that the inputs or parameters to the model also faithfully represent the system. In this study, we adapt and combine existing mathematical models to describe different physiological systems.

Benzene is myelotoxic and causes leukemia in humans when they are exposed to high doses by inhalation (> 1 ppm) for extended periods; however, leukemia risks in humans at lower exposures are uncertain. Benzene occurs widely in the work environment and in outdoor air, although mostly at concentrations below 1 ppm. Hence, we recognize the importance of assessing the risk to humans when they are exposed to benzene at low concentrations. In Chapter 2, we describe a physiologically based pharmacokinetic (PBPK) model for the uptake and elimination of benzene in humans to relate the concentration of inhaled benzene to the tissue doses of benzene and its key metabolites, benzene oxide, phenol, and hydroquinone. To account for variability among humans, the mathematical model must be integrated into a statistical framework that acknowledges sources of variation in the data due to inherent intra- and inter-individual variation, measurement error, and other data collection issues. The main contribution of Chapter 2 is the estimation of population distributions of key PBPK model parameters. In particular, a Markov Chain Monte Carlo (MCMC) technique is employed to fit the mathematical model to two data sets, thereby updating the estimated parameter distributions. We first considered only variability in metabolic parameters, as observed in previous *in vitro* studies, but found that it was not

sufficient to explain observed variability in benzene pharmacokinetics. Variability in physiological parameters, such as organ weights, must also be included to faithfully predict the observed human population variability.

Inhaled gases can also cause respiratory depression by irritating (stimulating) nerves in the nasal cavity. In order to better understand how the nervous system responds to such chemicals, we have created a model to describe how the presence of irritants affects respiration in the rat. By combining and adapting two previous models, one that evaluates the relationship between inhaled acrylic acid vapor concentration and the tissue concentration in various regions of the nasal cavity and another model which describes the baroreflex-feedback mechanism regulating human blood pressure, we created a system of equations that models the sensory irritant response in rats. The adapted model in Chapter 3 focuses on the dosimetry of these reactive gases in the respiratory tract, with particular focus on the physiology of the upper respiratory tract, and on the neurological control of respiration rate due to signaling from the irritant-responsive nerves in the nasal cavity. Further, the model is evaluated and improved through optimization of particular parameters to describe formaldehyde-induced respiratory response data and through sensitivity analysis. The model in Chapter 3 describes this formaldehyde data well and is expected to translate well to other irritants.

**Physiologically Based Model Development and Parameter Estimation:
Benzene Dosimetry in Humans and Respiratory Irritation Response in
Rodents**

by

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This work is dedicated to all of my family, including those who are related by blood as well as those who are not but claim me anyway.

Biography

The author was born in Columbia, Tennessee on the afternoon of November 12, 1976 to parents Thomas and Susan Yokley. She continued to live with her parents and one older brother, Todd, in Columbia until after her graduation from Columbia Central High School as valedictorian of the class of 1995. The author then spent the next four years at the University of Tennessee, Knoxville where she graduated summa cum laude with a Bachelor's Degree in Mathematics with a minor in Biology in May 1999. Continuing in her studies in math, the author began graduate work in applied mathematics in the fall of 1999 and completed a Master's of Science Degree in Applied Mathematics in the spring of 2002. This work is toward the completion of her Doctor of Philosophy in Applied Mathematics with an emphasis in Computational Mathematics.

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Chapter 1

Introduction

Modeling of physiological systems can incorporate many different methods and perspectives. Mathematical equations based on a combination of chemistry, physics, and biological information, inevitably using simplifying assumptions, can be derived to represent a physiological system. These representations may elucidate more about the physiological system than experimentation alone and allow one to extrapolate from quantitative experimental data to predict results for situations where we have no data. Although various mathematical approaches exist for modeling biological systems, we specifically will consider models described by differential equations.

One way to model chemical distribution throughout the body is through compartmentalization. If we look at an animal's body as composed of compartments (of tissues, organs, groups of organs, etc.), we can simplify how we consider the amount of chemical in the body as a whole. Hence, we can formulate equations only describing where a chemical is in a portion of the nasal cavity or in the blood flow to the kidneys. This way, we can better describe the local concentration of a chemical and further understand how that chemical is causing its effects in different parts of the body. For examples of models incorporating chemical movement through compartments, see [8, 20, 22, 29, 28, 36, 39] although [20] does not contain explicit equations. In order to model the flow of chemicals through the body, we must also consider mode of transport.

Chemicals are transported primarily by diffusion across concentration gradients and by simple fluid flow. First of all, diffusion is the process by which matter is transported

from one area to another as a result of random molecular motion [64]. As stated in [34], diffusion can be described using Fick's law and a diffusion coefficient, or it can be explained in terms of a mass transfer coefficient. Basically, both methods contain the same idea of diffusion, but sometimes it is easier to convey the derivation of a model using one set of terminology than with the other. Let us first consider Fick's Law of Diffusion and then extend the law to the idea of a mass transfer coefficient. Fick's Law states that the rate of diffusion of a gas across a fluid membrane is (1) proportional to the difference in partial pressure, (2) proportional to the area of the membrane, and (3) inversely proportional to the thickness of the membrane [1]. Mathematically, Fick's Law for the one-dimensional case is described

$$J = -D \frac{\Delta C(t)}{\Delta x},$$

where J is the particle flux (mass flow rate per unit area across which diffusion is occurring), C is the concentration of the solute, D is the diffusion coefficient, x is the distance into the substrate (i.e., the membrane), and t is the diffusion time [2, 3]. If we consider the movement in terms of across a cross-sectional area (i.e., surface area of the membrane), we can consider

$$\frac{dM}{dt} = -DA \frac{\Delta C}{\Delta x},$$

where M is the mass of substrate in the compartment from which mass is flowing and A is the interfacial area across which the substrate flows [4]. Knowing the concentration gradient, i.e., using the replacement $\Delta C = C_1 - C_2$, we can rewrite the above equation

$$\frac{dM_1}{dt} = -\frac{DA}{\Delta x}(C_1 - C_2),$$

where C_1 and C_2 describe concentrations on either side of the interface. Note that flow is coming from the area of C_1 and moving to increase C_2 . Further, since for biological membranes Δx is essentially constant, we can rewrite our constants ($DA/\Delta x$) as a single coefficient K [4]:

$$\frac{dM_1}{dt} = -K(C_1 - C_2).$$

K can be thought of as a mass transfer coefficient. As described in [34], we expect that the amount of chemical transferred is proportional to concentration difference across the interface and the area of that interface, i.e.,

$$N_1 = k(c_{1i} - c_1), \quad (1.1)$$

where N_1 is the flux at the interface into the compartment, c_{1i} is the concentration at the interface, and c_1 is the concentration in the bulk solution. In Chapter 3, we will formulate a model for sensory irritant response beginning with a transport model from [39]. We will not go into an entire derivation of this model, but we will demonstrate from a basic example how either Fick's Law or the idea of a mass transfer coefficient can be used in the model formulation. The model description in [39] begins with mass transport, modeled

$$N = K_g(C_g - C_l/P), \quad (1.2)$$

where

$$\begin{aligned} N &= \text{flux from gas to liquid phase} \quad (\mu\text{mol}/[\text{cm}^2 \times h]) \\ K_g &= \text{overall mass transfer coefficient} \quad (\text{cm}/h) \\ C_g &= \text{concentration in gas phase} \quad (\mu\text{mol}/\text{cm}^3) \\ P &= \text{the liquid:air partition coefficient (dimensionless)} \\ C_l &= \text{concentration in liquid phase} \quad (\mu\text{mol}/\text{cm}^3). \end{aligned}$$

Note that the formulation of (1.2) involves a partition coefficient as do many equations in the model used in Chapter 2 and listed in Appendix A. We should recall what a partition coefficient actually is through the use of Henry's Law, i.e, that the volume of a gas that will dissolve in a liquid at a given temperature is proportional to the partial pressure of the gas [5]. In particular,

$$p = KC_l,$$

where p represents partial pressure of the gas and K represents Henry's law constant for that particular substance. (Partial pressure is simply a measure of the gas-phase concentration in different units.) Note that the K above is not the same K in the definitions of Fick's Law mentioned earlier. Taking a section from [70],

Henry's law is applicable to layers of biological fluids and tissues. In this situation, the ratio at equilibrium of the concentrations in the two phases or layers is the ratio of the Henry's law constant of the air/solution system of one phase to the Henry's law constant of the air/solution system of the other phase. This ratio is called the "distribution coefficient" or "partition coefficient."

Returning to the flux equation, note that (1.2) is formulated as is (1.1) with mass transport coefficient $k = K_g$. Also note that in Chapter 3 we will use this same idea to model the loss of chemical to the rat nasal cavity wall assuming that the chemical concentration in the cavity wall is zero (or $c_{1i} = 0$). Further, in addition to the incorporation of Fick's Law in the model in Chapter 3, a simpler "flow in - flow out" formulation based on fluid flow from compartment to compartment is used in both the models discussed in Chapters 2 and 3 and listed in Appendices A and B. Movement by concentration gradient is not incorporated in the model in Chapter 2 and Appendix A, and that model is considered to be completely flow-limited. The flow-limited formulation of the model in Chapter 2 is assumed to be sufficient to describe the physiological system. We should note that care was taken to remove the spacial variable in the original formulation of that model from [28] and extended in Chapter 2. The liver was considered as three separate compartments in the benzene model so that the model would remain an ordinary differential equation system and be entirely flow-limited. Additionally, the description of flow through the nasal cavity in the model from [39] and adapted in Chapter 3 is also based on a "flow in minus flow out" formulation. We recognize that modeling in terms of concentration gradient is necessary for some situations, but we hope to capture enough of the chemical transport to faithfully represent the physiological system through only fluid flow in the benzene model in Chapter 2.

Once a model is formulated based on the physiological system, one must make sure that the inputs or parameters to the model also faithfully represent the system. Parameters

based on measurements such as body weight (as in the model discussed in Chapter 2) or nasal cavity surface area (as in Chapter 3) may be relatively easy to find, but parameters involved in changes within the body, such as chemical reaction rates, may be more difficult to access. Using optimizations methods with the model and experimental data, the parameters which give the best fit of the model to the data can be found as in [28] and as in Chapter 3. If, however, we want to incorporate variability across a population and have distributions instead of fixed values for certain parameters, other methods involving sampling can be used. We incorporate Bayesian methods in Chapter 2 to accomplish such a goal.

Several different iterative optimization algorithms exist, most of which can be described as gradient-based algorithms or deterministic sampling algorithms. One gradient based algorithm is the steepest descent method which updates the current iteration by the formula

$$x_+ = x_c - \lambda \nabla f(x_c),$$

where λ is a chosen steplength and $f(x)$ is the function to be minimized [55]. Note that for our purposes $\nabla f(x)$ would be partial derivatives with respect to the parameters being estimated, i.e., the sensitivity equations. Hence, the steepest descent method should be easy to implement if the sensitivity equations are known. If the sensitivity equations and their solutions are easily available, gradient-based methods work very quickly and very well. Sensitivity equations, however, can be tedious to obtain and may take time to solve numerically within the gradient-based optimization. If many parameters are being estimated, i.e., if many sensitivity equations are necessary to establish the gradient, choosing a deterministic sampling method may be better. Some deterministic algorithms include the Nelder-Mead simplex algorithm and the DIRECT algorithm. The Nelder-Mead algorithm keeps a simplex S of approximations to an optimal point. The $N + 1$ vertices are then ordered according to the function values

$$f(x_1) \leq f(x_2) \leq \cdots \leq f(x_{N+1}).$$

The Nelder-Mead algorithm then attempts to replace the worst vertex x_{N+1} through sampling [55]. Other similar algorithms include the Hooke-Jeeves algorithm and the Multidi-

rectional Search algorithm. These algorithms are slower than gradient based methods but require no sensitivity equations. The algorithm DIRECT is also a sampling algorithm, but it incorporates the division of the parameter space into hyper-rectangles or hyper-cubes in order to find the solution that produces the minimum [38, 55]. The algorithm DIRECT can be very helpful if reasonably small bounds are known for the estimated parameters. If a large parameter space is being searched, DIRECT can be very slow. All of these methods or a combination of these methods can be used in estimating the best fixed parameters for mathematical models.

Although the model presented in Chapter 3 is a model for rats, the overall intention of the formulation models of chemical exposure is to eventually better understand risk to humans. Modeling of the biological system presented in Chapter 3 is at an early stage, but the investigation of sensory irritation will hopefully lead to a model related to humans. Therefore, at this stage it makes sense to only be concerned with the optimization of fixed parameters and not to overly complicate the model. At some point, we could incorporate variability in parameters as in the model as in the model in Chapter 2. An older and more established model is extended to incorporate human variability in Chapter 2. Since the population of humans is so diverse, having constant parameters that indicate rates of reactions and cardiac flow for the entire population does not take many factors into consideration. Humans have different physiologies dependent on such things as age, sex, and diet as well as more subtle genetic differences. By looking at a few parameters as distributions in Chapter 2 we hope to capture some of the overall variability in benzene metabolism. We will use the Markov Chain Monte Carlo Method as is further explained in Section 2.2 to find distributions for investigated parameters for the established model from [28].

Hence, the two models discussed in this work both involve chemical disposition through fluid flow and both show different stages of the process of modeling to understand risk. In the extension of the rodent model to the human model in Chapter 2, incorporating variation across the population clearly shows a method of using modeling to better understand how various individuals are affected by benzene exposure. The formulation of the model in Chapter 3 does not show an immediate connection to humans but is definitely a starting point to understand how inhaled chemicals affect respiration.

Chapter 2

Physiologically Based

Pharmacokinetic (PBPK)

Modeling of Benzene in Humans:

A Bayesian Approach

2.1 Introduction

Benzene, a toxic industrial solvent, is a component of cigarette smoke and gasoline [76, 83] and is also widely used in the production of many products. High-level exposure to benzene causes many health problems ranging from dizziness and headaches to anemia and leukemia [9]. A recent analysis of a prospective cohort study from the Australian petroleum industry showed an increased risk of leukemia; for the highest exposed group (>16 ppm-years) exposure intensity was strongly correlated with leukemia risk, with the increase starting around 0.8-1.6 ppm [45]. These toxic effects likely result from metabolites of benzene formed internally [9, 84]; and hence studying the mechanisms of benzene uptake,

metabolism, and elimination through the body can assist in the assessment of acceptable levels of exposure.

Physiologically based pharmacokinetic (PBPK) models are standard tools that are now often used in risk assessment to better extrapolate from experimental animals to humans and from high to low exposures [46, 23]. In [29], the authors developed a PBPK model that predicts tissue concentrations of benzene and its key metabolites in mice using metabolic parameters obtained *in vitro*. The PBPK model tissue compartments include the liver, richly perfused and poorly perfused tissues, and adipose tissue. Two additional compartments, the stomach and the alveolar gas-exchange region, were also included to describe oral and inhalation exposures, respectively. This model was later extended to take into account the zonal distribution of enzymes and metabolism in the liver, rather than treating the liver as one homogeneous compartment [28]. A common characteristic of PBPK models, such as the model in [28], is that they have single-valued parameters and are deterministic.

However, when the PBPK models are extended to humans, accounting for the multiple sources of variability that will affect dosimetry in humans is important. This hierarchy of variances includes variability among: different studies, individuals within each study, and measurements taken from each individual. To properly account for the variability at any of these levels PBPK models should be integrated into a statistical framework that acknowledges these sources of variation.

In classical pharmacokinetic analysis of data from drug trials, models with relatively simple structures and few, empirical parameters are fit to data from a relatively large number of subjects, allowing for robust estimation of the distributions of those parameters. The fact that a volume of distribution, for example, would be estimated by fitting the model to the observed pharmacokinetic data was not considered a problem because the study population was assumed to be large and diverse enough to represent the ultimate target population for which predictions were desired. PBPK models have become popular in toxicology, however, because human data are rare and when available typically come from very small groups for environmental pollutants without therapeutic value. PBPK models overcome this limitation because they make use of measured values for tissue compartments and blood flows, which again are presumed to represent the larger population. Some concern arises then that updating population physiological parameters based on observations from a small sample will result in posterior distributions not truly representative of the

population as a whole. Tissue volumes and partition coefficients, for example, affect model predictions and allowing them to vary can result in better model predictions than keeping them fixed, just as fitting the volume of distribution in classical pharmacokinetic models provides the flexibility to fit most data. One may question, however, whether this flexibility results in a model that is more predictive of the population as a whole and if it masks other errors in model specification. Because of these concerns and questions, one might wish to perform analyses that treat physiological parameters as fixed while updating distributions for metabolic parameters, for which prior information is much weaker and which are known to vary considerably among individuals. In order to capture variability of these physiological parameters, we use Bayesian analysis to fit PBPK model parameter to sets of human data.

In this study, the Monte Carlo simulation program *MCSim* [18] was used to fit a PBPK model of benzene to sets of human data by performing a series of simulations along a Markov chain in the model parameter space. We hypothesized that the observed inter-individual variability resulted primarily from known or estimated variability in key metabolic parameters and that a statistical PBPK model that explicitly included variability in only those metabolic parameters (along with any known variation in body weight) would be sufficient to describe all observed variability. The result of MCMC fitting of the model to data produces samples from the Bayesian posterior distribution of the model parameters.

2.2 Materials and Methods

The PBPK model used in this study is based on a previously developed PBPK model for benzene metabolism in mice [28]. The symbols and abbreviations used in the model are listed and briefly explained in Section A.1. The system of ordinary differential equations derived from a flow-limited assumption for tissue uptake is given in Section A.2. A schematic description of the benzene model is contained in Figure 2.1. To modify this model for risk assessment in humans, several parameters had to be adjusted. In particular, body weight (*BW*) was set at 70 kg for all individuals with the exception of the three individuals whose weights were recorded [71]. All fixed parameters used in the modified PBPK model can be found in Table 2.1 and Table 2.2. We should note that since all the

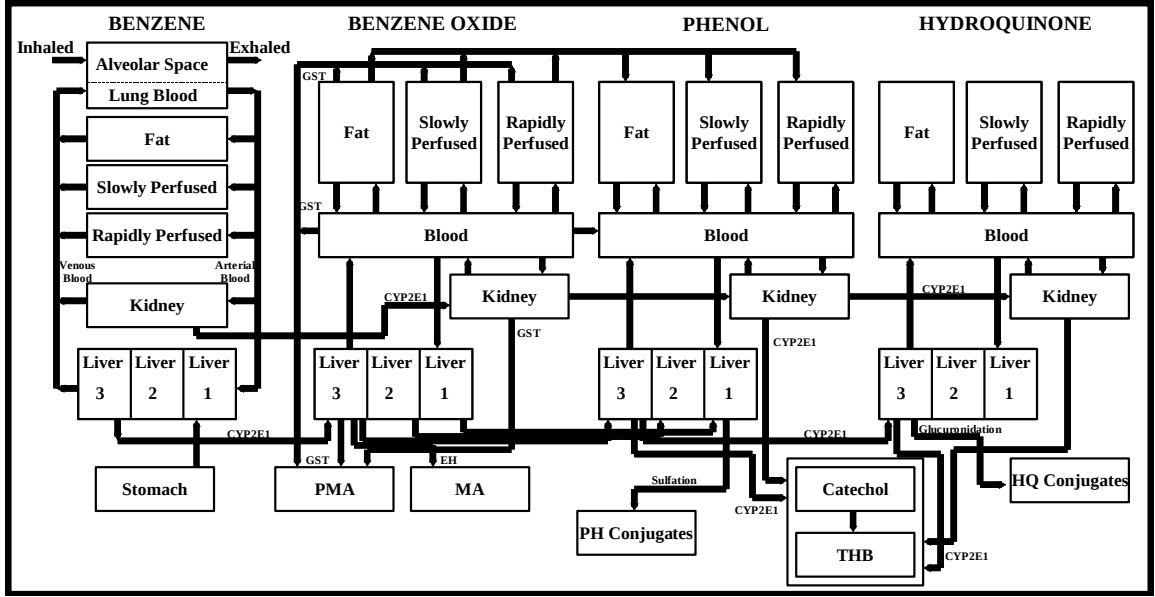


Figure 2.1: Schematic description of the benzene model from [28].

data used in this study is inhalation data, the parameter k_8 , the rate of uptake from the stomach to the liver, and the equation (A.27) have no effect on our solutions.

Total cardiac flow, Q_{Card} , and alveolar ventilation, Q_{AvV} , were assumed to be proportional to body weight and to each other. These values were defined by

$$Q_{Card} = k_{Card} \cdot BW$$

$$Q_{AvV} = k_{Q_{AvV}} \cdot Q_{Card},$$

and the proportionality constants k_{Card} and $k_{Q_{AvV}}$ were left for later investigation. The model from [28] used the parameter body weight; and since we hoped to change the model as little as possible, the decision was made not to alter the model to instead incorporate body mass index. All blood flow rates and organ volumes were changed based on reference values for a 70 kg man. Physiological values from [35] were calculated based on a reference weight of 70 kg and adjusted to satisfy the model requirement:

Table 2.1: Fixed parameters used in the PBPK model [28].

Parameter	Value	Unit	Source
Q_L	$0.2370Q_{Card}$	L/h	[35]
Q_F	$0.0425Q_{Card}$	L/h	[35]
Q_K	$0.2027Q_{Card}$	L/h	[35]
Q_S	$0.1717Q_{Card}$	L/h	[35]
Q_R	$0.3461Q_{Card}$	L/h	[35]
V_L	$0.025BW$	L	[50]
V_F	$0.1429BW$	L	[35]
V_K	$0.004BW$	L	[35]
V_S	$0.734BW$	L	[50]
V_R	$0.040BW$	L	[50]
V_{Bl}	$0.07429BW$	L	[35]
C^{CP}	14.5	mg/g	[32]
C^{MP}	58	mg/g	[32]
$K_{m,1}^{PH}$	1.4	μM	[78]
$K_{m,2}^{PH}$	220	μM	[78]
K_m^{HQ}	746	μM	[78]
A^{BZ}	0.0397	$1/\mu M$	[63]
A^{PH}	$1.30 \cdot 10^{-2}$	$1/\mu M$	[63]
A^{HQ}	10^{-7}	$1/\mu M$	[63]
k_1	$4.20 \cdot 10^{-2}$	$L/\mu mol$	[63]
k_2	32.16	$1/h$	[63]
k_5	$4.00 \cdot 10^{-2}$	$L/\mu mol$	[63]
k_6	$2.13 \cdot 10^{-3}$	$L/\mu mol$	[63]
k_7	$2.03 \cdot 10^{-4}$	$L/\mu mol$	[63]
k_8	374.9598	$1/h$	[28]
k_9	0.1163	$1/h$	[28]
k_{10}	0.1443	$1/h$	[28]

$$Q_{Card} = Q_F + Q_S + Q_R + Q_L + Q_K. \quad (2.1)$$

Partition constants $P_{Bl:Air}^{BZ}$, P_j^{BZ} , and P_j^{BO} (for compartments j = fat, liver, slowly perfused tissue, rapidly perfused tissue, and kidney) were also changed to the values in [20] because those values were thought to better represent human values. The values for the concentration of microsomal protein per gram of tissue in the liver, C^{MP} , and the concentration of cytosolic protein per gram of tissue in the liver, C^{CP} , were changed from the original model and taken from [32]. A number of metabolic rate constants were assumed

Table 2.2: Partition coefficients used in the PBPK model [28].

Parameter	Value	Source
$P_{Bl:Air}^{BZ}$	7.80	[20]
P_F^{BZ}, P_F^{BO}	54.50	[20]
P_L^{BZ}, P_L^{BO}	2.95	[20]
P_S^{BZ}, P_S^{BO}	2.05	[20]
$P_R^{BZ}, P_R^{BO}, P_K^{BZ}, P_K^{BO}$	1.92	[20]
P_F^{PH}	27.63	[60]
P_L^{PH}	2.17	[60]
P_S^{PH}	1.22	[60]
P_R^{PH}, P_K^{PH}	2.17	[60]
P_F^{HQ}	4.06	[60]
P_L^{HQ}	1.04	[60]
P_S^{HQ}	0.94	[60]
P_R^{HQ}, P_K^{HQ}	1.04	[60]

to be relatively invariant between species; hence the remaining parameters in the PBPK model are unchanged from their values in [28]. In addition, the PBPK model has equations describing the cumulative amount of exhaled benzene and in order to compare the model to data of the concentration of exhaled benzene, the following expression was used to compute the model value for concentration of benzene in exhaled air

$$C_E^{BZ} = (1 - f_{alv}) \cdot C_I^{BZ} + f_{alv} [Q_{Card} \cdot (CV^{BZ} - CA^{BZ}) + Q_{AvV} \cdot C_I^{BZ}] / Q_{AvV}. \quad (2.2)$$

The notation from the original model is preserved in (2.2) with the only new value being f_{alv} , which is the fraction of each inhaled breath that perfuses the alveolar space. This equation is essentially identical to a correction used by [53] and is derived by assuming that: air leaving the alveolar region satisfies the usual venous-equilibration model; air leaving the alveolar space mixes with air that was inhaled but only entered the physiological dead space (conducting airways; DS); that the DS air does not exchange with blood at all and hence stays at the inhaled concentration; and that the measured exhaled concentration is the result of this mixture. Thus the exhaled concentration equals f_{alv} times the concentration exiting the alveolar region plus $(1 - f_{alv})$ times the DS concentration that equals the inhaled concentration. The value for f_{alv} was expected to be around 0.67 [50] and was investigated as a distributional parameter with the Markov Chain Monte Carlo method. Additionally,

the PBPK model has cumulative equations for urinary metabolites, and hence the model prediction of the amount of urinary metabolite was divided by a standard value of urinary excretion as converted from 20 ml/kg/day to compute the predicted concentration over time [27].

To illustrate the statistical considerations, suppose that a multivariate PBPK model for benzene can be specified by the n -dimensional system of differential equations

$$\frac{dx}{dt} = f(t, x, q), \quad x(t_0) = x_0 \quad t_0 = 0. \quad (2.3)$$

The solution to this system of equations denoted by $g(t, q, x_0)$ is a function of parameters q (including inhalation exposure conditions), time t , and initial condition x_0 . Now, consider the case of *in vivo* data collected on each of m subjects exposed to benzene. Each of these subjects are assumed to follow the basic model (2.3), but with potentially different parameters and initial conditions, reflecting variation in pharmacokinetic parameters across the population. Although analysis of individual subject data provides insight into underlying biology, it fails to address the broader issue of how these parameters vary across individuals. Comprehensive application of PBPK models to these data requires that both levels of inquiry, individual and population, be addressed—not only to elucidate individual-specific parameter values but also to characterize the extent and nature of their variation across population.

Formally, for individual i , with intermittent observations available at time $t_{i1}, t_{i2}, \dots, t_{in}$, let $Y_{ij} = (Y_{i1j}, Y_{i2j}, \dots, Y_{imj})^T$ be the $(m \times 1)$ vector of observations on subject i at time t_{ij} ; for example, Y_{ij} may include measurements of benzene in blood and expired air. Thus, data collected on individual i are the vectors $Y_{ij}, j = 1, 2, \dots, n_i$, ideally assumed to be observations on the system (2.3). However, the measurements of benzene concentration in the exhaled air, benzene concentration in the blood, and metabolite amounts in the urine are subject to several sources of variation. To specify this explicitly, we may specify the individual statistical model

$$Y_{ij} = g(t_{ij}, q_i, x_{i0}) + \epsilon_{ij}, \quad j = 1, 2, \dots, n_i, \quad (2.4)$$

where ϵ_{ij} is a random vector representing deviations of observed data from the dynamic

model due to the combined effects of these sources at time t_{ij} , and q_i and x_{i0} are the parameters and initial conditions specific to individual i . Notice that the quantity of interest here is the distribution of parameters q_i .

The modified PBPK model was implemented into Frédéric Bois' and Don Maszle's Monte Carlo simulation program, *MCSim*, which uses Metropolis-Hasting sampling for its Markov Chain Monte Carlo simulations [18]. Markov Chain Monte Carlo simulations were run on the model in order to find distributions of specific metabolic parameters that had been held constant in the previous PBPK modeling studies [28]. The model parameters investigated included V_{2E1} , the CYP2E1 specific activity as determined by the oxidation of p-nitrophenol to p-nitrocatechol; V_{PH1} and V_{PH2} , the maximum rates of metabolism of phenol by two sulfate transferases; and V_{HQ} , the maximum rate of conjugation for hydroquinone (primarily glucuronidation). The two first order rates of metabolism of benzene oxide into phenylmercapturic acid and into muconic acid, k_3 and k_4 , respectively, were also expected to be distributed and so were incorporated into the *MCSim* program. The values for k_{Card} , $k_{Q_{AvV}}$, and f_{alv} were likewise expected to be distributed and were analyzed using *MCSim*.

The prior distributions for V_{2E1} , V_{PH1} , V_{PH2} , and V_{HQ} were determined by analyzing previous *in vitro* data obtained from human liver samples [78]. The initial rates of phenol sulfation and rates of hydroquinone glucuronidation from the *in vitro* study were each multiplied by factors yielded by the mathematical model used in [78]. The factors were 0.18 for V_{PH1} , 2.4 for V_{PH2} , and 11.1 for V_{HQ} . The CYP2E1 activity measurements were not multiplied by a factor. These vectors of data were converted to proper units then entered in Matlab. These four vectors were tested to see if they fit a normal, uniform, gamma, or Poisson distribution. The best fitting distribution for each parameter, i.e., the hypothesized distribution that was not rejected and had the highest p-value, was used as its prior. The parameters V_{2E1} , V_{PH1} , and V_{PH2} were expected to have gamma distributions based on the *in vitro* data, and the model parameter V_{HQ} was expected to be normally distributed. Since little information was available on the other investigated parameters, the remaining priors were based on previous constant values. The prior distributions for k_3 and k_4 were assumed to be normally distributed, and the means of these priors were the fixed values from the original mouse model [28]. The priors for k_{Card} , $k_{Q_{AvV}}$, and f_{alv} were also assumed to be normally distributed with small standard deviations with the means of these priors originating from reference man values [50]. The *MCSim* program was used to find

Table 2.3: Prior distributions for the PBPK model parameters analyzed using the Markov Chain Monte Carlo Method.

Parameter	Prior Distribution
k_3	Normal, $\mu = 0.7032$, $\sigma = 0.1$
k_4	Normal, $\mu = 15.1001$, $\sigma = 1$
V_{2E1}	Gamma, $a = 2.7506$, $b = 0.0284$
V_{PH1}	Gamma, $a = 6.8926$, $b = 0.0044$
V_{PH2}	Gamma, $a = 6.8926$, $b = 0.0585$
V_{HQ}	Normal, $\mu = 0.7484$, $\sigma = 0.3207$
f_{alv}	Normal, $\mu = 0.67$, $\sigma = 0.2$
k_{Card}	Normal, $\mu = 4.4571$, $\sigma = 0.3$
$k_{Q_{AvV}}$	Normal, $\mu = 0.965$, $\sigma = 0.05$

the distributional components for each of these model parameters, and the specific prior distributions used in the simulations are contained in Table 2.3.

Data taken from previous studies of human benzene exposure were incorporated into the *MCSim* program, and extra specifications were used in the case of multiple data sets for the same individual in order to find inter-individual variability as opposed to intra-individual variability. In one study, blood and exhaled air samples were collected from three healthy nonsmokers who were each exposed to four hour periods of both $10 \text{ cm}^3/\text{m}^3$ and $1.7 \text{ cm}^3/\text{m}^3$ benzene [71]. Thirty-five occupationally exposed individuals provided urine samples during their work shifts for metabolite data in a second study [75, 82]. Even though the time length of their shifts and the urine collection times varied, the exposure time for these workers was taken to be six hours in the model. The Markov Chain Monte Carlo simulation was run for 20,000 iterations, and the results were recorded every tenth iteration. The results were analyzed from iteration 15010 through 20000 in order to ascertain the distributions of the model parameters.

Originally the *MCSim* program was run five times with five different seedings for its random number generator. The distributions resulting from these five runs were analyzed, and the output for the model parameters V_{PH1} and V_{PH2} did not have any well-fitting parametric distributions. The output for V_{2E1} varied greatly among the five runs; specifically, three of the runs yielded much higher V_{2E1} output distributions than the other two. Additionally, even when simulations were run using selective subsets of the five output distributions, the resulting model solution distributions were very narrow. In order to account for greater variability, the prior standard deviations for k_{Card} and $k_{Q_{AvV}}$ were

changed from 0.1 to 0.3 and from 0.01 to 0.05, respectively. After this change, the *MCSim* program was run again. Only one long run was assumed to be sufficient as suggested in [43] although Bois and Maszle believe considering several pooled runs is a better approach [18].

After the posterior distributions were determined, the model was examined for sensitivity. The means of each posterior distribution were used for the investigated parameters to produce solutions from the model. In order to ascertain the model's sensitivity to each parameter, one parameter would be varied while all the other investigated parameters were kept at the mean values from their posterior distributions. For each investigated parameter, three solutions were produced holding the other eight of the parameters at their distributional means and then using a value at 95% of the confidence interval, a value at 5% of the confidence interval, and the mean of the currently analyzed parameter. Then the maximum distance from the mean solution to the solution above or below the mean curve was computed and used in the following formula

$$sensitivity = \frac{\Delta prediction / prediction}{\Delta parameter / parameter}. \quad (2.5)$$

In the above formula, *prediction* indicates the predicted solution at the mean and $\Delta prediction$ indicates the maximum difference between the predicted solution at the mean and the predicted solution using either a 95% or 5% confidence interval value. The values in the denominator of the above ratio are based on the varying investigated parameter and are defined similar to the predicted solutions. The only state variables of the model examined for sensitivity were those compared to data in this study in order to better understand which data sets influenced the results of each investigated parameter.

2.3 Results

The output from *MCSim* appeared to sample adequately from the posterior distributions and was analyzed using Matlab to find distributions which best fit the output data for each parameter. These posterior distributions for the nine investigated model parameters are shown in Table 2.4 as well as compared graphically to their priors in Figure 2.2 and Figure 2.3. For k_{Card} the mean, μ , and the standard deviation, σ , of its normal distribution are listed in the results table; and the appropriate parameters for the beta distribution

Table 2.4: The resulting distributions for the PBPk model parameters from the Markov Chain Monte Carlo Method.

Parameter	Posterior Distribution
k_3	Gamma, $a = 63.8027$, $b = 8.060 \cdot 10^{-3}$
k_4	Gamma, $a = 170.74$, $b = 0.07282$
V_{2E1}	Gamma, $a = 140.58$, $b = 1.286 \cdot 10^{-4}$
V_{PH1}	Gamma, $a = 7.310$, $b = 225.53$
V_{PH2}	Gamma, $a = 7.8377$, $b = 15.5516$
V_{HQ}	Gamma, $a = 20.2275$, $b = 0.05037$
f_{alv}	Beta, $a = 169.29$, $b = 65.7663$
k_{Card}	Normal, $\mu = 3.2635$, $\sigma = 0.2634$
$k_{Q_{AvV}}$	Gamma, $a = 276.63$, $b = 2.557 \cdot 10^{-3}$

are listed for f_{alv} . For the other parameters the resulting shape parameter, a , and inverse scale parameter, b , of the gamma distributions are given. The values for k_3 and k_4 are slightly below those found in the optimization with the mouse model [28], and the posterior distributions for the metabolic rates V_{PH1} and V_{PH2} allow for much higher values than *in vitro* data [78] would suggest. The posterior distribution for V_{2E1} has moved to the left within its prior distribution, which was based on the *in vitro* data from [78]. Although the prior of V_{HQ} is normal and its posterior distribution appears to be a gamma distribution, the values of this parameter have changed little through the use of MCMC. The values for k_{Card} and $k_{Q_{AvV}}$ are slightly below their priors, which were based on reference mean values. The posterior distribution for f_{alv} is narrower than its prior, but the mean of the posterior is slightly higher than the mean of the prior.

One hundred solution curves were computed from the 100 samples from the *MCSim* posterior distributions and were plotted versus time along with data points from the three individuals in the study from [71]. These plots are contained in Figures 2.4-2.7. Here, the solution curves are plotted for each individual in the study to determine if the data points fall in the area created by the range of the solutions. The same sampling was implemented using the prior distributions to find model solutions so that the solutions based on the posterior distributions could be compared to not only the data but also to the model prior to the use of the MCMC method. The prior distribution solutions, the posterior distribution solutions, and the data are presented on both linear and log scale to most fully represent the results. The solutions for the three individuals are plotted separately because their model solutions depended on different body weights-90 kg for subject 1, 55 kg for subject 2, and

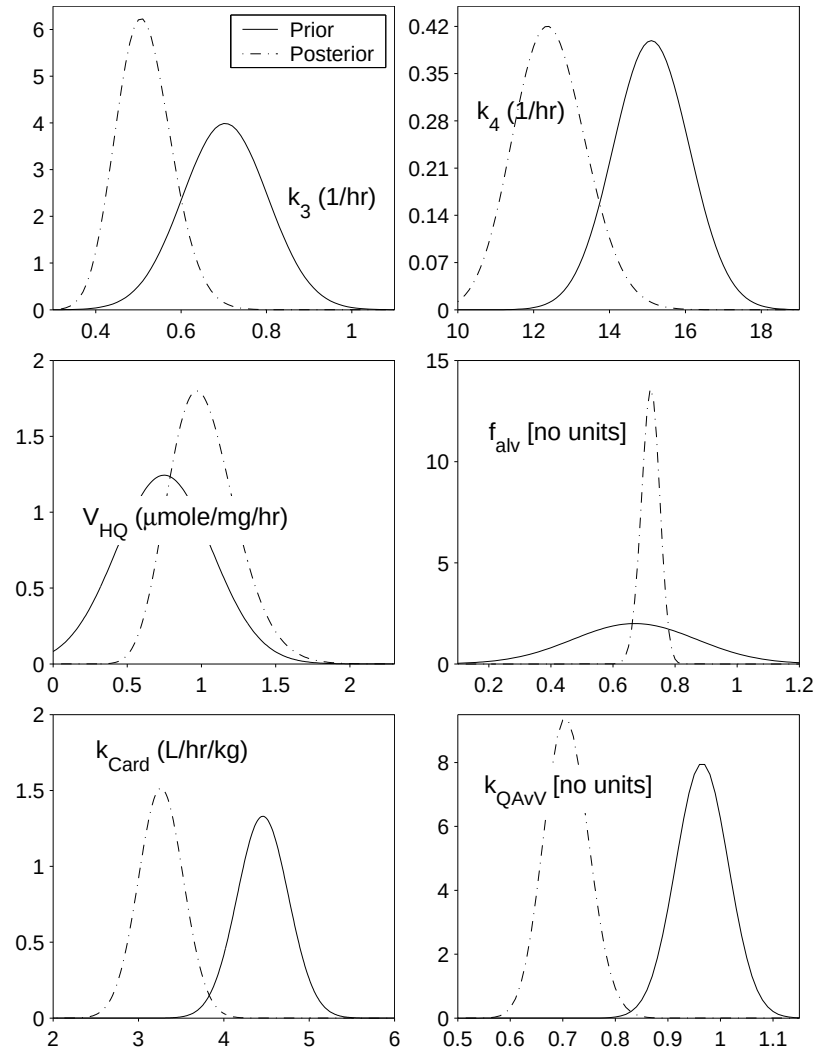


Figure 2.2: Prior distributions plotted alongside posterior distributions for six of the investigated parameters.

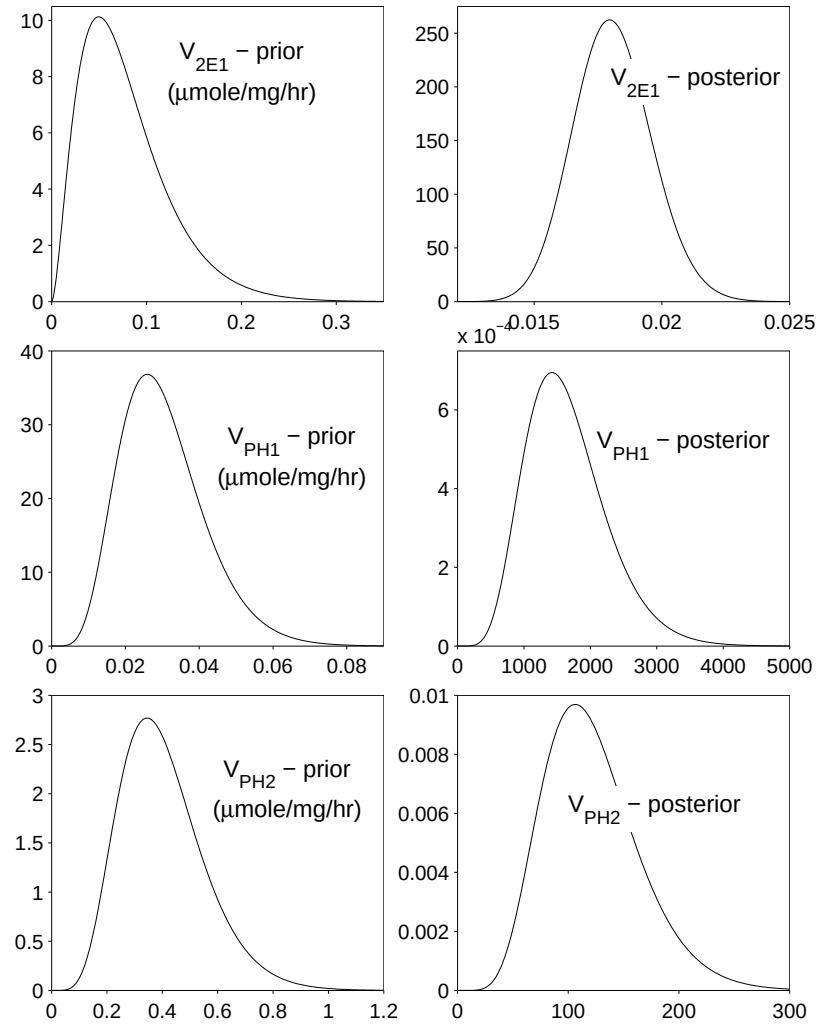


Figure 2.3: Prior distributions and posterior distributions for three of the investigated parameters. Note that the different distributions prevented plotting the prior and posterior of each of these parameters on the same set of axes.

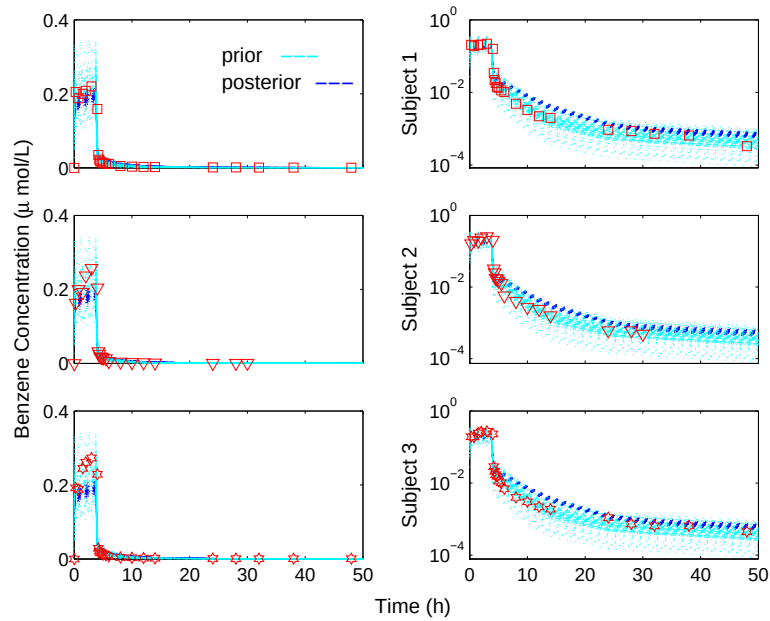


Figure 2.4: The model predictions versus data for benzene in exhaled air with higher exposure levels from [71].

73 kg for subject 3.

One hundred samples for each model parameter were drawn from the distributions found through *MCSim*, and 100 model solutions were computed using these parameters for different exposures using Matlab. The 100 solution values for different metabolites in the urine were plotted in Figure 2.8 versus the corresponding data values from the occupational exposure study [75, 82]. Each vertical line of x's represents the 100 predicted exhaled benzene concentrations ($\mu\text{moles}/L$) for the model for a particular inhalation concentration plotted versus an actual measurement from the study. A plot of the $y = x$ line is contained in all parts of Figure 2.8 for comparison. All five metabolite solutions seemed somewhat centered around the $y = x$ line except for the plot of the catechol and trihydroxy benzene concentration.

The results of the sensitivity analysis are listed in Table 2.5. The values in the table are based on the ratio of prediction change over parameter change as listed in Section 2.2. The columns represent the parameter being changed and rows represent the different urinary metabolites and benzene blood and exhaled air concentrations evaluated for sensitivity. The values for the concentration in exhaled air and in the blood were computed for both the

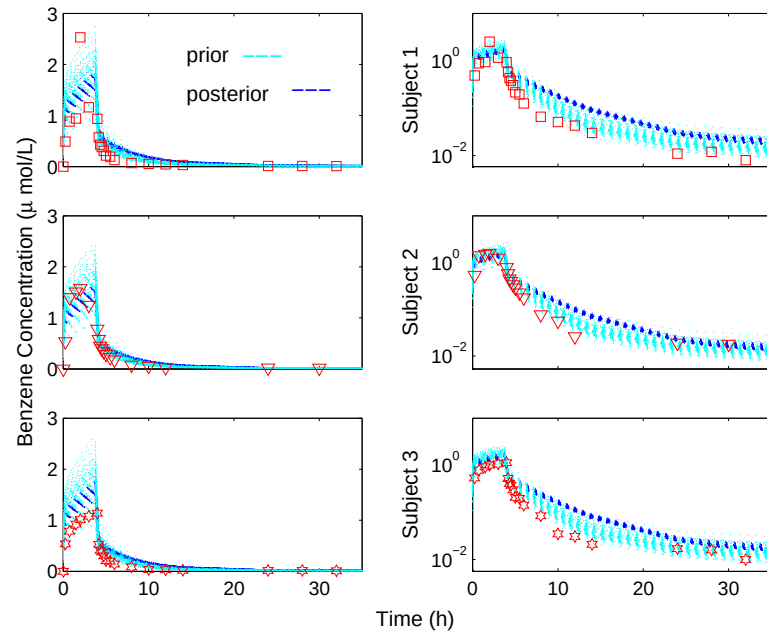


Figure 2.5: The model predictions versus data for benzene in blood with higher exposure levels from [71].

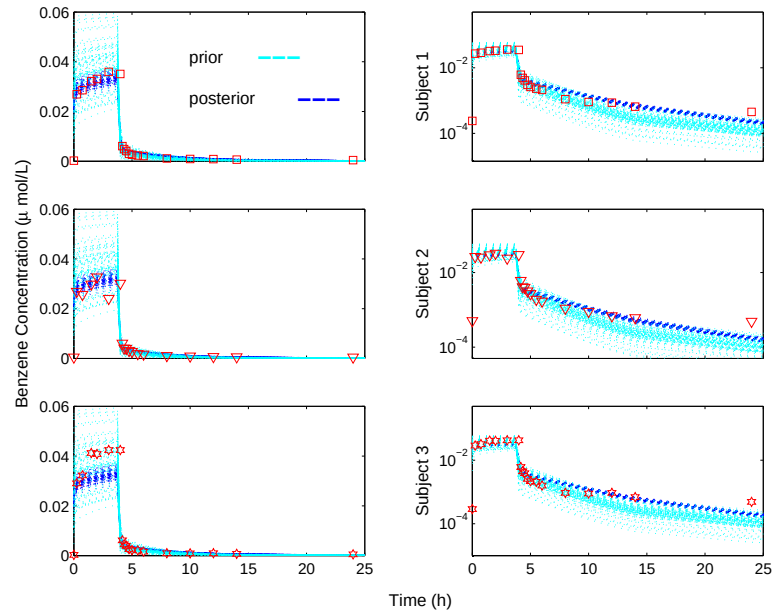


Figure 2.6: The model predictions versus data for benzene in exhaled air with lower exposure levels from [71].

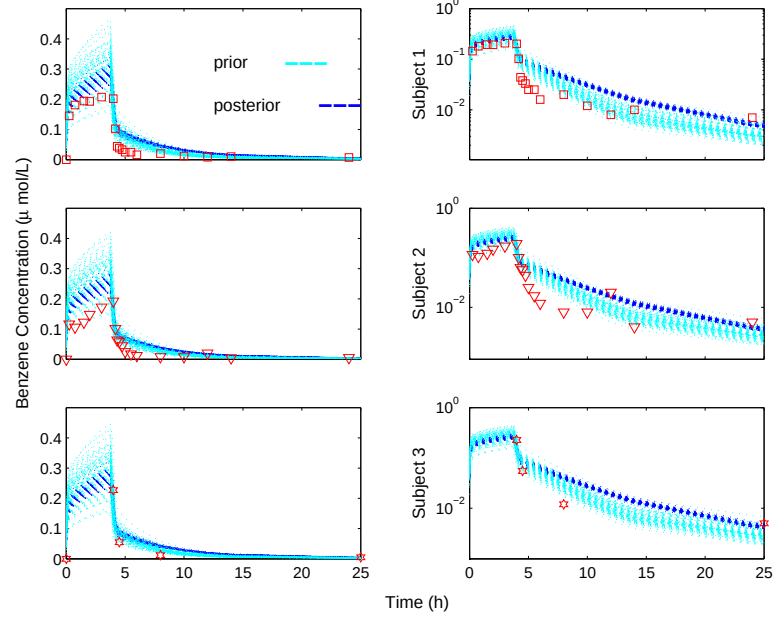


Figure 2.7: The model predictions versus data for benzene in blood with lower exposure levels from [71].

Table 2.5: The sensitivity analysis results for each investigated parameter.

	k_3	k_4	V_{2E1}	V_{PH1}	V_{PH2}	V_{HQ}	f_{alv}	k_{Card}	$k_{Q_{AvV}}$
MA	2.07	1.65	2.20	$6.9 \cdot 10^{-4}$	0.058	0.21	0	2.30	4.40
Cat-THB	1.66	2.00	2.18	$5.6 \cdot 10^{-4}$	0.014	0.13	0	1.51	3.89
PMA	0.99	2.04	1.98	$5.9 \cdot 10^{-4}$	0.015	0.17	0	2.33	4.23
PH	2.40	0.86	2.58	$7.8 \cdot 10^{-4}$	0.020	0.23	0	6.33	3.91
HQ	0.59	0.91	1.47	$2.1 \cdot 10^{-4}$	0.0053	0.67	0	0.69	1.51
C_E^{BZ} (high)	2.03	3.90	2.24	$2.3 \cdot 10^{-6}$	$3.2 \cdot 10^{-6}$	$4.2 \cdot 10^{-5}$	1.94	3.21	3.09
C_E^{BZ} (low)	0.089	1.56	2.01	$5.0 \cdot 10^{-6}$	$2.4 \cdot 10^{-5}$	$1.7 \cdot 10^{-7}$	1.94	4.55	3.63
$CA^{BZ} + CV^{BZ}$ (high)	2.03	3.90	2.24	$2.3 \cdot 10^{-6}$	$3.2 \cdot 10^{-6}$	$4.2 \cdot 10^{-5}$	0	3.21	3.15
$CA^{BZ} + CV^{BZ}$ (low)	0.089	1.56	2.01	$5.0 \cdot 10^{-6}$	$2.4 \cdot 10^{-5}$	$1.7 \cdot 10^{-7}$	0	4.55	3.60

two exposure levels from [71].

2.4 Discussion

The model predicted metabolite data well for muconic acid, phenylmercapturic acid, and phenol conjugates. The model somewhat over predicts metabolite data for hy-

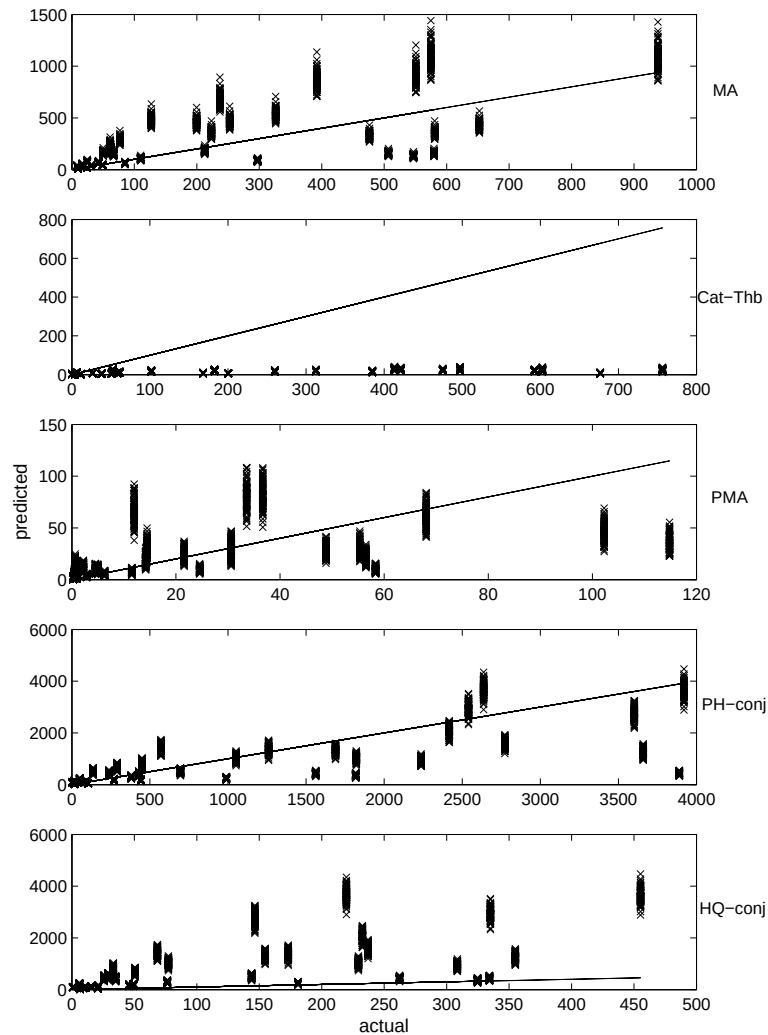


Figure 2.8: The model predictions versus metabolite data from [82]. The five urinary metabolites or metabolite groups simulated are: muconic acid (MA), catechol and trihydroxy benzene (Cat-Thb), phenol and phenol conjugates (PH), phenylmercapturic acid (PMA), and hydroquinone and hydroquinone conjugates (HQ).

droquinone conjugates, and the model greatly under-predicts the concentrations of catechol and trihydroxy benzene for the workplace data [75, 82]. Since Bayesian methods depend greatly on the accuracy of prior information, errors in the data used to estimate the priors could account for the need to alter the *MCSim* output for a better fit graphically. The model seems to predict the concentration of benzene exhaled and the concentration of benzene in blood well for the study in [71] although a wider range of solution curves capturing all data points was expected. Although the computed solutions using the posterior distributions do not greatly improve accuracy over the solutions computed using the prior distributions for this study, the range of posterior model solutions does narrow somewhat around the exposure data. Since the two studies probably varied in participant physical activity, further experiments focusing on activity levels might help the accuracy of the model.

The results for f_{alv} have a mean around 0.72, which is slightly higher than the ILSI value of 0.67 [50], but the presence of benzene may have increased the subjects' ventilation rates. Measurements of the dead space lung volume of subjects exposed to butadiene suggest that it lowers the dead space to around 171.3 *mL* [61], which is around 14.6% of the total lung volume [35]. Our results suggest that the dead space lung volume does decrease with inhaled benzene but only to about 28% of total volume. However, in the study from [71], the apparatus for sampling exhaled air may have introduced a slight source of error due to the difficulty to breathe normally. The three subjects may have unconsciously breathed with larger tidal volumes thus decreasing the relative dead space volume. Also, while it is normally assumed that no gas exchange occurs in the conducting airways, a small amount almost certainly occurs; and the larger f_{alv} could simply allow the model to correct for the fact that it only allows exchange in the alveolar space.

A significant portion of the data used in this investigation involved benzene concentrations in blood and exhaled air. In the PBPK model [28], the amount of benzene exhaled depends directly on the parameters Q_{AvV} , Q_{Card} , and $P_{Bl:Air}^{BZ}$. We have quantified Q_{AvV} and Q_{Card} as being proportional to k_{Card} and $k_{Q_{AvV}}$, respectively, and introduced the parameter f_{alv} for the fraction of inhaled air perfusing the alveolar region. Although the equation describing AM_E^{BZ} is connected to the rest of the ordinary differential equation system, the model dynamics of the exhaled concentration of benzene are therefore most closely related to the parameters f_{alv} , k_{Card} , $k_{Q_{AvV}}$, and the concentration of benzene in mixed venous blood, CV^{BZ} . The concentration of benzene in the venous blood, CV^{BZ} , in turn is expected to depend strongly on the rate of clearance in the liver, which is a function

blood flow to the liver (Q_L , which is proportional to k_{Card}) and the rate of metabolism in the liver, particularly V_{2E1} . The results of the sensitivity analysis in Table 2.5 show that f_{alv} , k_{Card} , $k_{Q_{AvV}}$, and V_{2E1} , as well as k_3 and k_4 (rate constants for conversion of benzene oxide to phenylmercapturic acid and muconic acid, respectively), affect the exhaled benzene. (An increase in k_3 or k_4 reduces the amount benzene oxide which would otherwise be converted to phenol, and hence the amount of phenol competing with benzene for CYP2E1.) Not surprisingly, these same parameters, except f_{alv} , also significantly affect the predicted concentration of benzene in blood.

Since the predictions of benzene concentrations in exhaled air and in blood depend most strongly on k_3 , k_4 , V_{2E1} , f_{alv} , k_{Card} , and $k_{Q_{AvV}}$, *MCSim* would primarily be able to affect the fit of the model to the exhalation and blood data by updating the distributions of these particular six parameters. Hence, the posterior distributions found by *MCSim* for k_3 , k_4 , V_{2E1} , f_{alv} , k_{Card} , and $k_{Q_{AvV}}$ were largely influenced by the process of fitting solution curves to the exhalation and blood data. Likewise, since changes in f_{alv} only alter the exhaled benzene predictions, only the exhalation data affects the f_{alv} posterior distribution in the MCMC simulations. The model does not seem to be very sensitive to changes in V_{PH1} , V_{PH2} , and V_{HQ} , although the effect is slightly higher when dealing with the metabolites. The sensitivity of model predictions for urinary metabolite concentrations to changes in k_3 , k_4 , V_{2E1} , V_{PH1} , V_{PH2} , V_{HQ} , k_{Card} , and $k_{Q_{AvV}}$ suggests that the data from the occupational study influences the distributions estimated for all investigated parameters except for f_{alv} .

When the model prediction of one output variable is less sensitive to a particular parameter, the *MCSim* program will be more influenced by the data of other output variables (that do show greater sensitivity) when finding the posterior distribution of that particular parameter. Hence, the effect the urinary metabolite data has on the distributions of V_{PH1} , V_{PH2} , and V_{HQ} is less than the occupational study data has on other parameters and is less significant than the effect the blood and exhalation data have on most other parameters. Further, any miscalculation due to the apparatus used by [71] will significantly affect our results for f_{alv} , and use of the data from [75, 82] cannot significantly compensate for such an error. Similarly, the results for V_{PH1} and V_{PH2} are primarily determined by metabolite data, but errors here seem not to greatly affect the model overall. Using a variety of types of data should result in better estimates of parameter distributions, but understanding that certain data sets are more critical than others in the determination of each model parameter is also critical in developing the most accurate model.

When both the mathematical model and the statistical model are fully specified at all levels, the approach is referred to as a parametric approach. Specifically in the PBPK model, the approach is considered parametric when assuming a distribution form (e.g., log-normal) for how well we know each individual's parameters and a distribution form for the set of parameters from all the individuals. A parametric approach is often used when the general form of the distribution in the problem is known. A statistical model is considered to be structured when the variables (distributions) are associated with specific underlying quantities, which occurs naturally with PBPK model. A parametric approach provides an efficient way for estimating the parameters of a PBPK model since it takes full advantage of the distribution structure.

A variety of statistical tools are available for fitting the mathematical models to data with structured variability. Model-fitting tools that do not incorporate prior information on parameter distributions, referred to as "frequentist," include maximum likelihood methods such as non-linear least squares [14]. The error structure in the data (how sources of error or variability are assigned) can be accommodated by modifying standard techniques to incorporate ideas from repeated measures and cross-over experimental designs. Alternatively, Bayesian statistical models provide a natural framework for analyzing models with hierarchical error structures [40]. One Bayesian technique that has been embraced by a great many applied statisticians in all fields of research is the Markov chain Monte Carlo (MCMC) method [44]. MCMC methods explore the joint posterior distribution of interest (i.e., the distribution of all parameters, given that the distributions may not be independent) by providing a mechanism whereby a set of realizations or samples from that distribution can be generated. This set is obtained by carrying out Monte Carlo simulations from a Markov chain that is constructed so that its stationary distribution is the relevant posterior. Various methodologies exist to carry out the required simulations including the Gibbs sampling algorithm and the Metropolis-Hastings algorithm. Because of the increasing complexities of statistical models encountered in practice, MCMC provides a much-needed unifying framework within which many complex problems can be analyzed.

Both Bayesians and frequentists need to integrate over possibly high-dimensional probability distributions, such as unknown parameters, to make inferences for the parameter of interest or to make predictions. This basic need underlies the potential role of MCMC methodology in statistical modeling and inference. The past several years have witnessed an explosive growth of interest in MCMC methodology from researchers in almost all areas

of statistics and biology. In particular, Bayesian population methods have made some significant contributions in the field of PBPK modeling. In [17] Bayesian statistical inference and physiological modeling were brought together to model the distribution and metabolism of benzene in humans. This approach of combining PBPK models and MCMC methodology for Bayesian inference has been extended to other chemicals such as toluene and styrene [52, 53]. The inclusion of the variability predicted by these approaches into risk assessments is expected to be an improvement over previous use of empirical uncertainty factors (e.g., [62]).

In [17], Bois also applied Bayesian analysis to a PBPK model of benzene in humans using the data of [71], which is also included in our analysis. The paper of Bois and co-workers was one of the first to demonstrate the application of Bayesian analysis to PBPK modeling and its use in predicting population variability, a significant advancement in the potential for mechanistic dosimetry modeling in risk analysis. The model used by Bois *et al.* in [17], however, only included a very simple description of benzene metabolites, with the assumption that phenolic metabolites are a fixed fraction of those metabolites. That model does not allow for prediction of target tissue concentrations of phenol itself (as opposed to phenol conjugates), nor of hydroquinone or benzene oxide, both of which are included in our model. Hydroquinone and phenol have been shown to strongly synergize in the induction of genotoxicity *in vivo* [12] and hydroquinone was shown to strongly enhance colony formation of murine bone marrow cells *in vitro* [51]. Benzene oxide has been shown to be tumorigenic in mice [21], and benzene exposure-related increases in benzene oxide-albumin adducts have been demonstrated in humans [72, 73]. Thus we believe the current model builds upon and is a considerable advancement of the innovative work by Bois and colleagues in that it predicts tissue levels of phenol, hydroquinone, and benzene oxide, all of which are likely contributors to benzene’s leukemogenic effects. Further, the current results are based on a much larger data set than that used in the previous analysis, providing for more robust and representative posterior distributions.

A known source of variability that has been better accounted for elsewhere is the effect of activity level on circulation and respiration [52, 53]. Not only were we faced with a lack of data on activity level among the subjects in the studies included here, but also we were working with many more metabolic parameters for which the priors are not strongly informative. However, the idea that the effect of known or estimated variability in these metabolic parameters could more than cover the observed variability in the data available

seemed possible. Therefore we decided to test the hypothesis that the observed variability in the data would be accounted for by incorporating distributions for only the metabolic parameters by fixing the values of most physiological variables to standard values used in PBPK modeling (e.g., [50]) and the measured partition coefficients to those measured or estimated elsewhere.

Incorporation of dependence on activity level and variability and uncertainty in partition coefficients would almost certainly have resulted in much closer correlations between predictions and the data. Hence activity considerations should probably be added before the benzene PBPK model is used in a human risk assessment, but we believe there is scientific value in first testing this more stringent assumption presented here. While we do not know precise activity levels for the individuals whose data are being simulated here, the authors of [52] found the best description of their data for toluene when "the increased perfusion of peri-renal fat was set to a constant level during all exercise levels," which indicates that categorical assignment of values based on general activity patterns (e.g., resting, some movement, light work, etc.) would be sufficient.

At the beginning of this study, additional data was considered from a study by Berlin *et al.* [15], which measured benzene concentrations in exhaled breath after inhalation exposures. Results reported in [15] were different enough from those of the Pekari study [71] that including both sets of data in our analysis became problematic. Since the data from the Pekari study seemed more informative, our attempt to include the data from the Berlin study was abandoned. In early studies incorporating the data, the model fits of benzene concentration in blood and exhaled air to the Pekari data were fairly good and appeared to be without significant bias. At least in those cases the model predicted the relationship between blood concentrations and exhaled air concentrations. Recognizing that the data set from the Berlin study and the occupational exposure study data [82] are from distinct populations, we note that there is a tendency for the model to over-predict both of those; i.e., it seems to over-predict both the amount in exhaled breath and urinary excretion when the [15] data is incorporated into the study. Since any benzene inhaled must either be excreted by one of these routes or bind to tissue macromolecules (first order rates from phenol and hydroquinone), the only way to decrease both exhaled breath predictions and urinary excretion predictions would be to either increase the amount predicted as binding to macromolecules or decrease the predicted inhalation rate. Since we believe the rate constants for binding to macromolecules to represent non-enzymatic reactions that should

be independent of species, their values were not updated from those estimated by [28] using mouse *in vivo* data.

Thus we could potentially "correct" the over-prediction of the [15] data and [82] data by updating k_9 and k_{10} . If we had allowed those parameters to be updated better fits probably could have been obtained without further insight. Instead the failure of the model to fit the data given the constraints of holding those parameters constants led us to the possibility that we had over-predicted the rate of uptake by inhalation. Benzene has a blood:air partition coefficient of 7.8 [20]. While this is relatively low and benzene has low aqueous solubility, one might expect a limited wash-in/wash-out effect that would lower absorption from the amount predicted by the classic venous ventilation model used here [42]. After this analysis, we decided not to use the data from [15] in our study rather than alter k_9 or k_{10} or the blood:air partition coefficient. In addition to not utilizing the Berlin data, we did update the cardiac flow and alveolar ventilation rate through the parameters k_{Card} and $k_{Q_{AvV}}$. After the decision to neglect the data from [15] in our analysis, k_9 and k_{10} were investigated briefly through the MCMC method using priors based on values from [28]. The intention was to improve the results with catechol and tryhydroxy benzene, but no significant improvement resulted in the fit to data from either the [71] study or the occupational data from [75, 82].

The difference between a model adjustment by increasing the macromolecule binding constants and decreasing predicted inhalation rates is potentially significant because the latter would result in a reduction in the prediction of total phenol and hydroquinone production and hence in potential target tissue dosimetry of active metabolites. Future work on benzene PBPK modeling for humans should probably first seek to implement a more anatomically accurate inhalation model, such as those described by [77, 33] before updating the macromolecule binding constants. If after making such structural changes to eliminate model bias the predicted pharmacokinetic distributions still do not cover the data, we would then have greater support for including other sources of variability and possibly updating their distributions as well.

Given the constraints of fixing many model parameters to standard or previously reported values, the fact that it does a fairly good job of describing the data from two different studies suggests that the model structure is essentially sound and affirms the use of key parameters from *in vitro* or laboratory animal studies. It is fortunate that we have a number of human data for benzene to use in parameter estimation and demonstrate model

quality. However these results should also support similar *in vitro* to *in vivo* and animal to human extrapolations through PBPK modeling for other compounds with fewer or no human data available.

Chapter 3

Sensory Irritation Response in Rats

3.1 Introduction

Airborne irritants, such as formaldehyde, ozone, and chlorine, are capable of stimulating trigeminal nerve endings in the mucosa of the respiratory tract of rodents [6, 7, 13, 59]; and the presence of these chemicals can cause a painful burning sensation [6]. Stimulation of these endings has been shown to decrease respiratory frequency, increase tidal volume, and decrease overall respiratory minute volume in the rat [37] and in mouse neonates [81]. Formaldehyde, on which we will particularly focus, has been shown to be carcinogenic in rodents and is found in the environment as a result of both anthropogenic and natural mechanisms [24].

The decrease in rodent ventilation in the presence of irritants has been established in several studies without the investigation of trigeminal nerve activity. Cassee *et al.* showed minute volume decrease for adult albino male Wistar rats in the presence of formaldehyde, acrolein, acetaldehyde, and mixtures of the three [25]. Chang *et al.* collected data that shows a decrease in respiratory rate due to exposure to formaldehyde for naive rodents (F-344 rats and B₆C₃F₁ mice) and rodents subjected to whole body formaldehyde exposures

prior to the data collection [26]. Both studies showed a recovery in respiration after the exposure period ended.

Studies of the effects of inhaled irritants have often involved air flow and how the chemicals are deposited in the nasal cavity. In [56, 57, 58], studies focused on air flow simulations to predict formaldehyde deposition. Connections were made between fluid dynamic modeling and formaldehyde carcinogenicity in rats in [31]. By looking at flux and chemical disposition, researchers can better predict irritant effects. Modeling the flow disposition of inhaled irritants as in [8, 39, 41] can also aid in the understanding of responses to these chemicals.

In order to best model the overall decrease in minute ventilation due to inhaled irritants, we should incorporate the effects of the trigeminal stimulation as well as the air flow of the chemical through the respiratory tract. Many gases, such as formaldehyde and ammonia, are absorbed rapidly in the upper respiratory tract [48]; and hence, we must incorporate some loss of chemical to the nasal cavity walls in our assessment of chemical location. By considering the sensory activity in response to the presence of irritant in addition to modeling the flow of chemicals through the respiratory tract, we hope to better model the effects on respiration than by directly connecting exposure level to ventilation decrease.

In order to model the nervous response to formaldehyde or other sensory irritants, we need basically two parts to our model: (1) a model for the dosimetry of these reactive gases in the respiratory tract, with particular focus on the upper respiratory tract, and (2) a model of the neurological control of respiration rate due to signaling from the irritant-responsive nerves in the nasal cavity. In other words, we need a model of where the irritant is in the respiratory tract and a model for the response once a significant irritant concentration is in close proximity to the receptors. We can formulate a model for the nasal cavity based on the model from [39], and we can use a set-point function to model the nervous response in a similar way to previous models of the baroreflex-feedback mechanism regulating the cardiovascular system in [69] and [67]. A brief illustration of the system we are modeling is contained in Figure 3.1.

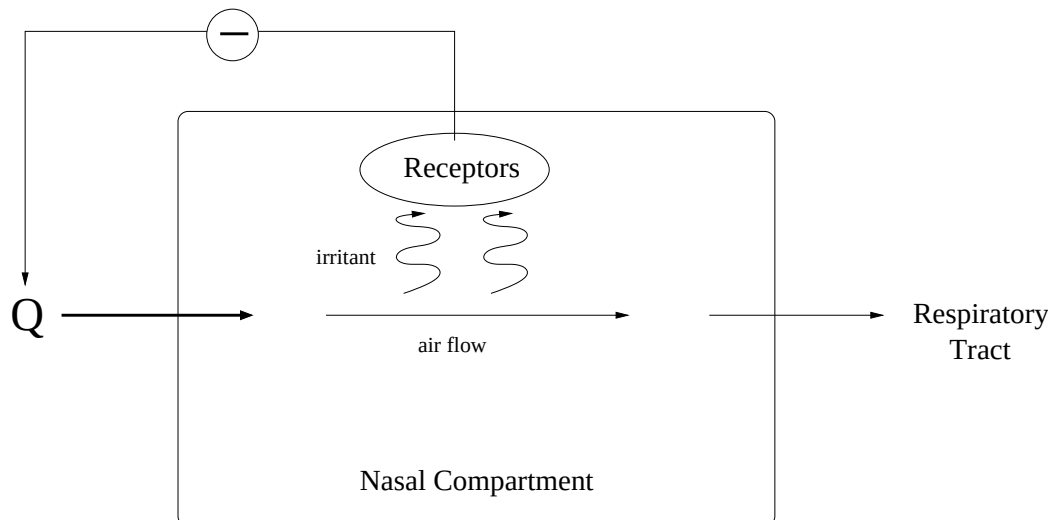


Figure 3.1: Brief illustration of the sensory response to irritants. Q represents the ventilation rate which decreases due to the receptor activity in the presence of irritant.

3.2 Sensory Irritant Model Formulation

3.2.1 Upper Respiratory Model

We will now review the CFD-PBPK model in [39], which is similar in structure to other models such as in [8, 16]; and we will describe how it can be adapted to our current problem. In [39], a hybrid CFD-PBPK inhalation model was developed to evaluate the relationship between inhaled acrylic acid vapor concentration (or air phase) and the tissue concentration (or liquid phase) in various regions of the nasal cavity. Note that computational fluid dynamic simulations were performed to find fixed values in the PBPK model, but the hybrid CFD-PBPK model itself is an ordinary differential equation model. The model was designed to incorporate species-specific anatomy and air flow patterns from CFD analyses and to be used in interspecies extrapolation for risk assessment. A modular description of nasal flow and the calculation of compartmental gas phase mass transfer coefficients for the nasal cavities of both rats and humans were necessary to the model for interspecies extrapolation. Exhalation and inhalation were simulated by alternately reversing unidirectional flow. The compartments were constructed as follows and are illustrated for the rat in Figure 3.2:

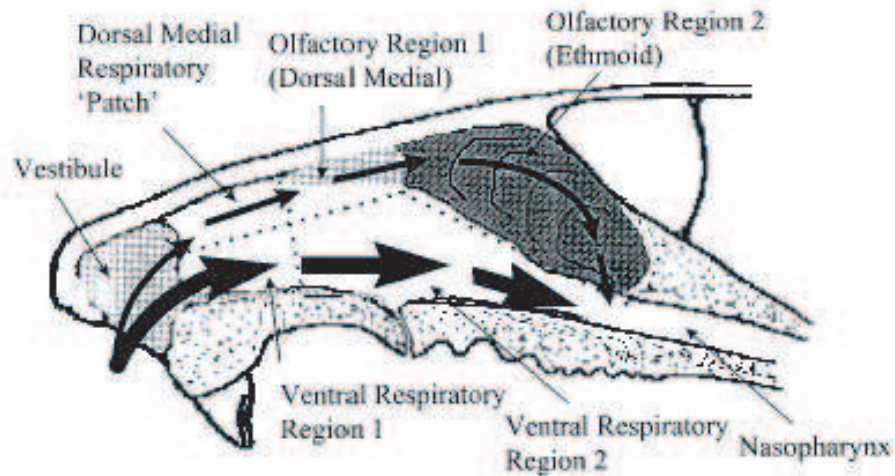


Figure 3.2: Illustration of the rat nasal anatomy divided into compartments corresponding to the epithelium lining the lumen. This illustration was taken from [39] where it was modified from its version in [65].

- Air flows consisted of the following:
 1. all inhaled air flowing across the nasal vestibule
 2.
 - dorsal medial air stream flowing over respiratory epithelium then olfactory epithelium
 - a second composite ventral and lateral air stream flowing over the remaining respiratory epithelium (divided into anterior and posterior compartments)
 3. all air then recombining and passing over a nasopharynx compartment
 4. air then entering a composite lower respiratory tract compartment
- The olfactory region of rodents was divided into a small dorsal anterior compartment and a large compartment representing the remaining olfactory epithelium on the septum and ethmoid turbinates.
- The olfactory region of the human nasal cavity (which does not have an equivalent to ethmoid turbinates) was described by one compartment.

Further, in each compartment, the vapor dosimetry was described in: (1) an air phase, (2) a mucus phase, (3) epithelial phases, and (4) a blood exchange region. In addition to considering the vapor in these phases, the model included a differential equation for the amount of chemical in the mucus buffer. Hence, for each compartment, the model has a system of at least five ordinary differential equations. The first equation for each compartment is the air phase:

$$V_{air} \frac{dC_{air}}{dt} = Q(C_{air-in} - C_{air}) - K_{gc} S_c (C_{air} - [X_{nonionized} C_{muc} / P_{muc:air}]),$$

where

$$\begin{aligned} C_{air} &= \text{concentration of non-ionized vapor exiting air compartment} \quad (\mu\text{mol}/\text{cm}^3) \\ C_{air-in} &= \text{concentration of non-ionized vapor entering air compartment} \quad (\mu\text{mol}/\text{cm}^3) \\ C_{muc} &= \text{total concentration of vapor (ionized \& non-ionized) in the} \\ &\quad \text{mucus layer} \quad (\mu\text{mol}/\text{cm}^3) \\ X_{[non-ionized]} &= \text{fraction of vapor present in non-ionized form} \quad (\text{dimensionless}) \\ P_{muc:air} &= \text{mucus:air partition coefficient of the non-ionized acid} \quad (\text{dimensionless}) \\ V_{air} &= \text{volume of air compartment} \quad (\text{cm}^3) \\ S_c &= \text{surface area of compartment } c \quad (\text{cm}^2) \\ V_{air} &= \text{volume of air in the compartment} \quad (\text{cm}^3) \\ K_{gc} &= \text{compartmental mass transfer coefficient} \quad (\text{cm}/\text{s}) \\ Q &= \text{the air flow in (and out) of the compartment} \quad (\text{cm}^3/\text{s}). \end{aligned}$$

The other phases are then connected to this equation through the movement of the vapor through the mucus and into the epithelium. If we are only concerned with a loss of chemical to the mucosa, we can greatly simplify the model from [39] as follows:

- The model from [39] includes five compartments in the nasal passageway, a dorsal respiratory compartment, two dorsal olfactory compartments, and two ventral respiratory compartments. We considered only using three nasal compartments—one dorsal respiratory compartment, one dorsal olfactory compartment, and one ventral respiratory compartment, but since most similar models do keep all five compartments we decided to be consistent with the other models. See Figure 3.3.
- We are not as concerned with the damage to the tissue in the nasal cavity or details of disposition within the tissue as we are with the overall nasal absorption and transfer of formaldehyde. Therefore we can simplify the removal of vapor from the air phase to a single loss term. Also see Figure 3.3.
- Since the current model will not track formaldehyde chemistry within the mucosa, the concentration of mucus buffer can be ignored and so we will not use this equation in our system at this time.

We can begin the model adaption to our system by looking at the first differential equation in the hybrid CFD-PBPK model that describes the concentration of vapor in the air phase:

$$V_{air} \frac{dC_{air}}{dt} = Q(C_{air-in} - C_{air}) - K_{gc} S_c (C_{air} - [X_{[nonionized]} C_{muc} / P_{muc:air}])). \quad (3.1)$$

The equation (3.1), subsequently altered for our model, could represent the air phase in each of our three respiratory compartments and two olfactory compartments. Since we are only concerned at this time with a loss to the mucosa we could rewrite this equation for the nasal vestibule and each of the five nasal passageway compartments as follows:

$$V_{NV} \frac{dC_{NV}}{dt} = Q(C_{inh} - C_{NV}) - K_{gc,NV} S_{NV} C_{NV} \quad (3.2)$$

$$V_{VR1} \frac{dC_{VR1}}{dt} = f_V Q(C_{NV} - C_{VR1}) - K_{gc,VR1} S_{VR1} C_{VR1} \quad (3.3)$$

$$V_{VR2} \frac{dC_{VR2}}{dt} = f_V Q(C_{VR1} - C_{VR2}) - K_{gc,VR2} S_{VR2} C_{VR2} \quad (3.4)$$

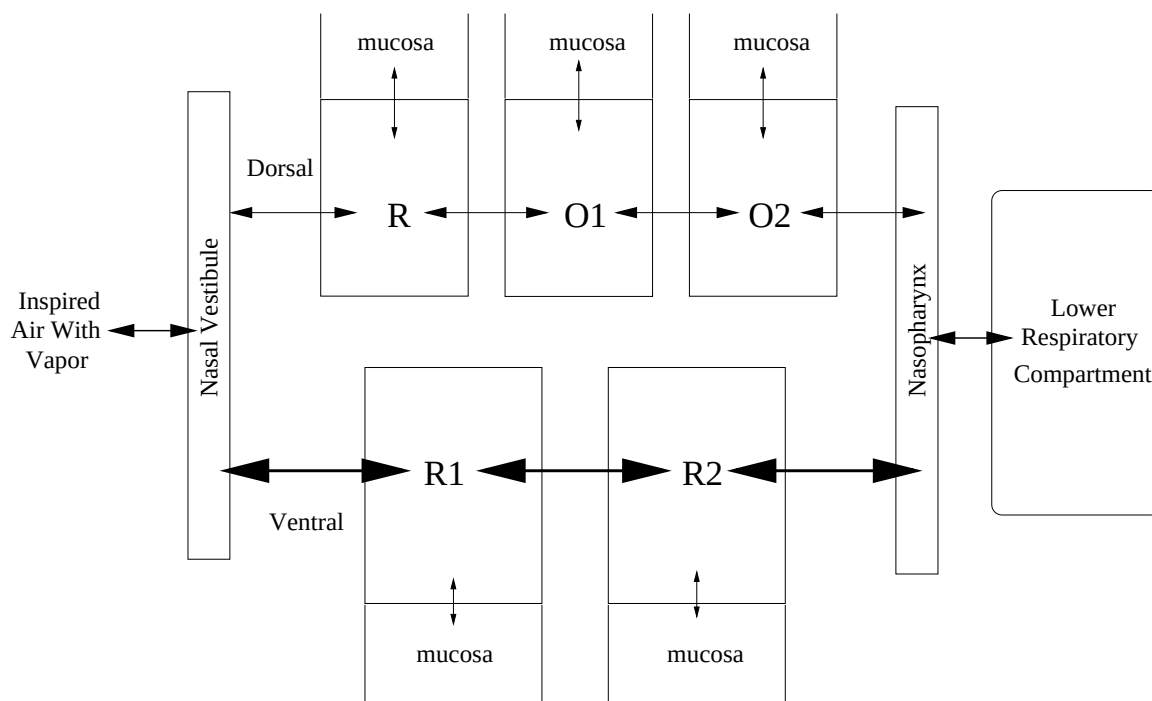


Figure 3.3: Schematic of model simplification.

$$V_{DR} \frac{dC_{DR}}{dt} = f_D Q (C_{NV} - C_{DR}) - K_{gc,DR} S_{DR} C_{DR} \quad (3.5)$$

$$V_{DO1} \frac{dC_{DO1}}{dt} = f_D Q (C_{DR} - C_{DO1}) - K_{gc,DO1} S_{DO1} C_{DO1} \quad (3.6)$$

$$V_{DO2} \frac{dC_{DO2}}{dt} = f_D Q (C_{DO1} - C_{DO2}) - K_{gc,DO2} S_{DO2} C_{DO2}, \quad (3.7)$$

where our compartments are described by NV (the nasal vestibule), $VR1$ and $VR2$ (the ventral respiratory compartments), DR (dorsal respiratory compartment), and $DO1$ and $DO2$ (dorsal olfactory compartments). The other terms are taken from the original model and are as follows:

- C_{inh} = the concentration of formaldehyde being inhaled ($\mu\text{mol}/\text{cm}^3$)
- C_i = concentration of formaldehyde in the given compartment i ($\mu\text{mol}/\text{cm}^3$)
- S_i = surface area of compartment i (cm^2)
- V_i = volume of air in compartment i (cm^3)
- $K_{gc,i}$ = compartmental mass transfer coefficient for compartment i (cm/s)
- f_V, f_D = the fraction of inspired air that goes through the ventral flow and through the dorsal flow, respectively,
 $f_V + f_D = 1$ (*dimensionless*)
- Q = the ventilation rate, i.e., the total air flow rate through the respiratory tract (cm^3/s).

We have simplified the loss terms in order to eliminate the mucus buffer and epithelial equations from the model and to handle the loss of formaldehyde to the respiratory walls. The proper resistance and uptake of formaldehyde is assumed to be included in the $K_{gc,i}$'s. Returning to (3.1) and the simplifications made in (3.2)-(3.7), we could add equations to describe additional compartments in lower parts of the respiratory tract as well:

$$V_{NP} \frac{dC_{NP}}{dt} = Q(f_D C_{DO2} + f_V C_{VR2} - C_{NP}) - K_{gc,NP} S_{NP} C_{NP} \quad (3.8)$$

$$V_{LRC} \frac{dC_{LRC}}{dt} = Q(C_{NP} - C_{LRC}) - K_{gc,LRC} S_{LRC} C_{LRC}. \quad (3.9)$$

Now, the notation is preserved from (3.2)-(3.7) with NP representing the nasopharynx and LRC representing the lower respiratory compartment, which should be clear pictorially from Figure 3.3. We should note that the equations shown in (3.8) and (3.9) are not necessary for the sensory response system we are considering, but they are included in the model formulation in case the lower respiratory tract requires focus in later work.

3.2.2 Nerve Response Control Equation

What remains is to describe our respiration rate (minute volume, although we will use different units), Q , in response to the irritant. We can get an initial model for nervous response by considering a model by J.T. Ottesen [69]. The study in [69] models the baroreflex-feedback mechanism which is the fastest control mechanism regulating human blood pressure. We are interested in this model because its description of the neurological control system could help us derive a control equation for the responses of nerves in the upper respiratory tract of rodents to inhaled irritants. The feedback model in [69] is evaluated using a simple model of the pulsatile cardiovascular system. The model of the feedback mechanism is divided into three parts: (1) the affector part, (2) the central nervous system part, and (3) the effector parts.

The first part of the model (the affector part) includes the part of the carotid sinus where the baroreceptors are located together with baroreceptor nerves. A change in carotid sinus arterial pressure causes deformation in the cross-sectional area of the sinuses (and hence the viscoelastic wall is deformed) which results in a change of activity of the baroreceptor nerves. This nerve activity is denoted as the firing rate; and the firing rate, n , is then described as a function of arterial pressure. In our system we will describe n as a function of the concentration of formaldehyde at the location of receptor nerves. The model for the firing rate n based on arterial pressure—also contained in [68]—is:

$$\Delta \dot{n}_1 = k_1 \dot{P}_c \frac{n(M-n)}{(M/2)^2} - \frac{1}{\tau_1} \Delta n_1 \quad (3.10)$$

$$\Delta \dot{n}_2 = k_2 \dot{P}_c \frac{n(M-n)}{(M/2)^2} - \frac{1}{\tau_2} \Delta n_2 \quad (3.11)$$

$$\Delta \dot{n}_3 = k_3 \dot{P}_c \frac{n(M-n)}{(M/2)^2} - \frac{1}{\tau_3} \Delta n_3, \quad (3.12)$$

where n is the firing rate; M is the maximal firing rate; $\dot{P}_c$ is the time derivative of the pressure at carotid sinus; and Δn_1 , Δn_2 , and Δn_3 denote the deviations from a normal, unstimulated value N . More precisely, N is the steady-state firing rate that occurs with no pressure signal. The equations (3.10), (3.11), and (3.12) each describe the three different time-scale responses from the receptors in the baroreflex system, and hence each Δn_i expresses the difference between the pressure-induced and time-dependent firing rate of that particular receptor and its normal firing rate N_i , i.e.,

$$\Delta n_i = n_i - N_i.$$

Our overall normal firing rate, N , and our total time-dependent firing rate, n , should be the sums of those values from the different receptor types; and hence, the solution to this differential equation system is such that

$$\Delta n_1 + \Delta n_2 + \Delta n_3 = \sum_i n_i - \sum_i N_i = n - N. \quad (3.13)$$

Although the parameters Δn_i can be considered as physically representative, they can also be considered as mathematically internal variables as in [10]. The parameters τ_1 , τ_2 , and τ_3 are time constants and describe the characteristic adaptation phenomenon measured, each depending on different kinds of receptors. The parameters k_1 , k_2 , and k_3 are weighting constants describing the contribution for each receptor type. We can also rewrite the above set of equations in integral form:

$$n = N + \int_{-\infty}^t (k_1 e^{-((t-s)/\tau_1)} + k_2 e^{-((t-s)/\tau_2)} + k_3 e^{-((t-s)/\tau_3)}) \left[\dot{P}_c \frac{n(M-n)}{(M/2)^2} \right] ds. \quad (3.14)$$

In our case we only consider one time scale of the irritant receptor, but the receptors are distributed in multiple tissue compartments. Hence, where Ottesen had equations for $\Delta \dot{n}_1$, $\Delta \dot{n}_2$, and $\Delta \dot{n}_3$, we will have an equation $\Delta \dot{n}_i$ for each tissue compartment, i . Since the same time scale is assumed for all receptors, a single adaptation time constant, τ_r , is assumed for all compartments. The relative contribution of each compartment, k_i , will depend on the intrinsic sensitivity of the receptor to a chemical, and we will denote that sensitivity k_0 . We will also include w_i , weighting factors for each compartment that will depend on nerve receptor number in the compartment. Additionally, where the model of Ottesen has a linear (multiplicative) dependence on pressure, we expect a response due to chemical concentration that will depend on occupancy of chemical receptors on the nerve receptor surface. In [47], the authors use a simple saturable model for chemical receptor occupancy in a model of nasal pungency:

$$occupancy = \frac{C}{C + K_D}, \quad (3.15)$$

where C is the concentration of the chemical in the tissue compartment and K_D is the receptor-chemical dissociation constant. Hau *et al.* [47] write their equation in terms of the association constant, $K_A = 1/K_D$, but (3.15) is equivalent to theirs. Note also that here we distinguish between the molecular chemical receptors that exist on the surface of irritant-sensitive nerves, referred to as nerve receptors above. Hau and colleagues go on to state that a minimum level of chemical receptor occupancy, or threshold, must be exceeded before an odor is detected. It is not clear that the “pungency” receptors considered in [47] are the same as the irritant receptors we wish to model, but it seems appropriate to introduce a threshold parameter, r_0 , that can be set to zero or greater than zero as indicated by the data. So the chemical receptor signal function we will use is

$$r(C) = \begin{cases} \frac{C}{C+K_D} - r_0, & \frac{C}{C+K_D} > r_0 \\ 0, & \frac{C}{C+K_D} \leq r_0. \end{cases} \quad (3.16)$$

After normalizing over the maximum firing rate (M), the nerve firing rate equation for compartment i then becomes

$$\Delta \dot{n}'_i = w_i k_0 r(C_i) n'_i (1 - n'_i) - \frac{\Delta n'_i}{\tau_r} \quad (3.17)$$

with $n' = n/M$ and with threshold firing rate $N' = N/M$. Note that we now consider n' as a firing rate relative to the maximum rate. For our system we will be considering $N' = 0$, i.e., that the receptors are essentially dormant prior to stimulation. Further reasoning for this choice will be discussed in the formulation of the differential equation for respiration Q . With $N' = 0$, our initial $\Delta n'_i$'s would also be zero, and this would leave (3.17) with only a trivial solution of $n(t) = 0$. In order to have a physical reasonable solution we replace $n'_i(1 - n'_i)$ with

$$\frac{(n' + \delta)(1 - n')}{(1 + \delta)^2},$$

where δ is chosen to be small. The formulation above gives a nontrivial solution for n , but the addition of the δ term is essentially artificial. For simplicity, the primes will be dropped from this point on, but one should understand that n is now a relative firing rate and exists in the interval $[0, 1]$. Hence, our differential equation system becomes

$$\Delta \dot{n}_{VR1} = w_{VR1} k_0 r(C_{VR1}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{VR1}}{\tau_r} \quad (3.18)$$

$$\Delta \dot{n}_{VR2} = w_{VR2} k_0 r(C_{VR2}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{VR2}}{\tau_r} \quad (3.19)$$

$$\Delta \dot{n}_{DR} = w_{DR} k_0 r(C_{DR}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DR}}{\tau_r} \quad (3.20)$$

$$\Delta \dot{n}_{DO1} = w_{DO1} k_0 r(C_{DO1}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO1}}{\tau_r} \quad (3.21)$$

$$\Delta \dot{n}_{DO2} = w_{DO2} k_0 r(C_{DO2}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO2}}{\tau_r}, \quad (3.22)$$

and our equivalent to (3.14) would be

$$\begin{aligned}
 n = N + \int_{-\infty}^t k_0 [w_{VR1} \cdot r(C_{VR1}) + w_{VR2} \cdot r(C_{VR1}) + w_{DR} \cdot r(C_{DR}) \\
 + w_{DO1} \cdot r(C_{DO1}) + w_{DO2} \cdot r(C_{DO2})] e^{-((t-s)/\tau_r)} \left[\frac{(n+\delta)(1-n)}{(1+\delta)^2} \right] ds. \quad (3.23)
 \end{aligned}$$

Note that in (3.18)-(3.22), we have preserved the basic behavior of the original model with the exception of the replacement of $r(C_i)$, which is described by (3.16), for $\dot{P}_c$.

The central nervous system part in [69] incorporates the parasympathetic and sympathetic responses which are based on the firing rate. Since we are primarily concerned with the response in ventilation and since the effector portion of the model does not depend on the central nervous system part, we will ignore parasympathetic and sympathetic responses. The third part of the model which is concerned with the effector parts of the system formulates ordinary differential equations for the control inputs (heart rate, contractibility, and resistance in the original model; ventilation for our purposes) based on set point functions and incorporating the firing rate, i.e.,

$$\frac{dx}{dt} = f(n), \quad (3.24)$$

for a function f where x is our control input. More specifically, the third part of the model in [69] is described by

$$x_{steady}(n) = \frac{x_{max} - x_{min}}{1 + \alpha(n/N)^p} + x_{min}, \quad (3.25)$$

where x in [69] represents heart rate, contractivity, or resistance; p controls the steepness of the sigmoid; and

$$\alpha = \frac{x_{max} - x_0}{x_0 - x_{min}}, \quad (3.26)$$

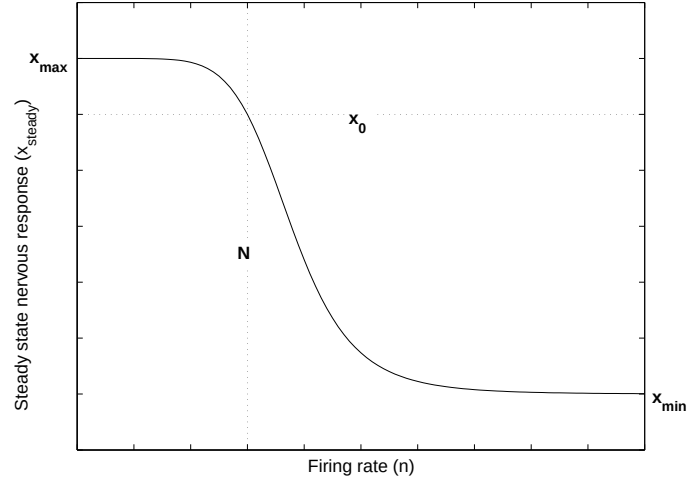


Figure 3.4: An example of a control function x_{steady} .

where x_0 is the desired value of x at $n = N$, x_{min} and x_{max} are the minimal and maximal values of x , n is the time-dependent firing rate, and N is normal firing rate. For the nervous response system, the response variable will be ventilation, Q . Returning to (3.18)-(3.22), note that when there is no chemical exposure, i.e. if $C_i = 0$ for all compartments, then the solution for n is $n = N = 0$. Hence, n/N would be undefined, so a modification of (3.25) will be needed for our model. An example of a sigmoidal function is contained in Figure 3.4 to illustrate the shape of x_{steady} . In particular,

$$\dot{x}(t) = \frac{1}{\tau_x}(x_{steady}(n) - x(t)), \quad (3.27)$$

where τ_x is the “characteristic time constant describing the transient.” First of all, we must slightly change the formulation of $x_{steady}(n)$ to be an appropriate $Q_{steady}(n)$. Biologically, we are unsure of an appropriate Q_{max} that exists above the ventilation under normal conditions, i.e., the ventilation rate when $n = N$. Hence, we will assume that the normal ventilation at base firing rate is its maximum and that $Q_{max} = Q_0$. Further, we must note that this causes a problem with the current setup because

$$\begin{aligned}
x_{max} &= x_0 = \frac{x_{max} - x_{min}}{1 + \alpha(N/N)^p} + x_{min} \\
&= \frac{x_{max} - x_{min}}{1 + \alpha} + x_{min} \\
\Rightarrow \left(1 - \frac{1}{1 + \alpha}\right) x_{max} &= \left(1 - \frac{1}{1 + \alpha}\right) x_{min} \\
\Rightarrow x_{max} &= x_{min}.
\end{aligned}$$

Since we would have a trivial system with our maximum and minimum values equal, we must change the equation to fit with the restriction that $Q_{max} = Q_0$. If we replace n/N with n and use the following representation of $Q_{steady}(n)$:

$$Q_{steady}(n) = \frac{Q_{max} - Q_{min}}{1 + \alpha n^p} + Q_{min}, \quad (3.28)$$

we see that we will have a similar problem unless we set the initial value of n equal to zero. Note that we could not leave $Q_{steady}(n)$ in the same format as the original $x_{steady}(n)$ from [69] with $N = 0$ because we would have a division by zero. Note that $Q_{steady}(n)$ will not ever reach Q_{min} . If n reaches its maximum of 1, the minimum for $Q_{steady}(n)$ would be

$$\frac{Q_{max} + \alpha Q_{min}}{1 + \alpha}.$$

We should also note that we choose $Q_{steady}(0) = Q_{max} = Q_0$ regardless of α . Hence we will not have an automatic representation for α as in the model from [69], and α will be determined by data. With the formulation in (3.28), we consider

$$\frac{dQ}{dt} = \frac{1}{\tau_Q} (Q_{steady}(n) - Q(t)). \quad (3.29)$$

We should observe that this control equation is used for a response that decreases as a function of firing rate, and ventilation should decrease as the nerves fire in response to

formaldehyde concentration. Therefore, we know that the proposed control equation (3.28)–and further, (3.27)–does make sense with our biological system. The simplification could be made to bypass the firing function and just consider dQ/dt as a function of a combination of concentrations in appropriate compartments. The formation of the controlled parameters in [67] is similar to the setup in [69] but does not incorporate n . We could also (or alternately) bypass the time-dependence of the respiration response (3.29) and simply equate Q with the function for Q_{steady} . We will, however, not explore this opportunity here. Our complete differential equation system is contained in Appendix B.

We recognize that other models or modifications of our model could be used as we will discuss further in Section 3.7. One could assume that n reaches a pseudo-steady-state so quickly that we could just consider a function for n formulated by setting all $\Delta n_i = 0$. This option was considered, but with $N = 0$ the parameters k_0 and τ_r only appear when multiplied together in the steady-state function for n . Hence, it would be difficult to optimize over those two parameters and find any individual information about either, and we decided to keep the model for n as it is in (3.18)–(3.22). We did still examine and explore a steady-state function in order to aid our analysis, and that analysis is contained in Section 3.5.

Most physiological parameters seem to be accessible biologically, but most of the parameters in the response part of the model should be identified using experimental data. Specifically the parameters p , τ_r , k_0 , τ_Q , α , and K_D should be determined through optimization. Assuming the nerves respond quickly and for simplicity, r_0 will be set to zero; and we can optimize the six parameters noted above with the use of available data. Presumably, the nerve adaptation time-constant, τ_r , will be informed by respiration responses after longer-term exposures. We recognize that minute ventilation is the product of tidal volume and respiration frequency, i.e.,

$$Q = TV * f_{resp}, \quad (3.30)$$

and that control of minute ventilation occurs through control of these two components. In this initial model we have lumped them together into the net ventilation rate, Q ; but they can potentially be modeled as separate entities since the two components of overall ventilation may indeed be differently affected by the presence of irritant [37, 81].

3.2.3 Fixed Parameter Values of the Respiratory Response Model

Fixed parameter values were taken from various sources, and the parameter values used in the respiratory model are contained in Table 3.1. Note that the lower respiratory compartment value for surface area taken from [85] was estimated by adding the total alveolar surface area to the surface area after 24 branches in the whole lung model as listed in Table 2 of that particular reference. Note that this parameter (as well as other parameters connected to the nasopharynx and lower respiratory compartment) is not necessary for the computation of sensory response and hence, not critical to our fit to data. We should note that the values for f_V and f_D taken from [16] were very close to values found by averaging over simulation flow rates from Table 4 in [39] (0.8300 and 0.1644). The $K_{gc,i}$ values were taken from [39] but were altered to be appropriate for the proper molecular weight. All the simulations were assumed to be for formaldehyde in order to match with data from [25] and since the values in [39] were for acrylic acid, the following conversion was used:

$$K_{gc,i\text{formaldehyde}} = K_{gc,i\text{acrylic acid}} \sqrt{\frac{MW_{\text{acrylic acid}}}{MW_{\text{formaldehyde}}}},$$

where MW indicates molecular weight. The $K_{gc,NP}$ value for acrylic acid was used in the computation of both $K_{gc,NP}$ and $K_{gc,LRC}$ for formaldehyde.

The fixed parameters from the sensory response portion of the model are contained in Table 3.2. Table 3.1 and Table 3.2 do not contain any parameters found through optimization. Since the model will never reach the value Q_{min} , Q_{min} was assumed to be zero and not set at that value from a specific source. A similar assumption was made in setting $r_0 = 0$ as was mentioned previously. The value for Q_{max} was found by taking the mean of normoxia values (for both males and females) from Table 1 in [66] and correcting for proper units. We should note that the w_i values are dimensionless because we have constructed n to be a relative measure and hence are dimensionless as well. The w_i 's were estimated from Figure 5 from [79]. Our values for the w_i 's are very much beginning estimations since our nasal compartments (e.g., $VR1$) are constructs to approximate physiology, and we recognize that our values for all w_i could be improved. The study in [79] does suggest greater nerve activity in the olfactory tissue and in the posterior regions of the nasal cavity which led to our chosen values of w_i . Errors in this parameter would be absorbed into our results for k_0 .

3.3 Existence and Uniqueness of the Sensory Irritant Model

Before we compare our model to data we must first evaluate the model itself and the nature of the solution to the model. In this section we will consider a general form

Table 3.1: Values of fixed parameters used in the respiratory portion of the sensory irritant model.

Parameter	Value	Units	Source
S_{NV}	0.44	cm^2	[39]
S_{VR1}	1.8	cm^2	[39]
S_{VR2}	4.5	cm^2	[39]
S_{DR}	0.2	cm^2	[39]
S_{DO1}	0.42	cm^2	[39]
S_{DO2}	6.33	cm^2	[39]
S_{NP}	0.1	cm^2	[39]
S_{LRC}	5823	cm^2	[85]
V_{NV}	0.01	cm^3	[39]
V_{VR1}	0.09	cm^3	[39]
V_{VR2}	0.09	cm^3	[39]
V_{DR}	0.004	cm^3	[39]
V_{DO1}	0.012	cm^3	[39]
V_{DO2}	0.054	cm^3	[39]
V_{NP}	0.001	cm^3	[39]
V_{LRC}	13.7	cm^3	[85]
f_V	0.86	dimensionless	[16]
f_D	0.14	dimensionless	[16]
$K_{gc,NV}$	0.0175	cm/s	[39]
$K_{gc,VR1}$	1546.13	cm/s	[39]
$K_{gc,VR2}$	1813.81	cm/s	[39]
$K_{gc,DR}$	249.23	cm/s	[39]
$K_{gc,DO1}$	142.11	cm/s	[39]
$K_{gc,DO2}$	2393.62	cm/s	[39]
$K_{gc,NP}$	0.155	cm/s	[39]
$K_{gc,LRC}$	0.155	cm/s	[39]

Table 3.2: Values of fixed parameters used in the sensory response portion of the sensory irritant model.

Parameter	Value	Units	Source
Q_{min}	0	cm^3/s	assumption
Q_{max}	2.9625	cm^3/s	[66]
w_{VR1}, w_{VR2}, w_{DR}	1	dimensionless	[79]
w_{DO1}, w_{DO2}	2	dimensionless	[79]
r_0	0	dimensionless	assumption
δ	0.001	dimensionless	chosen

of our model, $\dot{x} = g(x)$, and show that the solution to our model exists and is unique. We will establish existence and uniqueness by showing that the model is locally Lipschitz continuous.

Let us consider our differential equation model described by:

$$\dot{x} = g(x) \tag{3.31}$$

with initial condition $x(t_0) = x_0$. Note that

$$g(x) : U \rightarrow \mathbb{R}^n$$

where U is an open subset of $\mathbb{R}^n$, $x_0 \in \mathbb{R}^n$, and $t_0 \in \mathbb{R}$. In order to show that the solution to (3.31) both exists and is unique, we will first establish that g locally satisfies the Lipschitz condition, i.e.,

$$\|g_i(\phi) - g_i(\psi)\| \leq K\|\phi - \psi\| \tag{3.32}$$

for all $\phi, \psi \in U$ [19] for all components i . By examining g component by component, we can determine if g is locally Lipschitz. Before we begin to go through establishing that g is locally Lipschitz, we should point out that all of the states in the sensory irritant model are bounded. The equation for ventilation is constructed such that the maximum value of Q is the appropriately denoted Q_{max} . The states C_i cannot be any bigger than the dosage level C_{inh} because that is the only positive addition to the system (mathematically as well as biologically, incidentally). In the formulation of the equations for Δn_i , the derivatives are set such that the Δn_i values will decrease once n reaches 1 and hence, $\Delta n_i \leq 1$ for all $i = VR1, VR2, DR, DO1, DO2$. More succinctly, all states x_i satisfy

$$|x_i| < L, \quad \forall i. \tag{3.33}$$

If $x_0 = 0$ we can easily see that $L = \max\{C_{inh}, 1, Q_{max}\}$ although L would only differ from this if the maximum initial compartmental concentration was above C_{inh} .

In order to show that the model is Lipschitz, let us first establish the following lemma:

Lemma 1. *If $p \geq 0$ and X and Y are such that $0 \leq X, Y < C_1$ for some positive C_1 , then*

$$|Y^p - X^p| \leq \tilde{C} |Y - X| \quad (3.34)$$

where $\tilde{C}$ is a positive constant.

Proof. Note that for fixed $p \geq 0$, (3.34) follows from the Mean Value Theorem. $\square$

Remark 1. *Note that we could use the same logic to prove (3.34) under the less restrictive condition of finite p as long if we use a more restrictive condition on X and Y , i.e., if $0 < X, Y < C_1$.*

In our sensory irritation model each component function g_i has the following form for $i = 1, 2, \dots, 14$:

$$\begin{aligned} g_i(x) = & A_i x_q H(x_q) (a_i + b_i x_j H(x_j) + c_i x_k H(x_k) - d_i x_i H(x_i)) - B_i x_i H(x_i) \\ & + C_i \frac{x_v H(x_v)}{x_v H(x_v) + K_D} \left[\left(\sum_{n=l}^m x_n H(x_n) + \delta \right) \left(1 - \sum_{n=l}^m x_n H(x_n) \right) \right] \\ & + D_i \left[\frac{\beta}{1 + \alpha (\sum_{n=l}^m x_n H(x_n))^p} - x_q H(x_q) \right] + E_i. \end{aligned} \quad (3.35)$$

The function listed in (3.35) follows these guidelines:

- $A_i, B_i, C_i, D_i, E_i, a_i, b_i, c_i$, and d_i are nonnegative constants for all i .
- The indices j and k denote components of x other than i , specifically x_j and x_k denote compartmental irritant concentrations anterior to x_i , when x_i is also a compartmental concentration. (When x_i represents a state other than a compartmental concentration, $A_i = 0$.)
- β is a positive constant.
- The indices l and m indicate that for $i = l, l+1, \dots, m$, $x_i = \Delta n_i$, i.e., in the summation only a portion of the components of x are involved.
- The index q specifically refers to the component of x that represents respiration ($x_q = Q$) and $D_i = 0$ unless $i = q$.
- The index v indicates the appropriate concentrational component state for the current state i . The state indicated by v should not be the same state as indicated by i because that portion of the differential equation system corresponds to the Δn_i 's and v must represent the irritant concentration in the appropriate compartment, e.g. if $x_i = \Delta n_{VR1}$, then $x_v = C_{VR1}$.
- The function $H(x)$ is the Heaviside function given by

$$H(x) = \begin{cases} 1, & x_i \geq 0 \\ 0, & x_i < 0 \end{cases}.$$

We employ the use of the Heaviside function because our system is not biologically reasonable for negative components for x .

We will first show that each g_i locally satisfies the Lipschitz condition (3.32), and thus g is locally Lipschitz. Let the neighborhood $N_\epsilon(x_0)$ be such that

$$N_\epsilon(x_0) = \{x \in \mathbb{R}^n \mid \|x - x_0\| < \epsilon\}$$

where $\epsilon > 0$ and $\|\cdot\|$ is any equivalent norm in $\mathbb{R}^n$. Let ϕ and ψ be vectors in $N_\epsilon(x_0)$. We begin by looking at the difference in g_i evaluated at ϕ and ψ .

$$\begin{aligned}
|g_i(\phi) - g_i(\psi)| &= |A_i\phi_q H(\phi_q)[a_i + b_i\phi_j H(\phi_j) + c_i\phi_k H(\phi_k) - d_i\phi_i H(\phi_i)] - B_i\phi_i H(\phi_i) \\
&\quad + C_i \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \left[\left(\sum_{n=l}^m \phi_n H(\phi_n) + \delta \right) \left(1 - \sum_{n=l}^m \phi_n H(\phi_n) \right) \right] \\
&\quad + D_i \left[\frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p} - \phi_q H(\phi_q) \right] + E_i \\
&\quad - \{ A_i\psi_q H(\psi_q)[a_i + b_i\psi_j H(\psi_j) + c_i\psi_k H(\psi_k) - d_i\psi_i H(\psi_i)] - B_i\psi_i H(\psi_i) \\
&\quad + C_i \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \left[\left(\sum_{n=l}^m \psi_n H(\psi_n) + \delta \right) \left(1 - \sum_{n=l}^m \psi_n H(\psi_n) \right) \right] \\
&\quad + D_i \left[\frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p} - \psi_q H(\psi_q) \right] + E_i \} \\
&= |A_i\phi_q H(\phi_q)[b_i\phi_j H(\phi_j) + c_i\phi_k H(\phi_k) - d_i\phi_i H(\phi_i)] \\
&\quad - A_i\psi_q H(\psi_q)[b_i\psi_j H(\psi_j) + c_i\psi_k H(\psi_k) - d_i\psi_i H(\psi_i)] \\
&\quad + A_i a_i (\phi_q H(\phi_q) - \psi_q H(\psi_q)) - B_i (\phi_i H(\phi_i) - \psi_i H(\psi_i)) \\
&\quad + C_i \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \left[(1 - \delta) \sum_{n=l}^m \phi_n H(\phi_n) + \delta - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right] \\
&\quad - C_i \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \left[(1 - \delta) \sum_{n=l}^m \psi_n H(\psi_n) + \delta - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 \right] \\
&\quad + D_i \left[\frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p} - \phi_q H(\phi_q) \right]
\end{aligned}$$

$$\begin{aligned}
& \left\| -D_i \left[\frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p} - \psi_q H(\psi_q) \right] \right\| \\
= & \quad |A_i b_i \phi_q H(\phi_q) \phi_j H(\phi_j) - A_i b_i \psi_q H(\psi_q) \psi_j H(\psi_j) \\
& + A_i c_i \phi_q H(\phi_q) \phi_k H(\phi_k) - A_i c_i \psi_q H(\psi_q) \psi_k H(\psi_k) \\
& - d_i A_i \phi_q H(\phi_q) \phi_i H(\phi_i) + d_i A_i \psi_q H(\psi_q) \psi_i H(\psi_i) \\
& + A_i a_i [\phi_q H(\phi_q) - \psi_q H(\psi_q)] + B_i [\psi_i H(\psi_i) - \phi_i H(\phi_i)] \\
& + C_i (1 - \delta) \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \sum_{n=l}^m \phi_n H(\phi_n) \\
& - C_i (1 - \delta) \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \sum_{n=l}^m \psi_n H(\psi_n) \\
& + \delta C_i \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} - \delta C_i \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \\
& - C_i \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 + C_i \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 \\
& + D_i \frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p} - D_i \frac{\beta}{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p} \\
& - D_i \phi_q H(\phi_q) + D_i \psi_q H(\psi_q) \quad | \\
= & \quad |A_i b_i [\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)] \\
& + A_i c_i [\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)] \\
& + A_i d_i [\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)] \\
& + A_i a_i [\phi_q H(\phi_q) - \psi_q H(\psi_q)] + B_i [\psi_i H(\psi_i) - \phi_i H(\phi_i)] \\
& + D_i [\psi_q H(\psi_q) - \phi_q H(\phi_q)]
\end{aligned}$$

$$\begin{aligned}
& +C_i(1-\delta) \left(\frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \sum_{n=l}^m \phi_n H(\phi_n) - \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \sum_{n=l}^m \psi_n H(\psi_n) \right) \\
& +\delta C_i \left(\frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} - \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \right) \\
& +C_i \left(\frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 - \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right) \\
& +D_i \beta \left(\frac{1}{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p} - \frac{1}{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p} \right) \Bigg| \\
\leq & A_i b_i |\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)| \\
& +A_i c_i |\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)| \\
& +A_i d_i |\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)| \\
& +(A_i a_i + D_i) |\phi_q H(\phi_q) - \psi_q H(\psi_q)| + B_i |\psi_i H(\psi_i) - \phi_i H(\phi_i)| \\
& +C_i(1-\delta) \left| \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \sum_{n=l}^m \phi_n H(\phi_n) - \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \sum_{n=l}^m \psi_n H(\psi_n) \right| \\
& +\delta C_i \left| \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} - \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \right| \\
& +C_i \left| \frac{\psi_v H(\psi_v)}{\psi_v H(\psi_v) + K_D} \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 - \frac{\phi_v H(\phi_v)}{\phi_v H(\phi_v) + K_D} \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right| \\
& +D_i \beta \left| \frac{1}{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p} - \frac{1}{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p} \right| \tag{3.36}
\end{aligned}$$

Now, we must show that (3.36) satisfies the condition (3.32). In order to do this, we must first recognize some particular aspects of our problem. First of all, $0 < \delta < 1$ so we know that $(1 - \delta) > 0$. We should also note that for fixed K_D and fixed p , the boundedness of

our solutions implies that

$$\left| \frac{1}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \right| < M < \infty \quad (3.37)$$

and

$$\left| \frac{1}{\left(1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n)\right)^p\right) \left(1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n)\right)^p\right)} \right| \leq 1. \quad (3.38)$$

Further,

$$\begin{aligned} |g_i(\phi) - g_i(\psi)| &\leq A_i b_i |\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)| \\ &\quad + A_i c_i |\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)| \\ &\quad + A_i d_i |\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)| \\ &\quad + (A_i a_i + D_i) |\phi_q H(\phi_q) - \psi_q H(\psi_q)| + B_i |\psi_i H(\psi_i) - \phi_i H(\phi_i)| \\ &\quad + C_i (1 - \delta) \sum_{n=l}^m \left| \frac{\phi_v H(\phi_v) \phi_n H(\phi_n) (\psi_v H(\psi_v) + K_D)}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \right. \\ &\quad \left. - \frac{\psi_v H(\psi_v) \psi_n H(\psi_n) (\phi_v H(\phi_v) + K_D)}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \right| \\ &\quad + \delta C_i \left| \frac{\phi_v H(\phi_v) (\psi_v H(\psi_v) + K_D)}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \right. \\ &\quad \left. - \frac{\psi_v H(\psi_v) (\phi_v H(\phi_v) + K_D)}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \right| \\ &\quad + C_i \left| \frac{\psi_v H(\psi_v) (\phi_v H(\phi_v) + K_D)}{(\psi_v H(\psi_v) + K_D)(\phi_v H(\phi_v) + K_D)} \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 \right. \end{aligned}$$

$$\begin{aligned}
& - \frac{\phi_v H(\phi_v)(\psi_v H(\psi_v) + K_D)}{(\phi_v H(\phi_v) + K_D)(\psi_v H(\psi_v) + K_D)} \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \Bigg| \\
& + D_i \beta \left| \frac{1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p}{\left(1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right) \left(1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right)} \right. \\
& \quad \left. - \frac{1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p}{\left(1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right) \left(1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right)} \right| \\
\leq & A_i b_i |\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)| \\
& + A_i c_i |\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)| \\
& + A_i d_i |\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)| \\
& + (A_i a_i + D_i) |\phi_q H(\phi_q) - \psi_q H(\psi_q)| + B_i |\psi_i H(\psi_i) - \phi_i H(\phi_i)| \\
& + C_i M (1 - \delta) \sum_{n=l}^m |\phi_v H(\phi_v) \phi_n H(\phi_n) (\psi_v H(\psi_v) + K_D) \\
& \quad - \psi_v H(\psi_v) \psi_n H(\psi_n) (\phi_v H(\phi_v) + K_D)| \\
& + \delta C_i M |\phi_v H(\phi_v) (\psi_v H(\psi_v) + K_D) - \psi_v H(\psi_v) (\phi_v H(\phi_v) + K_D)| \\
& + C_i M \left| \psi_v H(\psi_v) (\phi_v H(\phi_v) + K_D) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 \right. \\
& \quad \left. - \phi_v H(\phi_v) (\psi_v H(\psi_v) + K_D) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right| \\
& + D_i \beta \left| \left[1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right] - \left[1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right] \right| \\
\leq & A_i b_i |\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)| \\
& + A_i c_i |\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)|
\end{aligned}$$

$$\begin{aligned}
& +A_i d_i |\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)| \\
& + (A_i a_i + D_i) |\phi_q H(\phi_q) - \psi_q H(\psi_q)| + B_i |\psi_i H(\psi_i) - \phi_i H(\phi_i)| \\
& + C_i M (1 - \delta) |\phi_v H(\phi_v)| |\psi_v H(\psi_v)| \sum_{n=l}^m |\phi_n H(\phi_n) - \psi_n H(\psi_n)| \\
& + C_i M (1 - \delta) K_D \sum_{n=l}^m |\phi_v H(\phi_v) \phi_n H(\phi_n) - \psi_v H(\psi_v) \psi_n H(\psi_n)| \\
& + \delta C_i M K_D |\phi_v H(\phi_v) - \psi_v H(\psi_v)| \\
& + C_i M |\psi_v H(\psi_v)| |\phi_v H(\phi_v)| \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right| \\
& + C_i M K_D \left| \psi_v H(\psi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 - \phi_v H(\phi_v) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right| \\
& + D_i \alpha \beta \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right|. \tag{3.39}
\end{aligned}$$

Now, before proceeding we should consider one term in particular. Note that

$$\begin{aligned}
& \left| \psi_v H(\psi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 - \phi_v H(\phi_v) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right| \\
& = \left| \psi_v H(\psi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^2 \right. \\
& \quad \left. - \psi_v H(\psi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right. \\
& \quad \left. + \psi_v H(\psi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right. \\
& \quad \left. - \phi_v H(\phi_v) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \right|
\end{aligned}$$

$$\begin{aligned}
& -\phi_v H(\phi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \\
& + \phi_v H(\phi_v) \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \\
& - \phi_v H(\phi_v) \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^2 \Big| \\
\leq & |\psi_v H(\psi_v)| \left| \sum_{n=l}^m \psi_n H(\psi_n) \right| \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)| \\
& + \left| \sum_{n=l}^m \psi_n H(\psi_n) \right| \left| \sum_{n=l}^m \phi_n H(\phi_n) \right| |\psi_v H(\psi_v) - \phi_v H(\phi_v)| \\
& + |\phi_v H(\phi_v)| \left| \sum_{n=l}^m \phi_n H(\phi_n) \right| \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)|.
\end{aligned}$$

Hence, we can rewrite this particular piece as less than

$$\begin{aligned}
& \left(|\psi_v H(\psi_v)| \left| \sum_{n=l}^m \psi_n H(\psi_n) \right| + |\phi_v H(\phi_v)| \left| \sum_{n=l}^m \phi_n H(\phi_n) \right| \right) \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)| \\
& + \left| \sum_{n=l}^m \psi_n H(\psi_n) \right| \left| \sum_{n=l}^m \phi_n H(\phi_n) \right| |\psi_v H(\psi_v) - \phi_v H(\phi_v)|. \tag{3.40}
\end{aligned}$$

Using (3.40), Lemma 1, and the boundedness of our solutions (3.33), we can see that we can further rewrite (3.39) as

$$|g_i(\phi) - g_i(\psi)| \leq A_i b_i |\phi_q H(\phi_q) \phi_j H(\phi_j) - \psi_q H(\psi_q) \psi_j H(\psi_j)|$$

$$\begin{aligned}
& +A_i c_i |\phi_q H(\phi_q) \phi_k H(\phi_k) - \psi_q H(\psi_q) \psi_k H(\psi_k)| \\
& +A_i d_i |\psi_q H(\psi_q) \psi_i H(\psi_i) - \phi_q H(\phi_q) \phi_i H(\phi_i)| \\
& +(A_i a_i + D_i) |\phi_q H(\phi_q) - \psi_q H(\psi_q)| + B_i |\psi_i H(\psi_i) - \phi_i H(\phi_i)| \\
& +C_i M(1-\delta) L^2 \sum_{n=l}^m |\phi_n H(\phi_n) - \psi_n H(\psi_n)| \\
& +C_i M(1-\delta) K_D \sum_{n=l}^m |\phi_v H(\phi_v) \phi_n H(\phi_n) - \psi_v H(\psi_v) \psi_n H(\psi_n)| \\
& +\delta C_i M K_D |\phi_v H(\phi_v) - \psi_v H(\psi_v)| \\
& +C_i M L^2 \tilde{C} \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)| \\
& +10 L^2 C_i M K_D \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)| \\
& +25 L^2 C_i M K_D |\psi_v H(\psi_v) - \phi_v H(\phi_v)| \\
& +D_i \alpha \beta \tilde{C} \sum_{n=l}^m |\psi_n H(\psi_n) - \phi_n H(\phi_n)|. \tag{3.41}
\end{aligned}$$

In order to show that (3.41) is less than a constant times the norm of our difference, $\|\phi - \psi\|$, we must deal with the different pieces and with the Heaviside function. Note that each piece on the right-hand side of (3.41) is of the form either

$$|\phi_a H(\phi_a) - \psi_a H(\psi_a)| \tag{3.42}$$

or

$$|\phi_a H(\phi_a) \phi_b H(\phi_b) - \psi_a H(\psi_a) \psi_b H(\psi_b)| \tag{3.43}$$

where a and b simply indicate where the indices differ. Now, let us first consider (3.42) and its various cases:

- If $\phi_a, \psi_a \geq 0$, then

$$\begin{aligned} |\phi_a H(\phi_a) - \psi_a H(\psi_a)| &= |\phi_a - \psi_a| \\ &\leq \|\phi - \psi\|. \end{aligned}$$

- If $\phi_a \geq 0, \psi_a < 0$, then

$$\begin{aligned} |\phi_a H(\phi_a) - \psi_a H(\psi_a)| &= |\phi_a| \\ &< \|\phi_a\| + \|\psi_a\| \\ &= |\phi_a - \psi_a| \leq \|\phi - \psi\|. \end{aligned}$$

(3.44)

Note that the same argument could be used for the case $\phi_a < 0, \psi_a \geq 0$.

- If $\phi_a, \psi_a < 0$, then

$$|\phi_a H(\phi_a) - \psi_a H(\psi_a)| = 0 \leq \|\phi - \psi\|$$

Thus,

$$|\phi_a H(\phi_a) - \psi_a H(\psi_a)| \leq \|\phi - \psi\|$$

for any a and b . Let us now consider the various cases of (3.43):

- If $\phi_a, \phi_b, \psi_a, \psi_b \geq 0$, then

$$\begin{aligned} |\phi_a H(\phi_a) \phi_b H(\phi_b) - \psi_a H(\psi_a) \psi_b H(\psi_b)| &= |\phi_a \phi_b - \psi_a \psi_b| \\ &= |\phi_a \phi_b - \phi_a \psi_b + \phi_a \psi_b - \psi_a \psi_b| \\ &\leq |\phi_a| |\phi_b - \psi_b| + |\psi_b| |\phi_a - \psi_a| \\ &\leq 2L \|\phi - \psi\| \end{aligned}$$

- If any of the following are true,

- $\phi_a, \psi_a < 0$
- $\phi_a, \psi_b < 0$
- $\phi_b, \psi_a < 0$
- $\phi_b, \psi_b < 0$,

then

$$\begin{aligned} |\phi_a H(\phi_a) \phi_b H(\phi_b) - \psi_a H(\psi_a) \psi_b H(\psi_b)| &= 0 \\ &\leq \|\phi - \psi\|. \end{aligned}$$

- if $\phi_a, \phi_b \geq 0, \psi_a < 0$, then

$$\begin{aligned} |\phi_a H(\phi_a) \phi_b H(\phi_b) - \psi_a H(\psi_a) \psi_b H(\psi_b)| &= |\phi_a \phi_b| \\ &\leq ||\phi_a \phi_b| + |\psi_a \phi_b|| \\ &= |\phi_a \phi_b - \psi_a \phi_b| \\ &\leq |\phi_b| |\phi_a - \psi_a| \\ &\leq L \|\phi - \psi\| \end{aligned}$$

Note that this argument also holds for the following combinations:

- $\phi_a, \phi_b \geq 0, \psi_b < 0$
- $\psi_a, \psi_b \geq 0, \phi_a < 0$
- $\psi_a, \psi_b \geq 0, \phi_b < 0$.

Note that we have now established that each component in (3.41) is locally Lipschitz. Therefore, (3.35) is locally Lipschitz. Hence, the existence and the uniqueness of our solution to (3.35) is guaranteed by the following theorem.

Theorem 1 (Existence and Uniqueness of Solutions of Ordinary Differential Equations). *Let $U \subset \mathbb{R}^n$ be an open set, and $g : U \rightarrow \mathbb{R}^n$ be a Lipschitz function. Let $\mathbf{x}_0 \in U$ and $t_0 \in \mathbb{R}$. Then, there exists an $\alpha > 0$ and a solution, $\mathbf{x}(t)$, of $\dot{\mathbf{x}} = g(\mathbf{x})$ defined for $t_0 - \alpha < t < t_0 + \alpha$ such that $\mathbf{x}(t_0) = \mathbf{x}_0$. Moreover, if $\mathbf{y}(t)$ is another solution with $\mathbf{y}(t_0) = \mathbf{x}_0$, then $\mathbf{x}(t) = \mathbf{y}(t)$ on their common interval of definition about t_0 . [74]*

We should also note that we can describe our system of sensitivity equations in a similar manner as we described the differential equation model component-wise in (3.35). (The sensitivity equations will be discussed in Section 3.5 and are contained in Section B.3.) We can describe the sensitivity model equations as follows:

$$\begin{aligned}
g_{i,s}(x) &= A_{i,1}x_{q,s}H(x_{q,s})(a_{i,1} + b_{i,1}x_jH(x_j) + c_{i,1}x_kH(x_k) - d_{i,1}x_iH(x_i)) \\
&+ A_{i,2}x_qH(x_q)(b_{i,2}x_{j,s} + c_{i,2}x_{k,s}H(x_{k,s}) - d_{i,2}x_{i,s}H(x_{i,s})) - B_i x_{i,s} \\
&+ C_{i,1} \frac{K_D x_{v,s} H(x_{v,s})}{(x_v H(x_v) + K_D)^2} \left[\left(\sum_{n=l}^m x_n H(x_n) + \delta \right) \left(1 - \sum_{n=l}^m x_n H(x_n) \right) \right] \\
&+ C_{i,2} \frac{x_v H(x_v)}{x_v H(x_v) + K_D} \left(1 - 2 \sum_{n=l}^m x_n H(x_n) - \delta \right) \left(\sum_{n=l}^m x_{n,s} H(x_{n,s}) \right) \\
&+ C_{i,3} \frac{x_v H(x_v)}{x_v H(x_v) + K_D} \left(\sum_{n=l}^m x_n H(x_n) + \delta \right) \left(1 - \sum_{n=l}^m x_n H(x_n) \right) \\
&+ C_{i,4} \frac{K_D x_{v,s} H(x_{v,s}) - x_v H(x_v)}{(x_v H(x_v) + K_D)^2} \left(\sum_{n=l}^m x_n H(x_n) + \delta \right) \left(1 - \sum_{n=l}^m x_n H(x_n) \right) \\
&+ D_{i,1} \frac{\left(\sum_{n=l}^m x_n H(x_n) \right)^{p-1}}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n) \right)^p \right]^2} \left(\sum_{n=l}^m x_{n,s} H(x_{n,s}) \right)
\end{aligned}$$

$$\begin{aligned}
& -D_{i,2} \frac{1}{1 + \alpha \left(\sum_{n=l}^m x_n H(x_n) \right)^p} \\
& -D_{i,3} \left[\frac{\left(\sum_{n=l}^m x_n H(x_n) \right)^p \left[\frac{p}{\sum_{n=l}^m x_n H(x_n)} \sum_{n=l}^m x_{n,s} H(x_{n,s}) + \ln \left(\sum_{n=l}^m x_n H(x_n) \right) \right]}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n) \right)^p \right]^2} \right] \\
& -D_{i,4} \left[\frac{\left(\sum_{n=l}^m x_n H(x_n) \right)^p + \alpha p \left(\sum_{n=l}^m x_n H(x_n) \right)^{p-1} \left(\sum_{n=l}^m x_{n,s} H(x_{n,s}) \right)}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n) \right)^p \right]^2} \right] \\
& + E_{i,1} x_i H(x_i) + E_{i,2}
\end{aligned} \tag{3.45}$$

where

- All values denoted by the capital letters A, B, C, D , and E are nonnegative constants for all subscripts.
- The index i refers to the state from the original model (14 total), and the index s refers to the parameter of investigation in that particular sensitivity equation (6 total investigated parameters). Hence, there are 84 components $g_{i,s}$.
- The x notations are the same from (3.35), with the additional notation difference from x_i and $x_{i,s}$. The notation x_i refers to a state from the original model, and $x_{i,s}$ refers to the derivative of that state with respect to a particular parameter. For example, if we looked at the sensitivity equation for $d/dt[\partial C_{NV}/\partial \tau_r]$, x_i would represent C_{NV} and $x_{i,s}$ would represent $\partial C_{NV}/\partial \tau_r$.

To solve the sensitivity equations, we must solve them along with the original model (i.e., we would need to solve all 96 equations simultaneously). Since we know that (3.35) is locally Lipschitz, we need only show that (3.45) is locally Lipschitz to show the existence and uniqueness of the solution to the coupled system. In order to do so, we make the assumption that the sensitivity equations have bounded solutions. We should further note that the

pieces of the right-hand side of (3.45) that involve the coefficients $A_{i,1}, A_{i,2}, B_i, C_{i,3}, D_{i,2}, E_{i,1}$ and $E_{i,2}$ are all of the same form as pieces that we dealt with when we established the locally Lipschitz behavior of (3.35). We can also see that the pieces with coefficients $C_{i,1}$ and $C_{i,4}$ only differ from the style of our earlier problem by the square of $x_v H(x_v) + K_D$ in the denominator and hence would be dealt with as before using the boundedness of our solutions. Further, the piece involving $C_{i,3}$ would be dealt with as would the $C_{i,3}$ piece so we can see that we have already established the locally Lipschitz behavior of this piece as well. Hence, we can establish the locally Lipschitz behavior of (3.45) by only examining the following function:

$$\begin{aligned}
h_{i,s}(x) &= D_{i,1} \frac{\left(\sum_{n=l}^m x_n H(x_n)\right)^{p-1}}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n)\right)^p\right]^2} \left(\sum_{n=l}^m x_{n,s} H(x_{n,s})\right) \\
&\quad - D_{i,3} \left[\frac{\left(\sum_{n=l}^m x_n H(x_n)\right)^p \left[\frac{p}{\sum_{n=l}^m x_n H(x_n)} \sum_{n=l}^m x_{n,s} H(x_{n,s}) + \ln \left(\sum_{n=l}^m x_n H(x_n)\right) \right]}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n)\right)^p\right]^2} \right] \\
&\quad - D_{i,4} \left[\frac{\left(\sum_{n=l}^m x_n H(x_n)\right)^p + \alpha p \left(\sum_{n=l}^m x_n H(x_n)\right)^{p-1} \left(\sum_{n=l}^m x_{n,s} H(x_{n,s})\right)}{\left[1 + \alpha \left(\sum_{n=l}^m x_n H(x_n)\right)^p\right]^2} \right]. \tag{3.46}
\end{aligned}$$

Before we proceed, we must note that we can only consider the sensitivity equations under the condition that $x \neq 0$. If this condition were not in place, the function listed in (3.46) would involve division by zero both explicitly and through the possibility of $p < 1$. Again, let us consider the difference between two solutions, ϕ and ψ , where $\phi, \psi \neq 0$:

$$|h_{i,s}(\phi) - h_{i,s}(\psi)| = \left| D_{i,1} \frac{\left(\sum_{n=l}^m \phi_n H(\phi_n)\right)^{p-1}}{\left[1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n)\right)^p\right]^2} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s})\right) \right.$$

$$\begin{aligned}
& -D_{i,3} \left[\frac{\left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \left[\frac{p}{\sum_{n=l}^m \phi_n H(\phi_n)} \sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) + \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right]}{\left[1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right]^2} \right] \\
& -D_{i,4} \left[\frac{\left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p + \alpha p \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right)}{\left[1 + \alpha \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right]^2} \right] \\
& -D_{i,1} \frac{\left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1}}{\left[1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right]^2} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \\
& +D_{i,3} \left[\frac{\left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \left[\frac{p}{\sum_{n=l}^m \psi_n H(\psi_n)} \sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) + \ln \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \right]}{\left[1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right]^2} \right] \\
& +D_{i,4} \left[\frac{\left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p + \alpha p \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right)}{\left[1 + \alpha \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right]^2} \right] \\
& \leq D_{i,1} \left| \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right) \right. \\
& \quad \left. - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right| \tag{3.47}
\end{aligned}$$

$$\begin{aligned}
& +pD_{i,3} \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right. \\
& \quad \left. - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right) \right| \tag{3.48}
\end{aligned}$$

$$\begin{aligned}
& +D_{i,3} \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \ln \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) \right. \\
& \quad \left. - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right| \tag{3.49}
\end{aligned}$$

$$+D_{i,4} \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right| \tag{3.50}$$

$$\begin{aligned}
& +\alpha p D_{i,4} \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right. \\
& \quad \left. - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right) \right|. \tag{3.51}
\end{aligned}$$

Note that we again used (3.38). We should note that we have basically three types of pieces to the above relation:

- Sections (3.47), (3.48), and (3.51)
- Section (3.49)
- Section (3.50).

Now the piece shown in (3.50) can be reduced using Lemma 1 as shown previously when establishing the locally Lipschitz behavior of (3.35). We can see that the expressions in (3.47), (3.48), and (3.51) can be reduced as follows with the help of (3.33):

$$\left| \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right) - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right|$$

$$\begin{aligned}
&\leq \left| \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \phi_{n,s} H(\phi_{n,s}) \right) - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right. \\
&\quad \left. + \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \left(\sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right) \right| \\
&\leq (5L)^{p-1} \sum_{n=l}^m |\phi_{n,s} H(\phi_{n,s}) - \psi_{n,s} H(\psi_{n,s})| \tag{3.52}
\end{aligned}$$

$$+ \left| \sum_{n=l}^m \psi_{n,s} H(\psi_{n,s}) \right| \left| \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^{p-1} - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^{p-1} \right|. \tag{3.53}$$

(Note that here L maybe greater than defined earlier because $x_0 \neq 0$, but the expression in (3.33) still holds.) We should note that the reduced piece shown in (3.52) further reduces easily into a type that was dealt with earlier, and the piece shown in (3.53) can be reduced to earlier forms with the use of Remark 1 as long as the sensitivity solutions are bounded. Once the locally Lipschitz behavior has been established for (3.49), we will have established the existence and uniqueness of solutions for the sensitivity equations. In order to establish the locally Lipschitz behavior of (3.49), we will make use of Lemma 2.

Lemma 2. *If X and Y are such that $X, Y > 0$, then*

$$|\ln(Y) - \ln(X)| \leq |Y - X|. \tag{3.54}$$

Proof. We will divide this proof into three cases.

Case 1: $0 < Y < X$

Note that $Y < X \Rightarrow Y < Xe^{|Y-X|}$, and further

$$\begin{aligned}
 |\ln(Y) - \ln(X)| &= \left| \ln\left(\frac{Y}{X}\right) \right| \\
 &< \left| \ln\left(\frac{Xe^{|Y-X|}}{X}\right) \right| \\
 &= |Y - X|.
 \end{aligned}$$

Case 2: $0 < X < Y$

Using the same logic as in Case 1, we see that

$$\begin{aligned}
 |\ln(Y) - \ln(X)| &= |\ln(X) - \ln(Y)| \\
 \left| \ln\left(\frac{X}{Y}\right) \right| &< \left| \ln\left(\frac{Ye^{|Y-X|}}{Y}\right) \right| \\
 &= |Y - X|.
 \end{aligned}$$

Case 3: $X = Y$

Clearly,

$$|\ln(Y) - \ln(X)| = 0 \leq |Y - X|.$$

□

Now, returning to (3.49),

$$\left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \ln \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right|$$

$$\begin{aligned}
&= \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \ln \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) - \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right. \\
&\quad \left. + \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right| \\
&\leq \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p \right| \left| \ln \left(\sum_{n=l}^m \psi_n H(\psi_n) \right) - \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right| \tag{3.55}
\end{aligned}$$

$$\left| \ln \left(\sum_{n=l}^m \phi_n H(\phi_n) \right) \right| \left| \left(\sum_{n=l}^m \psi_n H(\psi_n) \right)^p - \left(\sum_{n=l}^m \phi_n H(\phi_n) \right)^p \right|. \tag{3.56}$$

We can see that (3.55) can easily be reduced using Lemma 2, and (3.56) can be reduced using Lemma 1. At this point we have reduced all parts of (3.45) to locally Lipschitz pieces or forms that we have previously dealt with in the determination of the existence of the solution to 3.35). Hence, we have established the existence and uniqueness of the sensitivity equations through the use of Theorem 1, under the assumption that the solutions to our sensitivity equations are bounded.

3.4 Steady-State Analysis of the Firing Rate n

As stated in Section 3.2.2, the decrease in ventilation in the presence of irritant is so quick that we could only consider a steady-state formulation for n to model the firing rate. Although we choose not to use the steady-state formulation of n to entirely describe the sensory activity, we can learn about the system and how some of the parameters in our model (specifically τ_r , k_0 , τ_Q , p , α , and K_D) affect the end behavior by analyzing the steady state for n .

We previously described our firing rate n as a sum of pieces from different compartments,

$$n = N + \Delta n_{VR1} + \Delta n_{VR2} + \Delta n_{DR} + \Delta n_{DO1} + \Delta n_{DO2}, \tag{3.57}$$

where those additions from the different compartments are defined by the following differential equation system:

$$\Delta \dot{n}_{VR1} = w_{VR1} k_0 r(C_{VR1}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{VR1}}{\tau_r} \quad (3.58)$$

$$\Delta \dot{n}_{VR2} = w_{VR2} k_0 r(C_{VR2}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{VR2}}{\tau_r} \quad (3.59)$$

$$\Delta \dot{n}_{DR} = w_{DR} k_0 r(C_{DR}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DR}}{\tau_r} \quad (3.60)$$

$$\Delta \dot{n}_{DO1} = w_{DO1} k_0 r(C_{DO1}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO1}}{\tau_r} \quad (3.61)$$

$$\Delta \dot{n}_{DO2} = w_{DO2} k_0 r(C_{DO2}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO2}}{\tau_r}. \quad (3.62)$$

We know that the ventilation response to the irritant is very quick as is evident in [25, 26]. Hence we could make the assumption that the change in ventilation is such that a steady state firing rate is achieved rapidly enough that we could consider only a steady-state description for n . In order to better understand the model we will consider the steady-state description that we obtain by setting our equations for $\Delta \dot{n}_i = 0$:

$$0 = w_i k_0 r(C_i) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_i}{\tau_r} \quad (3.63)$$

$$\Rightarrow \frac{\Delta n_i}{\tau_r} = w_i k_0 r(C_i) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} \quad (3.64)$$

$$\Rightarrow \Delta n_i = \tau_r w_i k_0 r(C_i) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2}. \quad (3.65)$$

Further, using (3.57), we can describe the steady-state n

$$n = \tau_r k_0 \left[\sum_i w_i r(C_i) \right] \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} + N \quad (3.66)$$

$$\Rightarrow n = \tau_r k_0 \left[\sum_i w_i r(C_i) \right] \frac{-n^2 + (1 - \delta)n + \delta}{(1 + \delta)^2} + N \quad (3.67)$$

$$\begin{aligned} \Rightarrow 0 &= -\frac{\tau_r k_0 [\sum_i w_i r(C_i)]}{(1 + \delta)^2} n^2 + \left[\frac{(1 - \delta)}{(1 + \delta)^2} \tau_r k_0 [\sum_i w_i r(C_i)] - 1 \right] n \\ &\quad + N + \frac{\delta}{(1 + \delta)^2} \tau_r k_0 [\sum_i w_i r(C_i)]. \end{aligned} \quad (3.68)$$

Note that $n \geq N = 0$ and let

$$\mathcal{X} = \tau_r k_0 \left[\sum_i w_i r(C_i) \right],$$

where

$$r(C_i) = \frac{C_i}{C_i + K_D}.$$

Using the quadratic formula,

$$n = \frac{-\left(\frac{(1-\delta)}{(1+\delta)^2} \mathcal{X} - 1\right) \pm \sqrt{\left(\frac{(1-\delta)}{(1+\delta)^2} \mathcal{X} - 1\right)^2 - 4 \left(-\frac{\mathcal{X}}{(1+\delta)^2}\right) \left(\frac{\delta}{(1+\delta)^2} \mathcal{X}\right)}}{\frac{-2\mathcal{X}}{(1+\delta)^2}} \quad (3.69)$$

$$= \frac{(1 - \delta)\mathcal{X} - (1 + \delta)^2 \mp (1 + \delta)^2 \sqrt{\left(\frac{(1-\delta)}{(1+\delta)^2} \mathcal{X} - 1\right)^2 + \frac{4\delta}{(1+\delta)^4} \mathcal{X}^2}}{2\mathcal{X}} \quad (3.70)$$

$$= \frac{(1 - \delta)\mathcal{X} - (1 + \delta)^2 \mp (1 + \delta)^2 \sqrt{\frac{1}{(1+\delta)^2} \mathcal{X}^2 - \frac{2(1-\delta)}{(1+\delta)^2} \mathcal{X} + 1}}{2\mathcal{X}} \quad (3.71)$$

$$= \frac{(1 - \delta)\mathcal{X} - (1 + \delta)^2 \mp (1 + \delta)\sqrt{\mathcal{X}^2 - 2(1 - \delta)\mathcal{X} + (1 + \delta)^2}}{2\mathcal{X}}. \quad (3.72)$$

For simplicity, we choose the positive root. Hence, we can describe n as follows:

$$n = \frac{(1 - \delta)\mathcal{X} - (1 + \delta)^2 + (1 + \delta)\sqrt{\mathcal{X}^2 - 2(1 - \delta)\mathcal{X} + (1 + \delta)^2}}{2\mathcal{X}}, \quad (3.73)$$

where $i = VR1, VR2, DR, DO1, DO2$. After an initial drop in ventilation, the rat's breathing reaches somewhat of a steady-state value until the exposure ends [25]. By considering a steady-state version of the model, we can better understand how the parameters we are investigating will affect the solution. The formulation in (3.73) was used for n and $Q(t)$ was considered to be Q_{steady} in order to establish the pseudo-steady-state behavior of the model. The differential equations for the compartmental irritant concentrations were not changed. Using this formulation of our model we can focus on a subset of our six investigated parameters: τ_r , k_0 , τ_Q , α , p , and K_D . If we only consider n as defined in (3.73) and set $Q(t) = Q_{steady}$, we eliminate dependence on τ_Q , and the parameters τ_r and k_0 only appear as a multiplied term $\tau_r \cdot k_0$ in $\mathcal{X}$. Hence, we can use data from the portion of exposure once ventilation has steadied and get a better idea of the four values: $\tau_r \cdot k_0$, α , p , and K_D . Data was collected from scanned graphs from [25] using DataThief [49, 80] and was converted to an appropriate form for our model. The data from [25] was reported as percent decrease of respiratory rate. Hence, the data taken from the graph was multiplied by our Q_{max} value, and additionally, the time values were corrected for units. More information on the data in [25] is contained in Section 3.6. This data was compared to the steady-state representation for our model. Figure 3.5 illustrates the model solutions for three different exposure levels using a particular set of values for the four parameters that remain. The values of the parameters involved in the steady state formulation in Figure 3.5 and Figure 3.6 were used as a starting point for the sensitivity analysis in Section 3.5. We should note that the steady-state solutions shown in Figure 3.5 do not describe the data well, but the error seems less prominent when observing the relationship between inhalation dose and steady-state in Figure 3.6. Hence, one set of parameters will probably not describe all three data sets; and we may need to include dose-dependence in one or more of the parameters.

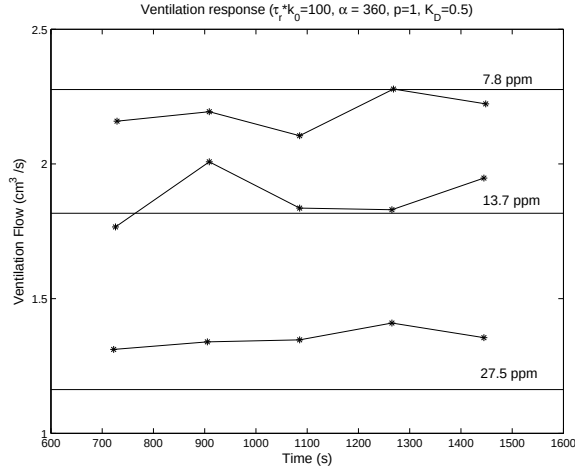


Figure 3.5: Plot of pseudo-steady-state solution for ventilation $Q(t)$ in the presence of formaldehyde. Three solutions for three different exposures (7.8 ppm, 13.7 ppm, 27.5 ppm) were computed and compared to data from [25] that was retrieved using DataThief. Note that the steady-state solutions are the three horizontal lines. Values for the investigated parameters that were involved in the steady-state representation were set to be $\tau_r * k_0 = 100$, $\alpha = 360$, $p = 1$, and $K_D = 0.5$.

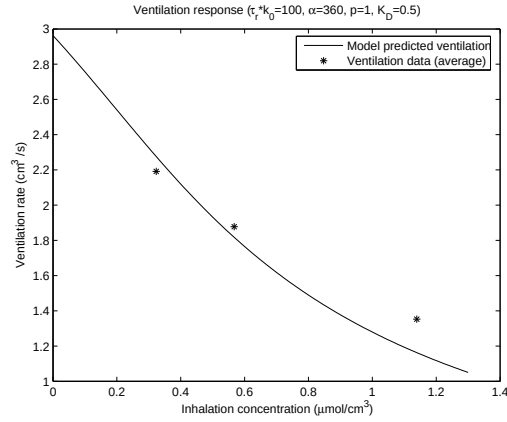


Figure 3.6: Plot of pseudo-steady-state values for ventilation $Q(t)$ in the presence of formaldehyde versus inhalation concentration. The curve represents steady-state solutions computed for various inhalation concentrations. The data represent averages for ventilation data from three different exposures from [25] that was retrieved using DataThief. The data points averaged were assumed to be after ventilation had achieved a pseudo-steady-state. Values for the investigated parameters that were involved in the steady-state representation were set to be $\tau_r * k_0 = 100$, $\alpha = 360$, $p = 1$, and $K_D = 0.5$.

When n reaches a steady state, the function $Q(t)$ also reaches the steady state Q_{steady} . Now recall the function for Q_{steady} when $Q_{min} = 0$:

$$Q_{steady}(n) = \frac{Q_{max}}{1 + \alpha n^p}. \quad (3.74)$$

We can get an average for the data at the ends of the three exposures in [25], (A), which represents the percentage decrease from Q_{max} . Therefore, we can estimate the relationship between α and p once n has reached a steady state value of n_{ss} :

$$\begin{aligned} Q_{max} * A &= \frac{Q_{max}}{1 + \alpha n_{ss}^p} \\ \Rightarrow \alpha &= \frac{1 - A}{A n_{ss}^p}. \end{aligned}$$

Hence, we can estimate α for any K_D , $k_0 \cdot \tau_r$, and p values using (3.75) before doing any numerical optimization. However, when we use steady-ventilation data for A and various values of the investigated parameters, at this point α has no discernible pattern. In other words, at this point in the investigation, an appropriately dose based function for α is not apparent. We should make two important observations based on the steady-state analysis:

1. Many of the investigated parameters are involved in the computation of the steady state. We would have liked to have ascertained some parameter values based on data of the steady state alone, but the parameters appear too interconnected.
2. At least one of the investigated parameters in this model appears to be dose-dependent. Although we consider α as dose-dependent in this section, we recognize that the dependence may lie with another parameter.

We will return to the issue of dose-dependent parameters in the optimization discussed in Section 3.6.

3.5 Sensitivity Analysis of the Model

In order to ascertain which parameters to optimize, we must first analyze the sensitivity of the parameters. Although we have six parameters that we are already considering, we would like to make sure that the model is sensitive to all six before proceeding. Further, by analyzing sensitivity, we not only learn how much the model changes due to individual parameter changes; but we also gain insight into *how* the parameters change the model in terms of qualities such as the shape of the solution curves. We are currently considering optimization over the following parameters:

τ_r	an adaptation time constant for firing rate n
k_0	the intrinsic sensitivity of the receptor to a chemical
τ_Q	time constant characterizing the time it takes for the nervous response to take effect
p	parameter controlling the steepness of the sigmoid Q_{steady}
α	parameter controlling the lower bound of Q_{steady}
K_D	the receptor-chemical dissociation constant

The sensitivity equations for each of these parameters are contained in Section B.3. From this point forward, the vector of parameters τ_r , k_0 , τ_Q , p , α , and K_D may also be referred to as the vector q . The 84 sensitivity equations (plus the 14 equations of the sensory model itself) were coded into Matlab and solved using *ode15s* for various fixed q . Note that what was actually solved was the normalized sensitivity equations as in [11], i.e., the sensitivity equations were each multiplied by the parameter for which the derivative was being determined. The sensitivity equations were normalized so that one parameter would not show greater sensitivity simply because that parameter was considerably larger than another, i.e., we consider changes that are equivalent regardless of the magnitude of the parameter. C_{inh} was set at 7.8 ppm (about $0.3231 \mu\text{mol}/L$). Originally, the values for q were chosen to match with the steady-state analysis, but the results generated from that set of parameters ($\tau_r = 1$, $k_0 = 100$, $\tau_Q = 30$, $p = 2$, $\alpha = 360$, $K_D = 0.5$) did not seem to best illustrate model sensitivity. Hence, different values were chosen, and the values for q were started at those listed in Table 3.3.

Note that τ_r is a reasonable start as compared to the values for $\tau_1 = 0.5$, $\tau_2 = 5.0$ and $\tau_3 = 500$ seconds from equivalent portion of the Ottesen model [69]. Although the model from [69] models a different system in different animals, the values used in the original model give insight to nerve values, especially with the lack of information on the response system

we are modeling. We should also note that τ_r was chosen as small in order to properly satisfy integration tolerances as will become more clear in the analysis. Our beginning τ_Q is somewhat larger than the equivalent values of $\tau_H, \tau_S = 2$ seconds and $\tau_R = 6$ seconds from the Ottesen model. This was chosen in order to allow the model a greater response time and hence better agreement with data. The magnitude for the starting k_0 value is higher than the equivalent Ottesen values. The values of k_1, k_2 and k_3 roughly correspond (in concept) to our values of $w_i k_0$. In the Ottesen model $k_i \in \{1, 2\}$ and since for our model $w_i \in \{1, 2\}$ our starting value for k_0 is much higher than the Ottesen values. The value for k_0 was originally chosen such that $\tau_r \cdot k_0 = 100$ since that was the value achieved through trials with the steady-state formulations of n and Q , but k_0 was increased to 150 to better illustrate the differences in sensitivity to each parameter. We note that our chosen value for k_0 for the sensitivity analysis is quite different from the equivalent values used in the model in [69]; but given that we do not know how sensitive the baroreflex system is compared to our irritant response system, the value of $k_0 = 150$ is not necessarily unreasonable. The parameter p was set initially at $p = 2$ (which is higher than what was found in the steady-state analysis) because the ventilation solution became close to vertical with $p < 1$ and considering a region of $p \in \{1, 2, 4\}$ would be more suitable for evaluating sensitivity than investigating a region with fractional p values. The value for K_D was taken from the trials with the steady-state formulation, and the value for α was set larger than found in the steady-state analysis for the same reason that k_0 was increased. We should note, however, that α plays a very different role in our formulation than in Ottesen's because our n exists only on a domain of $[0, 1]$. Since our formulation of Q_{steady} does not allow Q to asymptotically approach Q_{min} , α can conceivably be set quite large.

The model and the normalized sensitivity equations were solved for the fixed values

Table 3.3: Beginning values for the parameters in the sensitivity analyses.

Parameter	Value
τ_r	1
k_0	150
τ_Q	60
p	2
α	500
K_D	0.5

of five of the parameters listed in Table 3.3 while the remaining parameter was set at three different values in order to ascertain sensitivity. For p , the value was set at the value in the table with the upper value being the table value multiplied by two and the lower value being the table value divided by two. If we consider τ_r , k_0 , and K_D to be the values in the table, the three different values for each would be $\{\tau_r/1.15, \tau_r, 1.15\tau_r\}$, $\{k_0/1.15, k_0, 1.15k_0\}$, and $\{K_D/1.15, K_D, 1.15K_D\}$, respectively. The upper and lower values for α and τ_Q were computed by multiplying and dividing the table values by a factor of ten, respectively. The computed solutions when τ_r is varied are plotted in Figure 3.7 and Figure 3.8. The solutions for variations in k_0 are graphed in Figure 3.9 and Figure 3.10. Similar plots for variations in τ_Q are contained in Figure 3.11 and Figure 3.12, and plots for variations in p are contained in Figure 3.13 and Figure 3.14. The solutions for variations in α and in K_D are contained in Figure 3.15-Figure 3.18. All solutions were computed over a time period of 240 seconds (or 4 minutes) in order to show adequate time for the initial decrease that occurs in the first few minutes in recorded data [25, 26].

We can see by Figure 3.7 and Figure 3.8 that small changes in τ_r did make changes to our Δn_i values (and hence more significant changes to n) and the solution for Q , but only small changes occurred to the compartmental concentration values. The higher value for τ_r was set to be 1.15 because even slightly higher numbers made the solutions grow or decrease so quickly that numerical integration was difficult. Hence we can see definite changes to the solutions due to changes in τ_r , and the model seems to be sensitive to this parameter, especially when $\tau_r > 1$. Further, we should note that very small changes in τ_r produced changes in the model solution for ventilation; therefore, not only is the model sensitive to τ_r , but also the model sensitivity to τ_r is high.

Similar results occur for changes in k_0 as we can see in Figure 3.9 and Figure 3.10. We would expect to see changes mainly in the Δn_i 's (and hence changes in Q) due to changes in τ_r and k_0 solely based on their placement in the model as well. The fact that k_0 and τ_r are connected once the model achieves a steady state suggests that changes in these two parameters would have similar results. We have the situation where we do see significant changes in n and in Q due to changes in k_0 , and we again have a situation where the model shows greater sensitivity to larger values of the investigated parameter and can grow too rapidly for integration tolerance if k_0 is too large. Hence, since we do see changes in the solution to small changes in k_0 , we see a high sensitivity to k_0 as we saw with the parameter τ_r .

As we can see in Figure 3.11 and Figure 3.12, the resulting changes in compartmental concentration and in Δn_i values due to changes in τ_Q are negligible, and we see that changes in τ_Q only result in noticeable changes in Q . Since τ_Q only occurs in the equation for Q and since the changes to Q are too small to significantly affect the other states, seeing only sensitivity to τ_Q in the solution for ventilation makes sense. Note that the three different solutions were produced by τ_Q values that differed by factors of ten. The resulting changes in ventilation were minor so we can conclude that the model sensitivity to the parameter τ_Q is not very high. The solution to Q is mildly sensitive to the parameter τ_Q , and data concerning ventilation over time could only help us to estimate the optimal value of τ_Q somewhat. Further, changes in the value of τ_Q seem to have their greatest effect on the shape of the graph of Q which will still make this parameter important in optimization.

We should note that in Figure 3.13, the ventilation solution for $p = 4$ is visually a horizontal line near the top of the vertical scale. The solution for $p = 2$ does decrease below the solution for $p = 4$, but the model shows more sensitivity between $p = 1$ and $p = 2$. Solutions for Q get very close to each other when p grows large, and Q decreases too quickly to satisfy integration tolerances when p gets much smaller than 1. Further, we should see more sensitivity to smaller values of p because $0 \leq n \leq 1$ implies that the n^p term will become negligible when $p \gg 1$. We should also note that the absolute change of ventilation is very high relative to the results of changing the other investigated parameters. Similar to the situation in Figure 3.13, in Figure 3.14, the sensitivity solution for ventilation when $p = 4$ cannot be easily distinguished from the x-axis. We do see relatively significant changes to compartmental concentrations, relatively significant changes to the solution for n , and very significant changes in the ventilation solution when we vary p by a factor of 2. Hence, the model sensitivity to p appears to be high.

In Figure 3.15 and Figure 3.16, we see that when we change α by a factor of ten, we only see small changes in Q and small relative changes in the values for C_i and for Δn_i . Since α only occurs in the formulation of Q_{steady} , we could expect to see Q show greater sensitivity to this parameter than the firing rate or the compartmental concentration. We should note that we see similar changes in Q with these changes in α as we do with smaller changes in τ_r and k_0 . Hence, the model is somewhat sensitive to changes in α , but it is not as sensitive to this parameter as it is to some others.

In Figure 3.17 and Figure 3.18, we see very small changes to the compartmental concentration due to changes in K_D . We do see changes in the value of n and Q due to

changes in K_D , and the changes are greater for smaller values of K_D . As with some of the other investigated parameters, the solutions decreased or increased too quickly with small values of K_D to satisfy integration tolerances. We should note that we see similar changes in Q as when τ_r and k_0 were varied, and here K_D is varied by the same factor of 1.15. Hence, as with the parameters τ_r and k_0 , the model seems to have high sensitivity to K_D .

In total, we see model sensitivity to five of the six parameters, but the sensitivity is greater for τ_r , k_0 , p , and K_D than for α . Although we see very little model sensitivity to changes in τ_Q , this parameter is important to the shape of the solution for Q . Hence we will also optimize over τ_Q , but we will make use of our knowledge that the model is not as sensitive to τ_Q in Section 3.6.

3.6 Parameter Optimization

Formaldehyde-induced respiration response data were taken from graphs in [25] with the use of the software DataThief [49, 80]. In the study in [25], Cassee *et al.* measured the decrease in minute ventilation in young albino Wistar rats after inhalation of different irritants. The data were reported as percentage of control ventilation, so the collected data numbers were multiplied by Q_{max} . The graph with the formaldehyde data from [25] is contained in the top portion of Figure 3.19. Note that the ventilation drops quickly from 100% of the control value and then begins to recover to a steady state.

After beginning values for the investigated parameters were found through the steady-state analysis, the data was used with the full ordinary differential equation model in a least squares minimization. Let us describe our system of equations as $\dot{x} = f(t, x, q)$ where q is our vector of parameters τ_r , k_0 , τ_Q , p , α , and K_D . Note that our vector of parameters is in the set of positive reals (which will be denoted by X below), and hence, we are solving the problem

$$J^* = \min_{q \in X} J(q) = \min_{q \in X} \sum_{i=1}^n |x(t_i, q) - d_i|^2 \quad (3.75)$$

where $x(t, q)$ is our solution to the model and d is a vector of our data points.

The first attempt at optimization was made by minimizing to find J^* using the

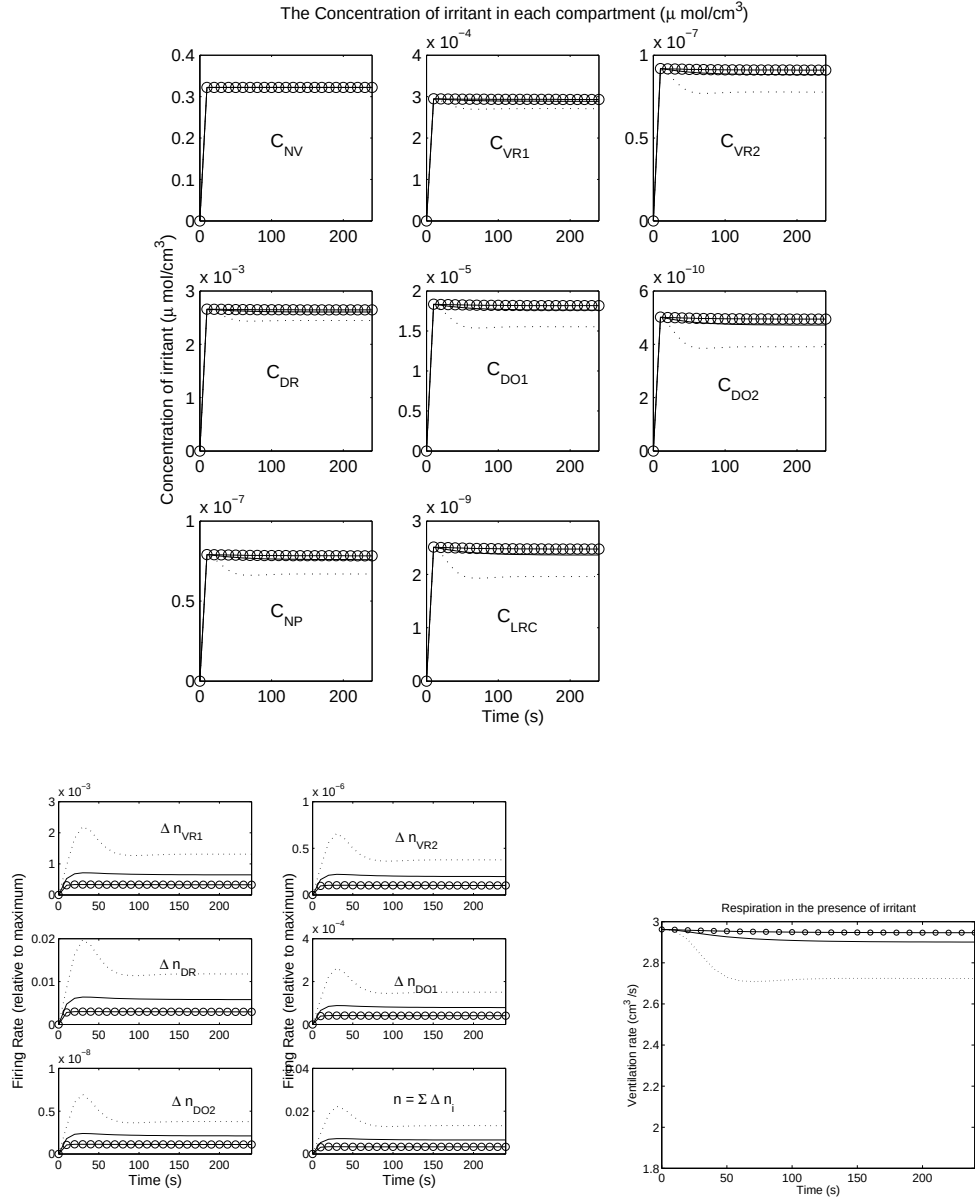


Figure 3.7: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter τ_r . The graph with open circles represents the solution when $\tau_r = 1/1.15 \approx 0.8696$, the solid line is for the solution when $\tau_r = 1$, and the dotted line is for the solution when $\tau_r = 1.15$. The values of the other fixed parameters are listed in Table 3.3.

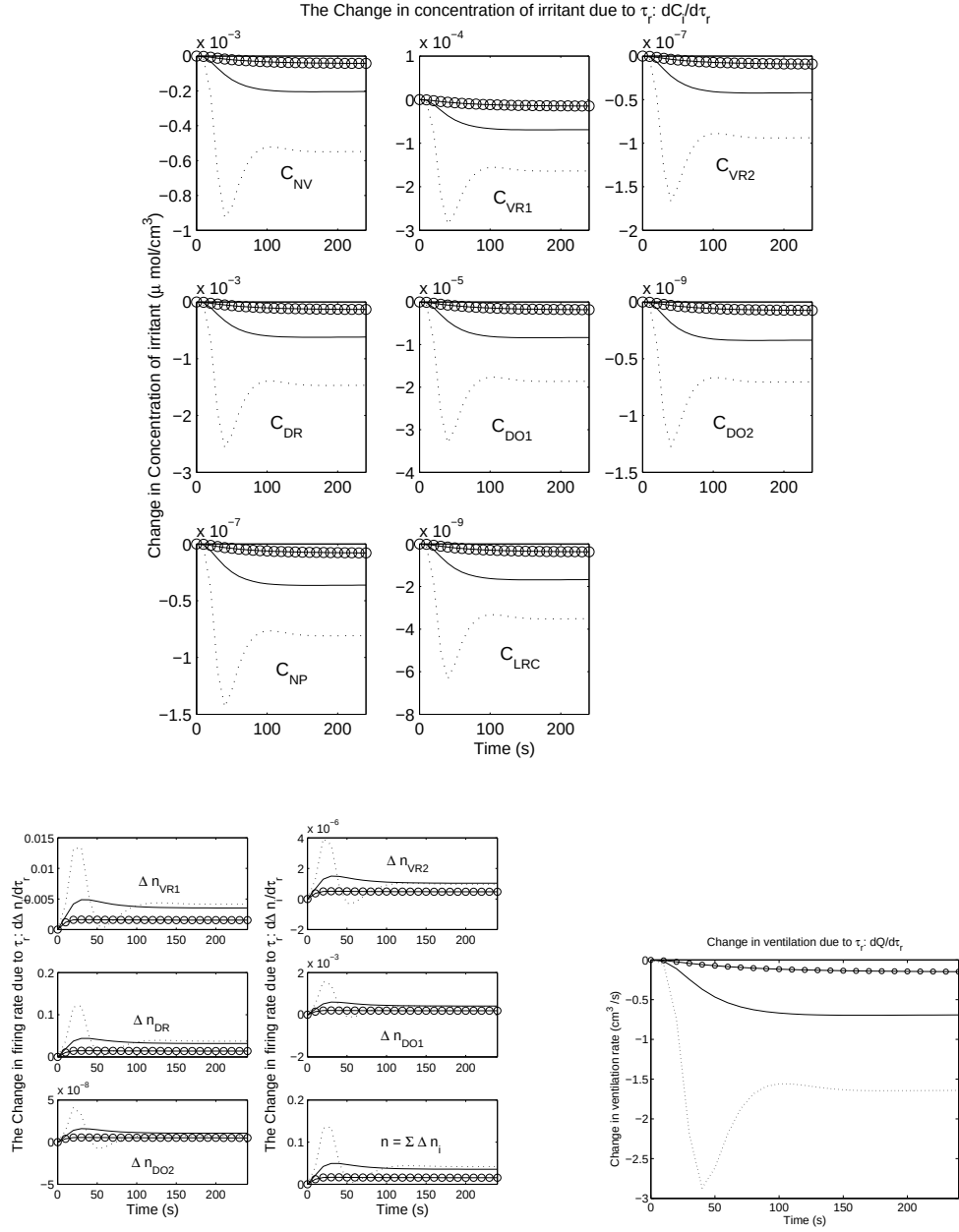


Figure 3.8: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in τ_r . The graph with open circles represents the solution when $\tau_r = 1/1.15 \approx 0.8696$, the solid line is for the solution when $\tau_r = 1$, and the dotted line is for the solution when $\tau_r = 1.15$. The values of the other fixed parameters are listed in Table 3.3.

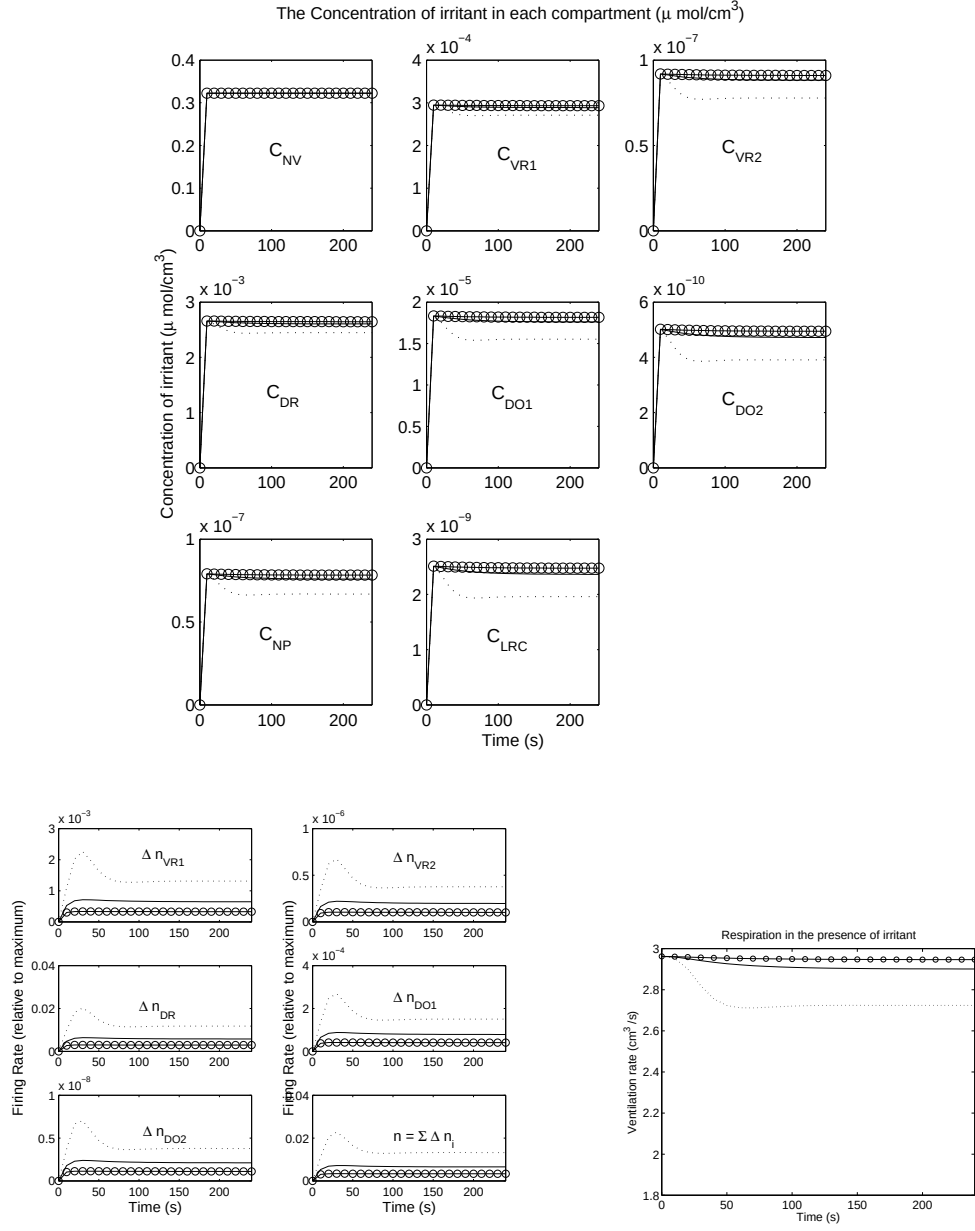


Figure 3.9: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter k_0 . The graph with open circles represents the solution when $k_0 = 150/1.15 \approx 130.4348$, the solid line is for the solution when $k_0 = 150$, and the dotted line is for the solution when $k_0 = 172.5$. The values of the other fixed parameters are listed in Table 3.3.

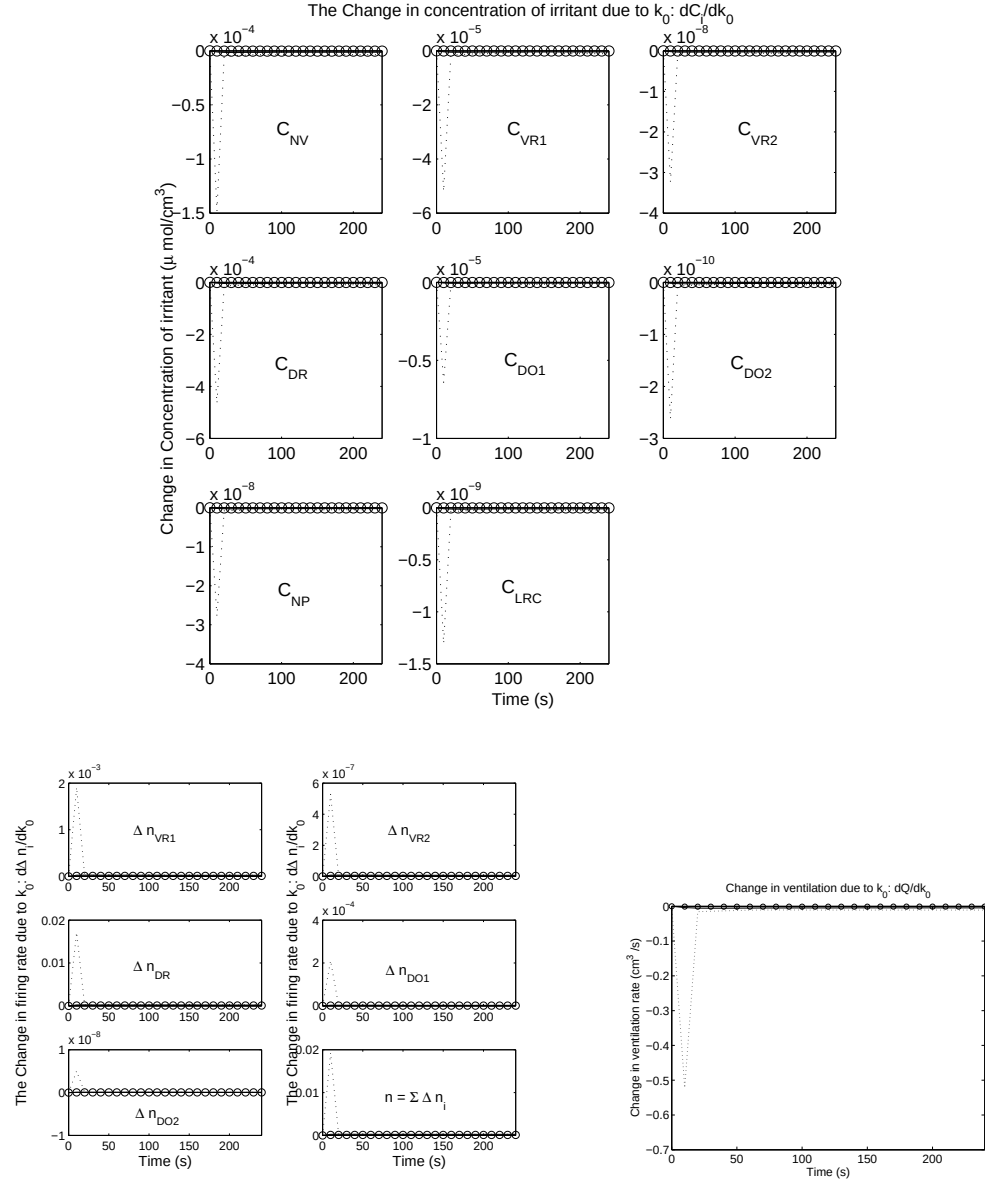


Figure 3.10: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in k_0 . The graph with open circles represents the solution when $k_0 = 150/1.15 \approx 130.4348$, the solid line is for the solution when $k_0 = 150$, and the dotted line is for the solution when $k_0 = 172.5$. The values of the other fixed parameters are listed in Table 3.3.

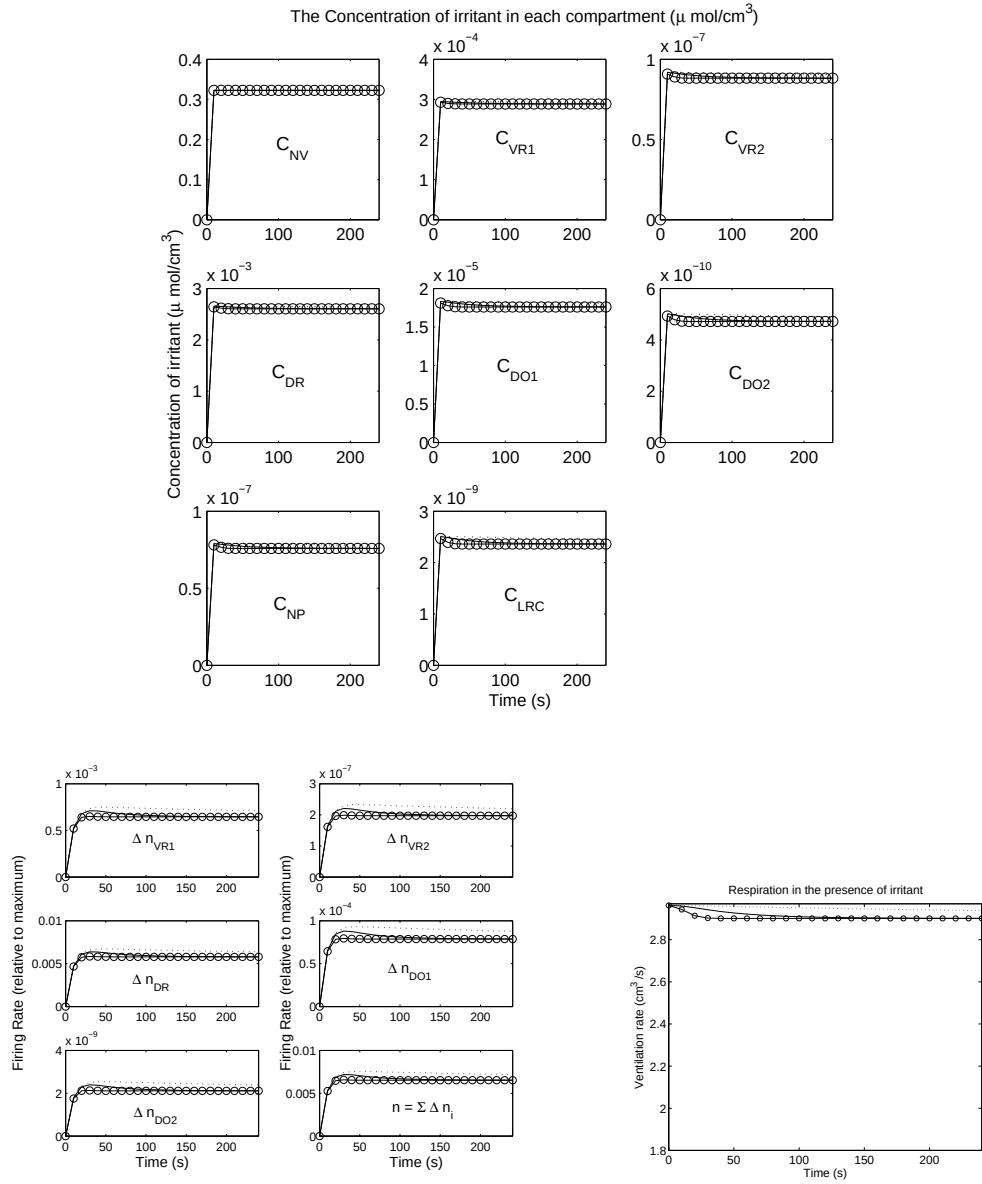


Figure 3.11: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter τ_Q . The graph with open circles represents the solution when $\tau_Q = 6$, the solid line is for the solution when $\tau_Q = 60$, and the dotted line is for the solution when $\tau_Q = 600$. The values of the other fixed parameters are listed in Table 3.3.

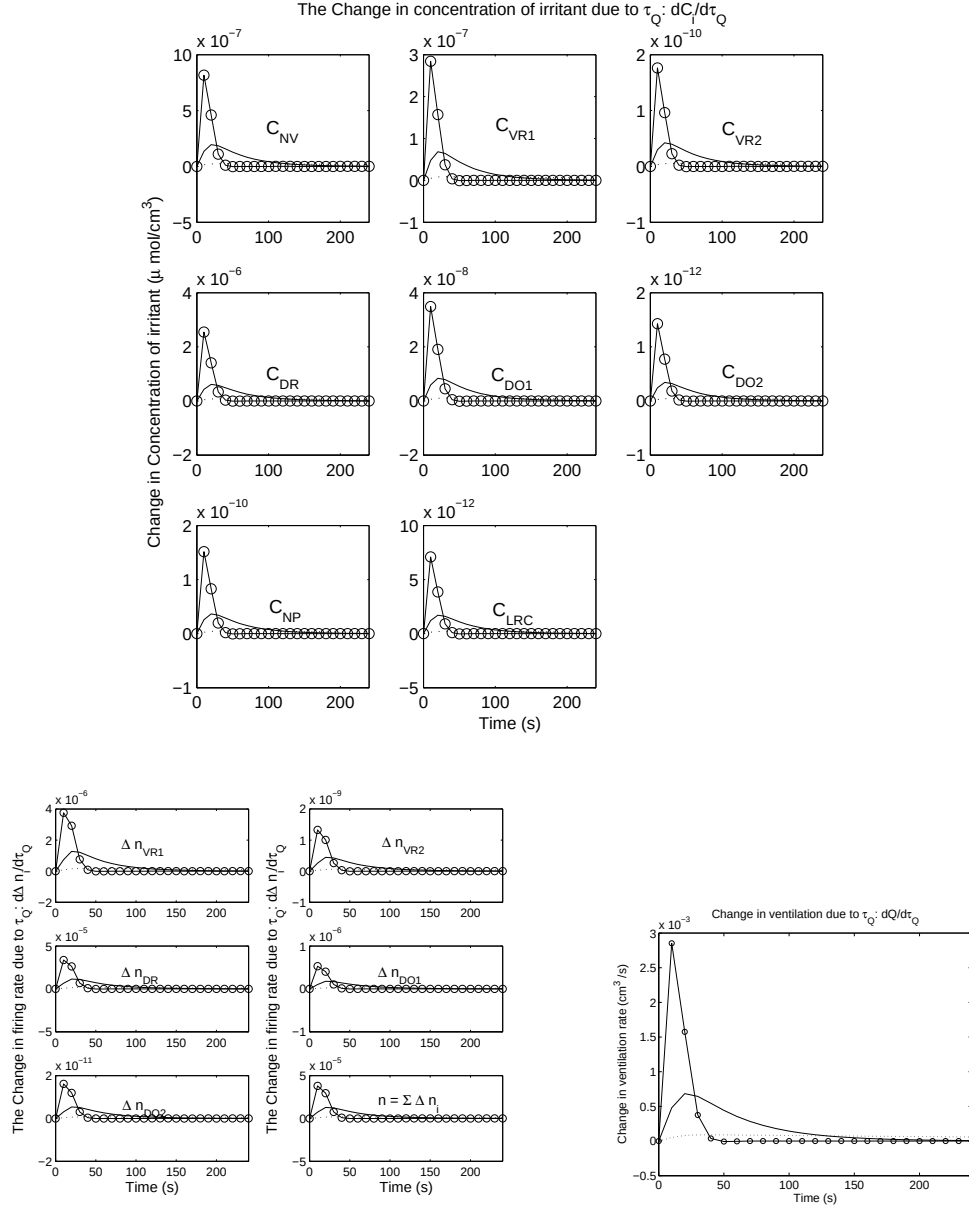


Figure 3.12: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in τ_Q . The graph with open circles represents the solution when $\tau_Q = 6$, the solid line is for the solution when $\tau_Q = 60$, and the dotted line is for the solution when $\tau_Q = 600$. The values of the other fixed parameters are listed in Table 3.3.

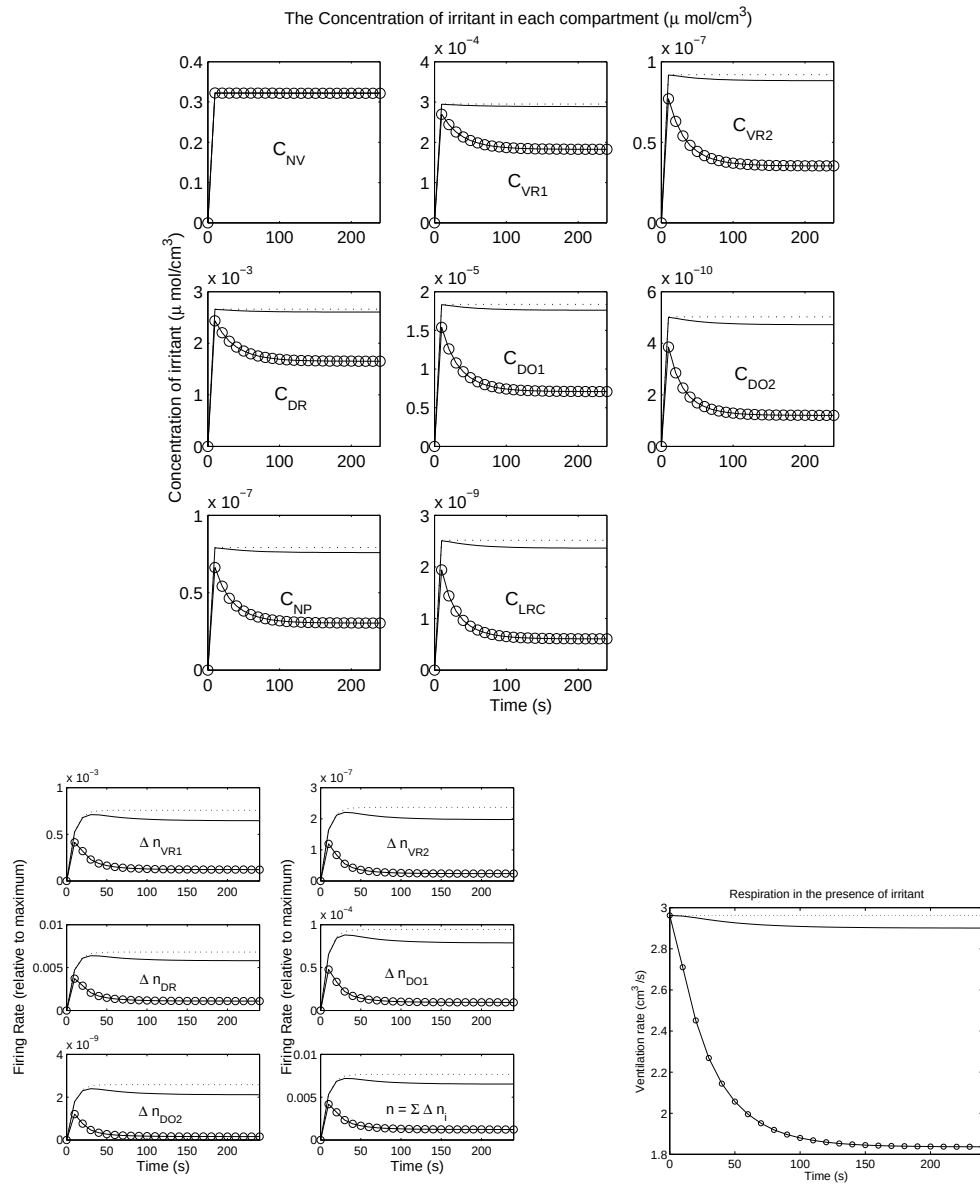


Figure 3.13: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter p . The graph with open circles represents the solution when $p = 1$, the solid line is for the solution when $p = 2$, and the dotted line is for the solution when $p = 4$. The values of the other fixed parameters are listed in Table 3.3.

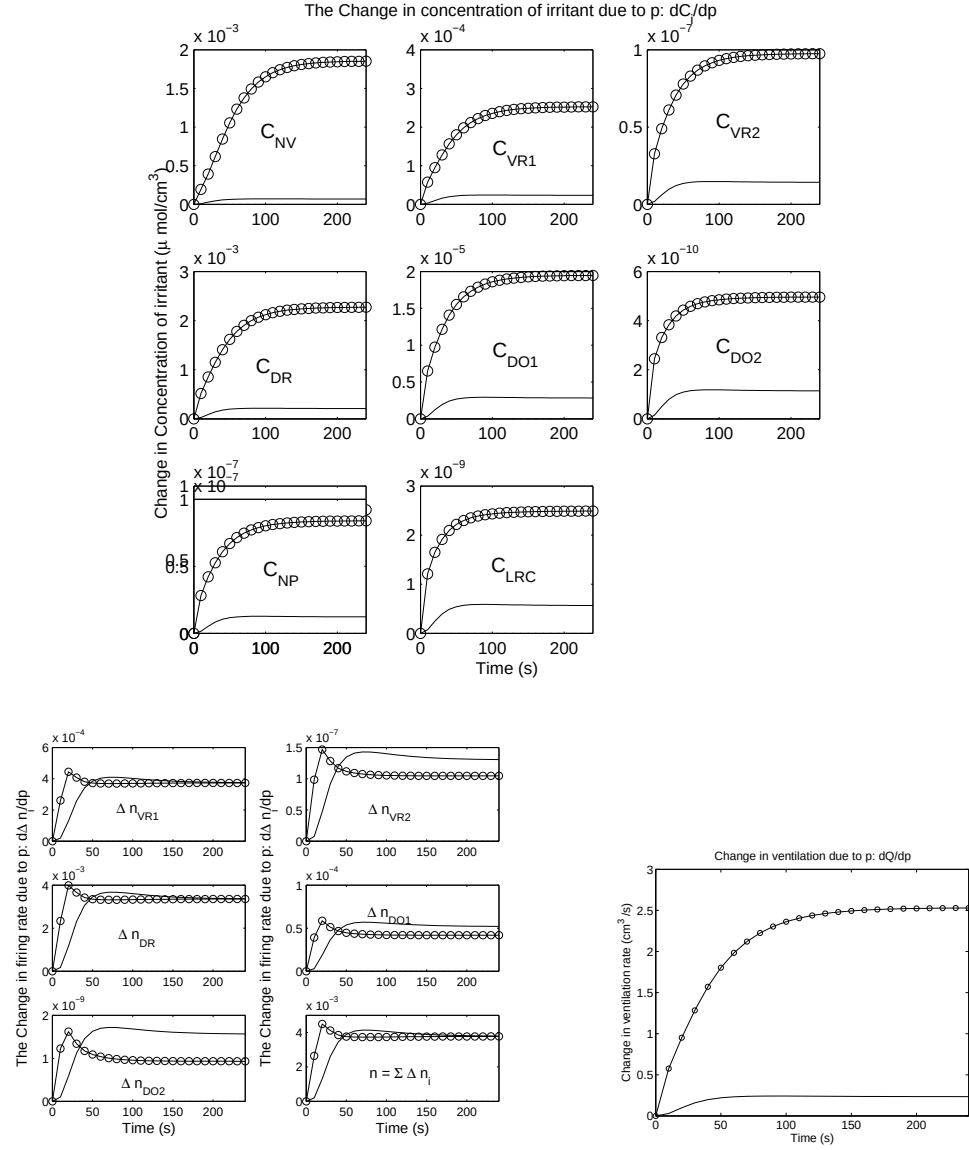


Figure 3.14: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in p . The graph with open circles represents the solution when $p = 1$, the solid line is for the solution when $p = 2$, and the dotted line is for the solution when $p = 4$. Note that the graph for $p = 4$ cannot be easily distinguished from the x-axis. The values of the other fixed parameters are listed in Table 3.3.

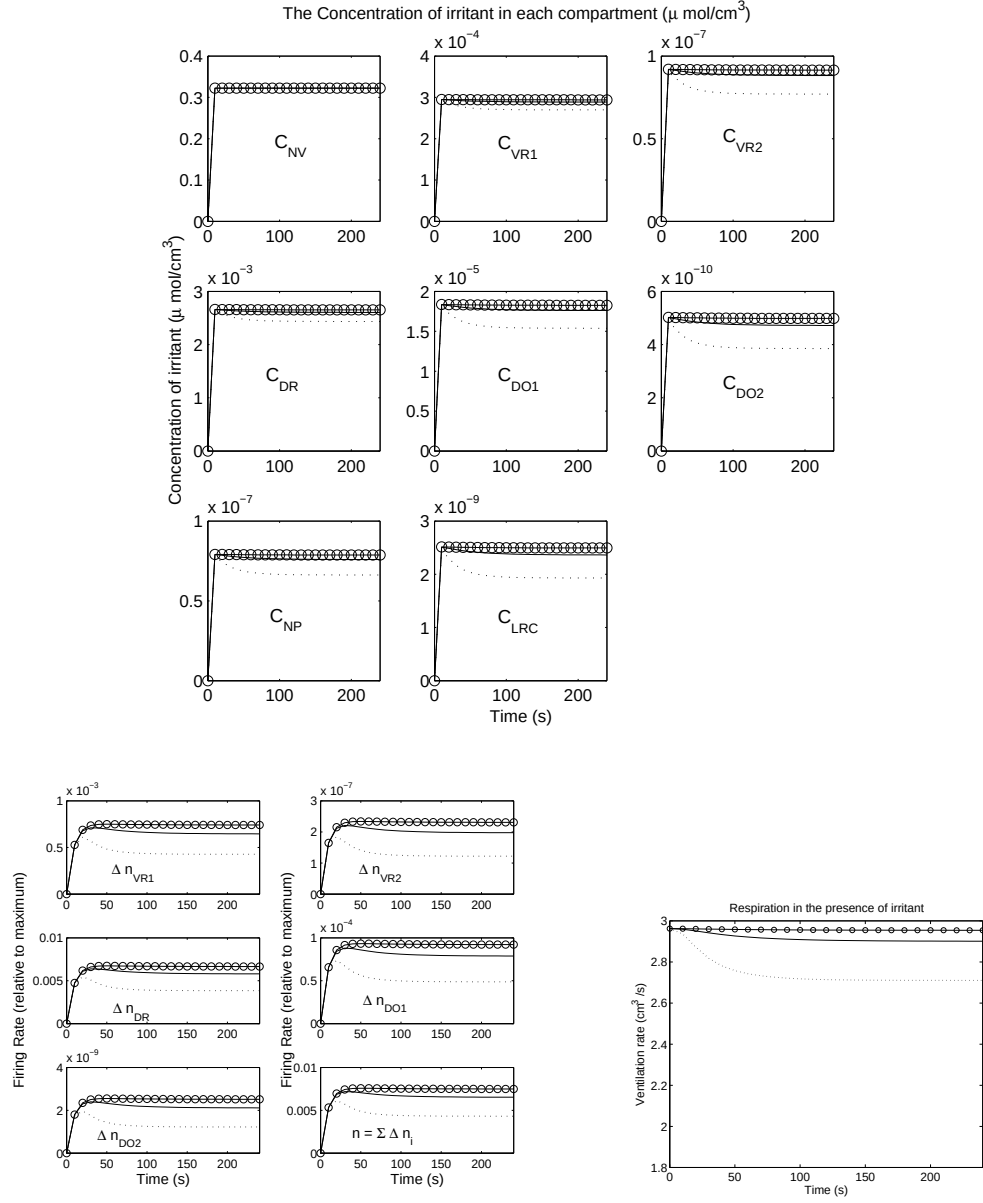


Figure 3.15: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter α . The graph with open circles represents the solution when $\alpha = 50$, the solid line is for the solution when $\alpha = 500$, and the dotted line is for the solution when $\alpha = 5000$. The values of the other fixed parameters are listed in Table 3.3.

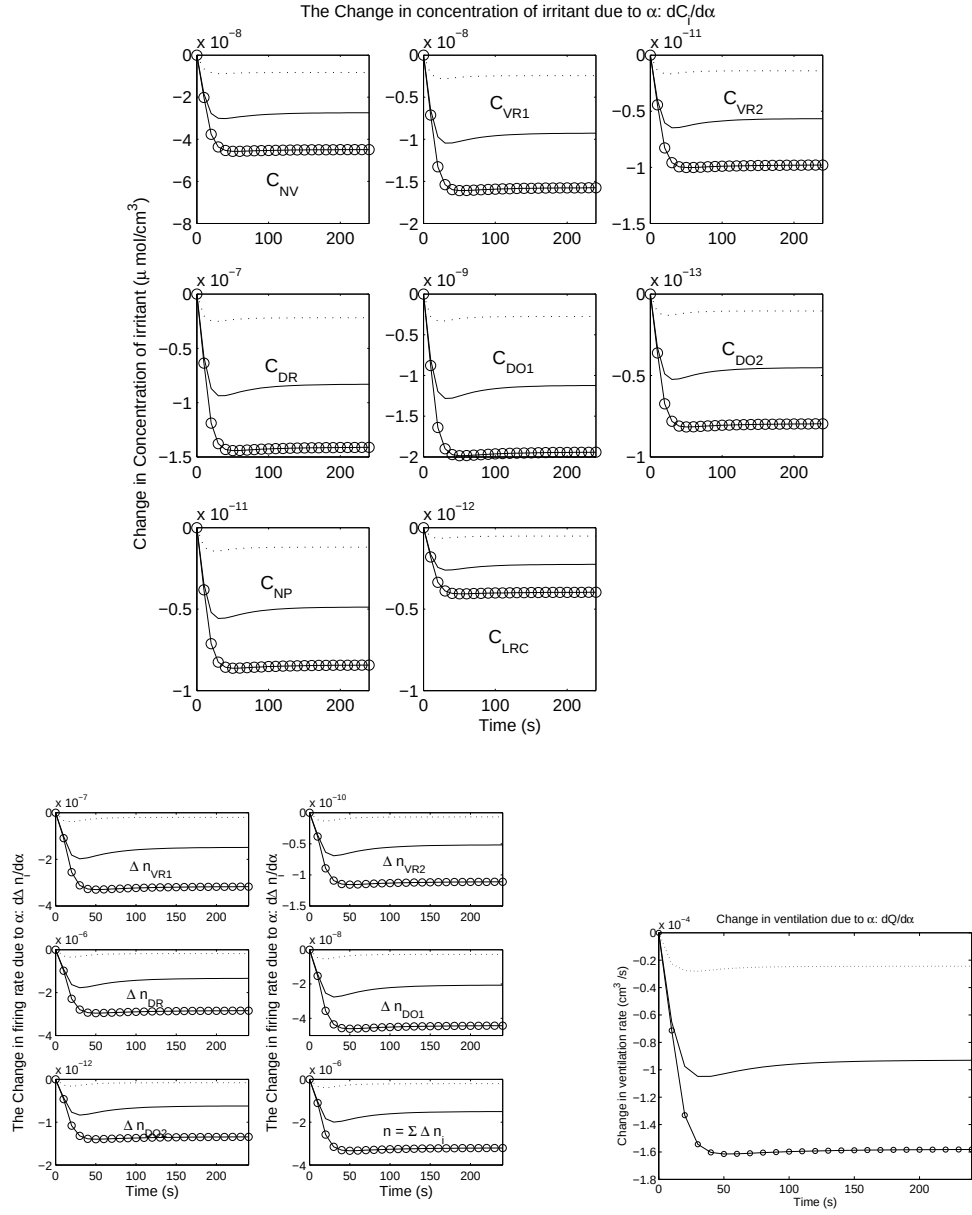


Figure 3.16: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in α . The graph with open circles represents the solution when $\alpha = 50$, the solid line is for the solution when $\alpha = 500$, and the dotted line is for the solution when $\alpha = 5000$. The values of the other fixed parameters are listed in Table 3.3.

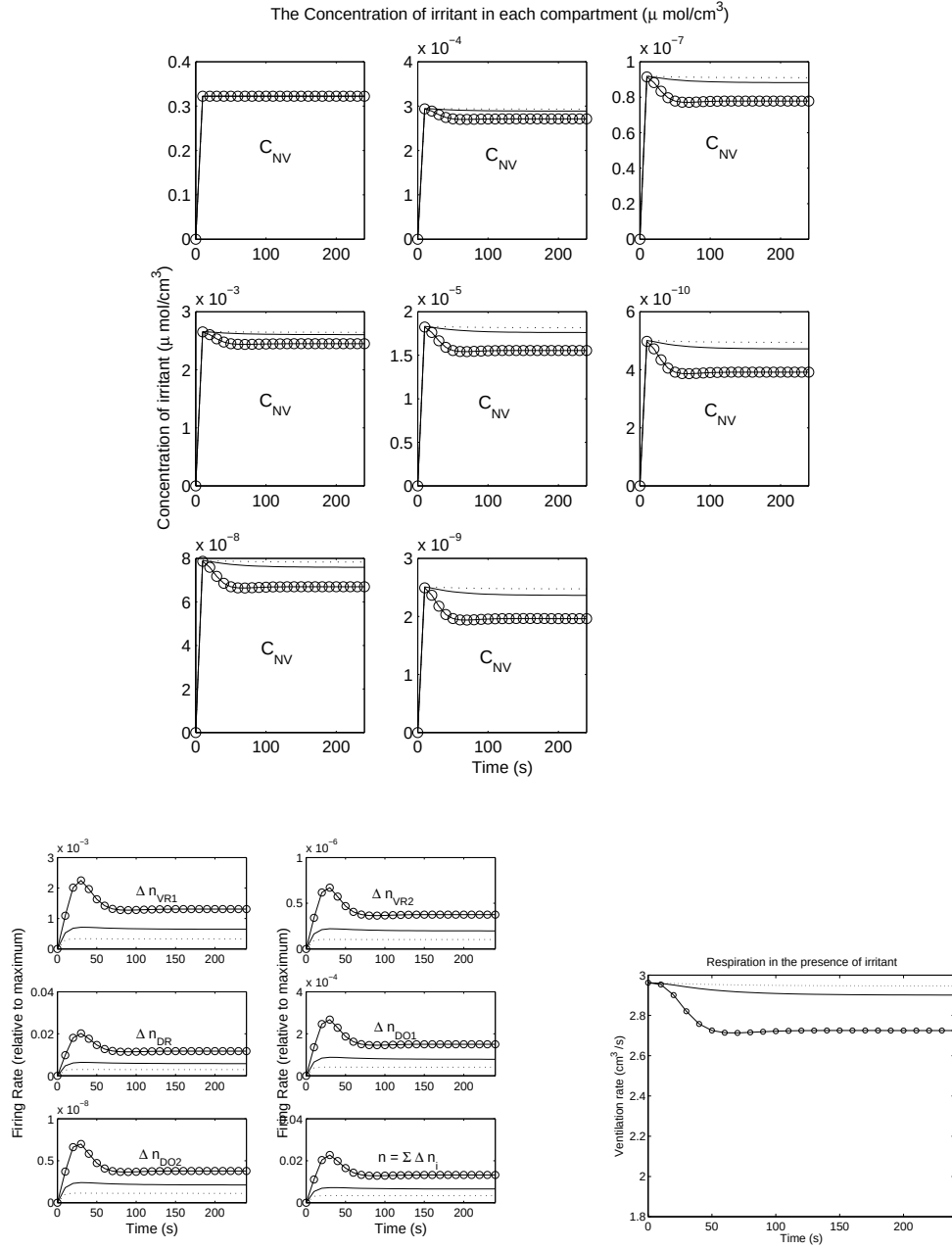


Figure 3.17: The solutions to the model for the concentration of the irritant in various compartments, the solutions for the firing rate in various compartments, and the solutions for ventilation while varying the parameter K_D . The graph with open circles represents the solution when $K_D = 0.5/1.15 \approx 0.4348$, the solid line is for the solution when $K_D = 1/2$, and the dotted line is for the solution when $K_D = 0.5 * 1.15 = 0.5750$. The values of the other fixed parameters are listed in Table 3.3.

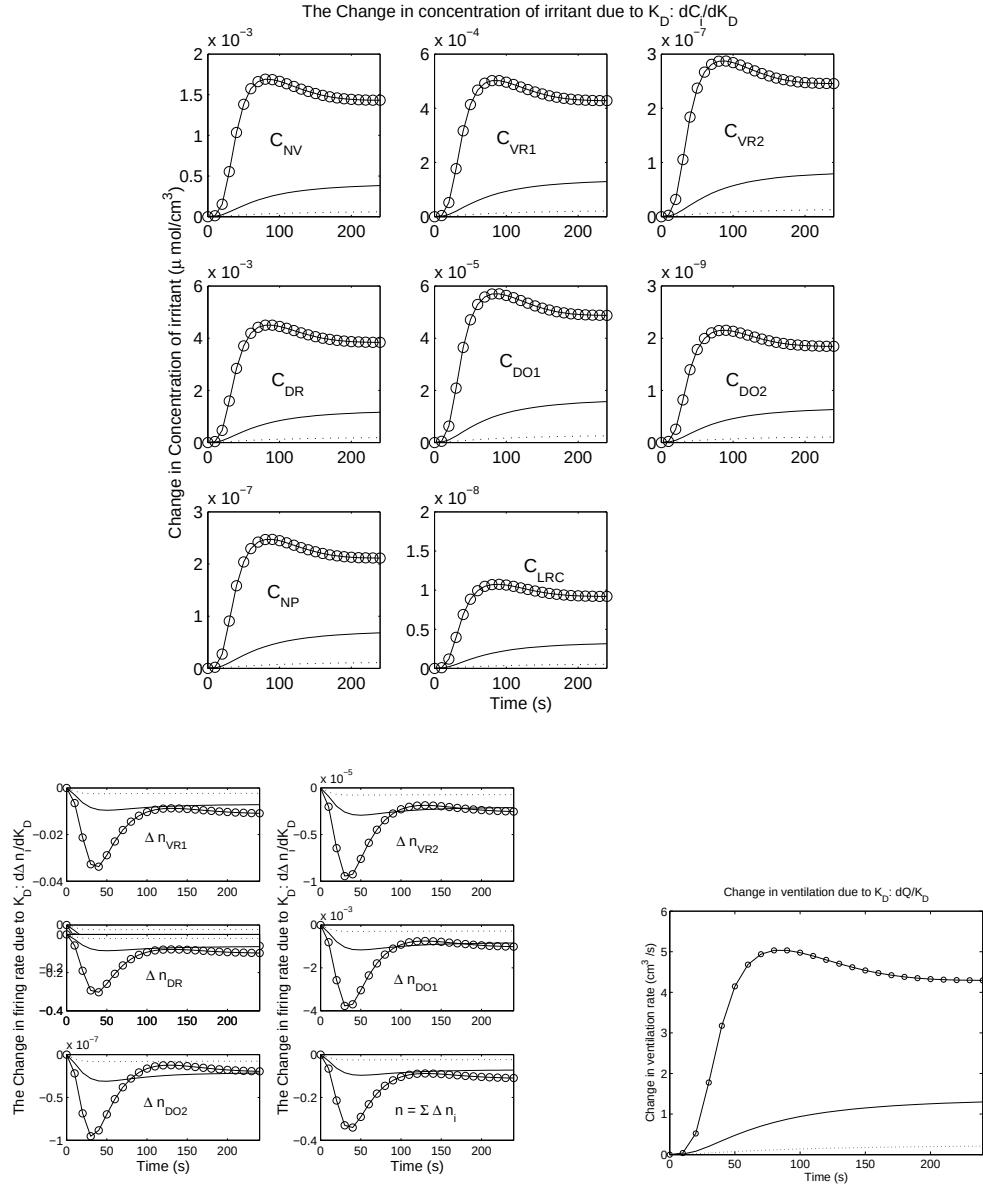


Figure 3.18: The solutions to the normalized sensitivity equations of the compartmental concentrations, the firing rates, and the ventilation rates to changes in K_D . The graph with open circles represents the solution when $K_D = 0.5/1.15 \approx 0.4348$, the solid line is for the solution when $K_D = 1/2$, and the dotted line is for the solution when $K_D = 0.5 * 1.15 = 0.5750$. The values of the other fixed parameters are listed in Table 3.3.

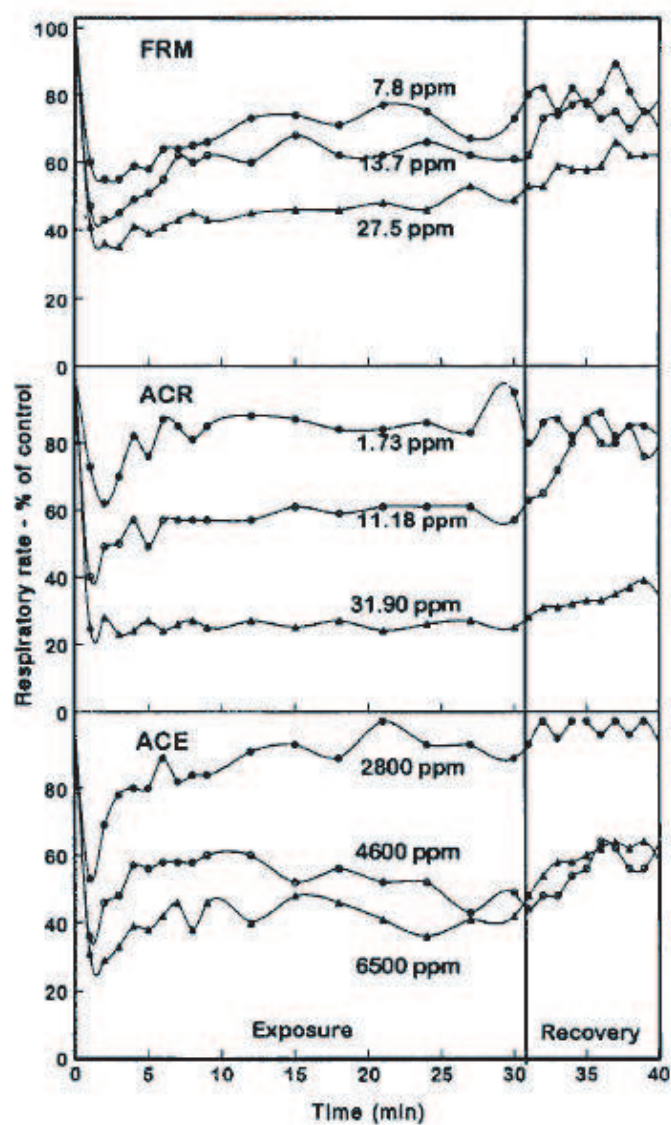


Figure 3.19: The graph of the inhalation exposure studies from [25] for exposure to formaldehyde (FRM), acrolein (ACR), and acetaldehyde (ACE). Each line represents the average of four rats. The vertical line around 30 minutes represents the end of exposure.

Nelder-Mead algorithm in the form of the built in Matlab function *fminsearch* to minimize an unweighted least squares function like the one in (3.75). The starting values for the optimization were chosen based on the steady-state analysis. Originally, one set of parameters was hoped to describe all three different exposure levels of data taken from [25], but this did not seem possible as suggested in the steady-state analysis in Section 3.4. The algorithm DIRECT was also used in order to find a well-fitting solution to the data from [25]. Several attempts were made to optimize the model to data, using both *fminsearch* and C.T. Kelley's DIRECT code [54] with different beginning parameter values and/or weighted cost functions, i.e.,

$$J_{\omega}^* = \min_{q \in X} J_{\omega}(q) = \min_{q \in X} \sum_{i=1}^n \omega_i |x(t_i, q) - d_i|^2 \quad (3.76)$$

where $\omega_i > 0$ varies from data point to data point. None of these attempts truly captured the drop and recovery behavior of the data, and simple optimization methods seem to fall into the minimum of an average of the data. Hence, restrictions on different parameters were also used to try to force a positive derivative dQ/dt in an appropriate region. One idea was to impose constraints on parameters so that we would have a positive derivative in the region our data recovers. In order to do this we must return to our differential equation for Q :

$$\begin{aligned} \frac{dQ}{dt} &= \frac{Q_{steady}(n) - Q}{\tau_Q} \\ &= \frac{Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p}{\tau_Q(1 + \alpha n^p)}. \end{aligned} \quad (3.77)$$

Now, the denominator in (3.77) is always positive, so (3.77) will be positive if the numerator is positive. Further,

$$\begin{aligned} 0 &< Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p \\ \Rightarrow \alpha &< \frac{Q_{max} - Q}{(Q - Q_{min})n^p}. \end{aligned} \quad (3.78)$$

Note that $Q - Q_{min} > 0$. Now, we basically need α such that the condition in (3.78) is true in the region that we need $dQ/dt > 0$, i.e., we need Q and α to satisfy the above for part but not all of the domain. This is a difficult condition to impose because the solution Q is dependent on α as well as the components of n and the parameter p . We can, for any fixed set of parameters τ_r , k_0 , τ_Q , p , and K_D , integrate and check the condition in (3.78) and reset an appropriate α . If we repeatedly perform the three steps of integration, checking, and resetting, α will settle into a value that will have the recovery behavior we would like. When α was higher than (3.78) in the interval of increasing Q , α was reset to be 75% of the right-hand side of (3.78). Specifically the region where the forcing was used was (186,486) seconds. Since this manual forcing of the parameter α did not work as well as needed, a stronger condition on α was devised in a similar way. The restriction (3.78) was derived solely to force a *positive* derivative, but that positive derivative could be so small in magnitude that it appears flat. Hence, a restriction that guarantees a more significant increase in Q might produce better results. Let us return to our restriction of α at (3.77) and set dQ/dt larger than some positive, nonzero tolerance ϵ :

$$\begin{aligned}
\epsilon &< \frac{Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p}{\tau_Q (1 + \alpha n^p)} \\
\tau_Q (1 + \alpha n^p) \epsilon &< Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p \\
\tau_Q \epsilon + \tau_Q \alpha n^p \epsilon &< Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p \\
\alpha (Q n^p - Q_{min} n^p + \tau_Q n^p \epsilon) &< Q_{max} - Q - \tau_Q \epsilon \\
\alpha &< \frac{Q_{max} - Q - \tau_Q \epsilon}{Q n^p - Q_{min} n^p + \tau_Q n^p \epsilon}
\end{aligned} \tag{3.79}$$

Note again that this analysis works because $Q > Q_{min}$. Also, since we are only enforcing (3.79) in a particular region away from $t = 0$, n will not cause a division by zero. Now, using a small $\epsilon > 0$, we hoped to be able to better force the optimization to capture the behavior of the data. We used the same procedure as with restricting α by (3.78), i.e., we repeatedly iterated and checked values, and α values that are too high were reset to 75% of the right-hand side of (3.79). Using this newer, stronger restriction on α in the region that dQ/dt needs to be positive, the Nelder-Mead algorithm was again utilized to minimize the unweighted least squares problem shown in (3.75). Still the results seemed no better than

before, so the approach was reused with a different parameter. In the steady-state analysis, we observed how α needed to change as dose did to better represent the data, but we could find no obvious function of dosage for α . Perhaps no clear connection exists between α and dosage because the variation with dosage occurs within another parameter. When manually changing the parameters to obtain a good shape for the solution, α appears to need to be large relative to the other parameters. This somewhat contradicts our restrictions (3.78) and (3.79). These restrictions both contain the parameter p , so we hoped to get to our desired solution by restricting p instead of α . We returned to the beginning of the derivation of (3.79), and this time considered how we can restrict p :

$$\begin{aligned}
\epsilon &< \frac{Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p}{\tau_Q (1 + \alpha n^p)} \\
\tau_Q (1 + \alpha n^p) \epsilon &< Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p \\
\tau_Q \epsilon + \tau_Q \alpha n^p \epsilon &< Q_{max} + \alpha Q_{min} n^p - Q - \alpha Q n^p \\
n^p (\alpha Q - \alpha Q_{min} + \alpha \tau_Q \epsilon) &< Q_{max} - Q - \tau_Q \epsilon \\
n^p &< \frac{Q_{max} - Q - \tau_Q \epsilon}{\alpha (Q - Q_{min} + \tau_Q \epsilon)} \\
p \ln(n) &< \ln \left[\frac{Q_{max} - Q - \tau_Q \epsilon}{\alpha (Q - Q_{min} + \tau_Q \epsilon)} \right] \\
p &> \frac{\ln \left[\frac{Q_{max} - Q - \tau_Q \epsilon}{\alpha (Q - Q_{min} + \tau_Q \epsilon)} \right]}{\ln(n)}. \tag{3.80}
\end{aligned}$$

Note that we know that $\ln(n) < 0$ because $n \leq 1$. We used the same recursive formulation that we tried with α except that we set the new p to be 1.1 times the right-hand side of (3.80). Then the Nelder-Mead algorithm was used to minimize the least squares cost function $J(q)$ while imposing (3.80) in a region where $dQ/dt > 0$. Again no significant improvement was seen in the optimization to data and hence more changes were needed. Different values of ϵ were used with both the updated restriction for α in (3.79) and for (3.80). Perhaps ϵ was chosen unwisely, making the sign of the numerators in the restrictions inappropriate and hence, causing the imposition of either restriction to fail in its purpose.

Since we could get some of the behavior of the data through optimization but not all, other optimization algorithms than Nelder-Mead were explored. The multidirectional

search (MDS) method has bounded condition numbers of its simplices which addresses the possible ill-conditioning of the Nelder-Mead algorithm [55]. Although in our situation, Nelder-Mead is finding a minimum that is logical (just not ideal according to the data) so the bounding of condition numbers probably was not going to alone help to find a better minimum. Still, attempting another method such as MDS was thought to be beneficial. The multidirectional search method was used with the unweighted least squares cost function (3.75) to optimize the 7.8 ppm data set. The bounding of the condition number was found not to matter at all, as this method found exactly the same values as the unweighted but α -restricted optimization using Nelder-Mead.

Since our problem is not noisy and simplex methods (e.g., Nelder-Mead) do not seem to capture all appropriate behavior, gradient based methods were used as well. In order to use a gradient based method, however, we must have a function that computes the gradient of our cost function. Let us return to our function J and we can see that

$$\begin{aligned}
 J(q) &= \sum_{i=1}^n |x(t_i, q) - d_i|^2 \\
 \frac{\partial J}{\partial q_j} &= \sum_{i=1}^n \frac{\partial}{\partial q_j} [|x(t_i, q) - d_i|^2] \\
 &= \sum_{i=1}^n 2 |x(t_i, q) - d_i| \frac{\partial x(t_i, q)}{\partial q_j}.
 \end{aligned} \tag{3.81}$$

Note that the only component of x we are considering is our ventilation Q so we can really think of (3.81) as

$$\frac{\partial J}{\partial q_j} = 2 \sum_{i=1}^n |Q(t_i, q) - d_i| \frac{\partial Q(t_i, q)}{\partial q_j}. \tag{3.82}$$

Hence, we can use our already formulated sensitivity equations to calculate the gradient of our cost function. The method of steepest descent from [55] via the algorithm `steep.m` (found in [54]) was utilized to optimize our system using (3.75) and (3.82) and the regional α restriction shown in (3.78). Various beginning parameters were used, but problems were found with Matlab's integration tolerances, either with the initial iterate or with subsequent

steps of the steepest descent algorithm with or without extra parameter restrictions (such as (3.78), (3.79), (3.80)). Hence the use of gradient-based methods was abandoned early in the optimization.

Since the model fits up to this point had not represented the data, we began to look at things somewhat differently. We should note that the curve traced by the data from the three data sets is not symmetric in the concave up portion in the beginning of the time period. In other words, the drop is quicker than the recovery. Hence, we may need to consider two components to our time constant τ_Q instead of just one. In order to try and capture the behavior of the data, we can look at τ_Q as dependent on whether or not ventilation has begun to recover from the initial decrease. For example, we can consider the parameter τ_Q as a combination of other parameters, i.e.,

$$\tau_Q = \frac{1}{2}\tau_{Q_1} \left(1 - \text{sign}\left(\frac{dQ}{dt}\right)\right) + \frac{1}{2}\tau_{Q_2} \left(1 + \text{sign}\left(\frac{dQ}{dt}\right)\right), \quad (3.83)$$

where τ_{Q_1} and τ_{Q_2} are positive constants and sign is the function such that

$$\text{sign}(x) = \begin{cases} 1, & x > 0 \\ 0, & x = 0 \\ -1 & x < 0 \end{cases}.$$

We should note that with τ_Q defined by (3.83), $\tau_Q = \tau_{Q_1}$ when $dQ/dt < 0$ and $\tau_Q = \tau_{Q_2}$ when $dQ/dt > 0$. Note that τ_Q is the average of τ_{Q_1} and τ_{Q_2} when $dQ/dt = 0$. After initially describing τ_Q as in (3.83), this set up was changed slightly so that $\tau_Q = \tau_{Q_2}$ once the recovery stage has begun. Problems arose with the definition of τ_Q in (3.83) because the derivative can become negative again before steady state occurs. Since the curve often decreases and increases slightly, settling into the steady-state, the definition of τ_Q in (3.83) can cause errors in data fitting. If the value of τ_Q is allowed to change after the recovery has begun, we see significant variation when the solution is close to or at steady-state. Hence the definition of τ_Q was changed so that $\tau_Q = \tau_{Q_2}$ once the recovery had begun regardless of the sign of dQ/dt after that point. We can consider our new description of τ_Q biologically as well. We can think of τ_{Q_1} as the time constant characterizing the time that it takes for the response to have its initial effect, and we can consider τ_{Q_2} as characterizing the

time it takes for ventilation to recover and adapt to the presence of irritant. The idea that the rat physiological system responds differently in its initial response and its beginning recovery to steady state seems reasonable biologically and does make sense with the data. A Nelder-Mead optimization (with the Matlab function *fminsearch*) was run on the first data set (with selective data points removed) and the resulting optimal values are contained in Table 3.4 and shown in Figure 3.20. The optimization was rerun for the second data set (with selective data points removed) and the parameters resulting from that optimization are contained in Table 3.5, and the ventilation solution with these parameters is shown in Figure 3.21. The optimization was rerun for the third data set (also with selective points removed) and the results of that optimization are contained in Table 3.6. Note that in all optimization graphs of ventilation the curves begin at the Q_{max} value which corresponds to the 100% of the beginning ventilation value. A data point is not placed at $(0, Q_{max})$ because this initial value is built into the model, but we should reiterate that the steep drop at the beginning of exposure is representative of the physiological response.

Now, the parameter values do vary, and we should note how they differ. The parameter τ_{Q_1} does not seem to vary greatly among the three data sets, and neither do p nor K_D . We do see variation in α , but since the model is not overly sensitive to α perhaps we should not focus on how to alter this parameter. We do see variation in τ_r and τ_{Q_2} , and we can note that the k_0 optimal value for the third data set differs from the results from the other two exposure levels. Since the magnitude of many of the values is similar across the optimizations for all three exposure levels, perhaps we can get most of the parameters the same for all data sets with careful selection. Many one parameter optimizations were

Table 3.4: Resulting values from an unweighted least squares minimization on the first data set (with five data points removed) using the Nelder-Mead algorithm and starting values $\tau_r = 9.1$, $k_0 = 86$, $\tau_{Q_1} = 72.2$, $p = 2.8$, $K_D = 1.5$, $\tau_{Q_2} = 737.5$, and $a = 993.1$. The cost function value for these parameters was $J^* = 0.0723$ for the data points used.

Parameter	Optimized Value
τ_r	9.09
k_0	167.3
τ_{Q_1}	83.3
τ_{Q_2}	1532.3
p	3.52
α	64949.4
K_D	3.16

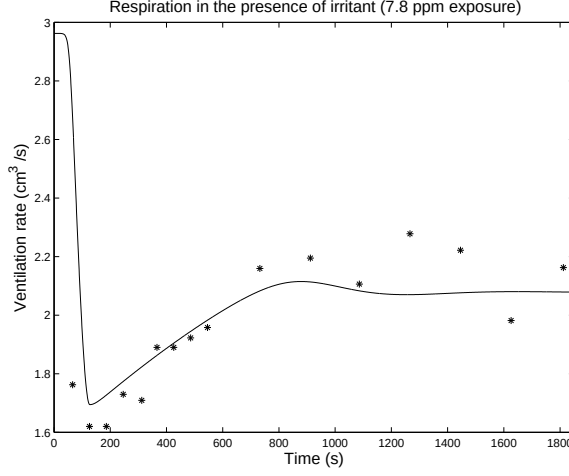


Figure 3.20: Solution for ventilation for 7.8 ppm exposure using parameters optimized over only this data set. The parameter values used in this solution are: $\tau_r = 9.09$, $k_0 = 167.3$, $\tau_{Q_1} = 83.3$, $\tau_{Q_2} = 1532.3$, $p = 3.52$, $\alpha = 64949.4$, and $K_D = 3.16$. The lowest exposure optimization was performed on all data points in this set except for the first, fourth, twelfth, thirteenth, and fifteenth data points.

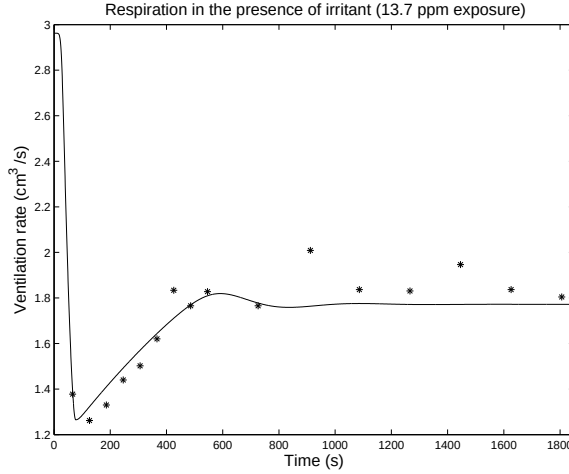


Figure 3.21: Solution for ventilation for 13.7 ppm exposure using parameters optimized over only this data set. The parameter values used in this solution are: $\tau_r = 6.70$, $k_0 = 166.0$, $\tau_{Q_1} = 46.0$, $\tau_{Q_2} = 1095.4$, $p = 3.246$, $\alpha = 78035.1$, and $K_D = 3.50$. The middle exposure optimization was performed on all data points in this set except for the eleventh and fourteenth data points.

run, i.e., the Matlab function *fminsearch* was used again but to only find one optimal parameter for a data set while using the other six parameters from results with another data set. The results from the second data set seemed to give the best results for varying one parameter at a time, but those results were still insufficient to capture all appropriate behavior. Hence the second data set was used with double parameter estimations, and the results from those optimizations are contained in Table 3.7. The first column indicates what two parameters were varied and the next two columns indicate the costs of the new parameters for both the first and third data sets. Unless otherwise stated, the unvaried parameters were held fixed at the values in Table 3.5, and the estimated parameters were given initial values from that table as well. Parameters were varied in pairs based on the analysis of the differing optimization results, on model sensitivity, and (specifically in the case of τ_{Q_2}) on the qualitative effect of the parameter. The parameters k_0 and τ_r were not

Table 3.5: Resulting values from (a weighted then) an unweighted least squares minimization on the second data set (with two data points removed) using the Nelder-Mead algorithm and starting values $\tau_r = 6.89$, $k_0 = 160$, $\tau_{Q_1} = 84.4$, $p = 3$, $K_D = 3.5$, $\tau_{Q_2} = 1049.6$, and $a = 64768.1$. The cost function value for these parameters was $J^* = 0.0462$ for data points used.

Parameter	Optimized Value
τ_r	6.70
k_0	166.0
τ_{Q_1}	46.0
τ_{Q_2}	1095.4
p	3.246
α	78035.1
K_D	3.50

Table 3.6: Resulting values from an unweighted least squares minimization on the third data set (with three data points removed) using the Nelder-Mead algorithm and starting values $\tau_r = 6.7$, $k_0 = 166$, $\tau_{Q_1} = 46$, $p = 3.246$, $K_D = 3.50$, $\tau_{Q_2} = 1095.4$, and $a = 78035.1$. The cost function value for these parameters was $J^* = 0.0142$ for data points used.

Parameter	Optimized Value
τ_r	3.68
k_0	65.7
τ_{Q_1}	51.6
τ_{Q_2}	2567.4
p	4.04
α	184989
K_D	1.13

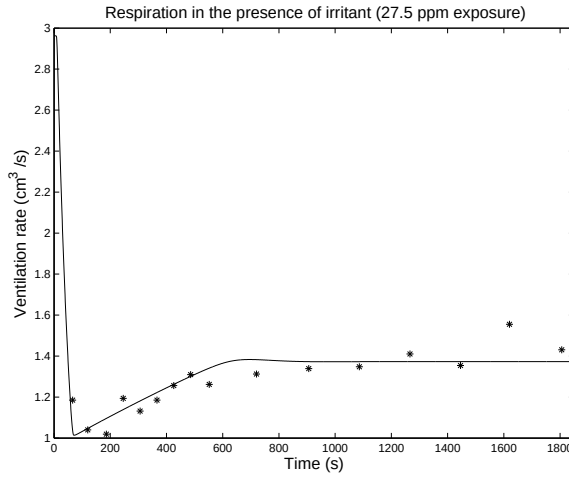


Figure 3.22: Solution for ventilation for 27.5 ppm exposure using parameters optimized over only this data set. The parameter values used in this solution are: $\tau_r = 3.68$, $k_0 = 65.7$, $\tau_{Q_1} = 51.6$, $\tau_{Q_2} = 2567.4$, $p = 4.04$, $\alpha = 184989$, and $K_D = 1.13$. The highest exposure optimization was performed on all data points in this set except for the first, fourth, and fifteenth data points.

optimized as a pair because they have similar effects on the solutions. The best fitting two-parameter optimization resulted from varying the parameters τ_r and τ_{Q_2} , and the graphs of the ventilation solutions for those fits to the first and third exposure levels are contained in Figure 3.23 and Figure 3.24.

Although the results shown in Figure 3.21, Figure 3.23, and Figure 3.24 all seem to have good fits, we should consider the likelihood of having all parameters the same across the exposure levels except for τ_r and τ_{Q_2} . The parameters τ_r and τ_{Q_2} both represent

Table 3.7: Resulting values from unweighted least squares double parameter minimizations on the first (7.8 ppm exposure) and third (27.5 ppm exposure) data sets using the Nelder-Mead algorithm and parameter values fixed at those in Table 3.5 unless otherwise specified. The cost function values reflect the values for only the selective points used.

Parameters Varied	Parameter Values/Cost (Data Set 1)	Parameter Values/Cost (Data Set 3)
τ_r, τ_{Q_2}	$\tau_r = 10.07, \tau_{Q_2} = 1688.9/J^* = 0.1084$	$\tau_r = 4.29, \tau_{Q_2} = 1856.2/J^* = 0.0352$
τ_r, p	$\tau_r = 10.74, p = 4.09/J^* = 0.1509$	$\tau_r = 4.51, p = 3.26/J^* = 0.0652$
τ_r, α	$\tau_r = 10.25, \alpha = 75860.9/J^* = 0.1608$	$\tau_r = 4.545, \alpha = 54683.8/J^* = 0.0649$
τ_r, K_D	$\tau_r = 8.21, K_D = 2.81/J^* = 0.1648$	$\tau_r = 5.00, K_D = 3.90/J^* = 0.0640$
k_0, τ_{Q_2}	$k_0 = 247.4, \tau_{Q_2} = 1803.6/J^* = 0.1032$	$k_0 = 106.0, \tau_{Q_2} = 1424.6/J^* = 0.0596$
k_0, p	$k_0 = 254.46, p = 3.31/J^* = 0.1662$	$k_0 = 121.3, p = 4.43/J^* = 0.0683$

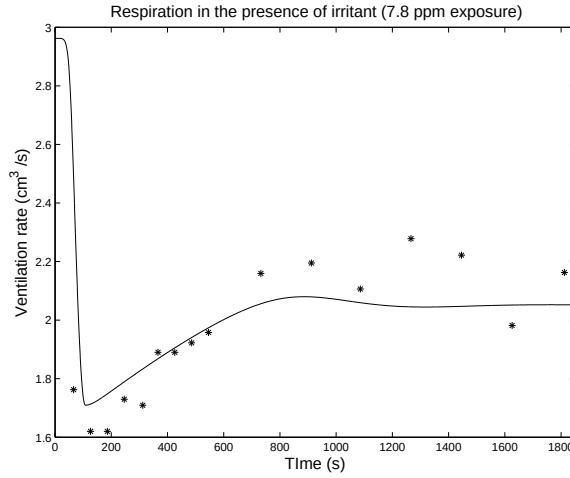


Figure 3.23: Solution for ventilation for 7.8 ppm exposure after using five parameters from the optimization from only the second data set and optimizing over τ_r and τ_{Q_2} . The parameter values used in this solution are: $k_0 = 166$, $\tau_{Q_1} = 46.0$, $p = 3.246$, $\alpha = 78035.1$, $K_D = 3.5$, $\tau_r = 10.07$, and $\tau_{Q_2} = 1688.9$. The two-parameter optimization was performed using all data points in the first data set except for the first, fourth, twelfth, thirteenth, and fifteenth data points.

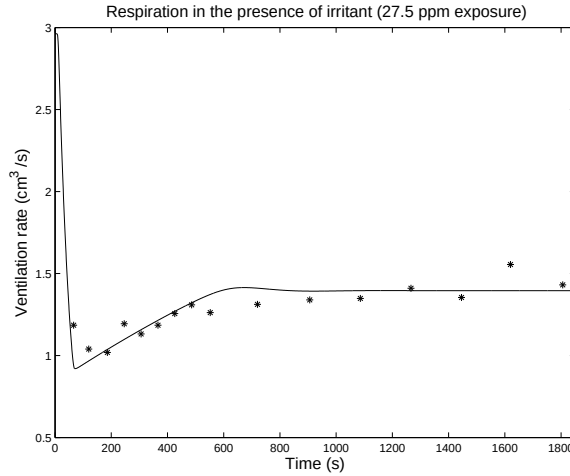


Figure 3.24: Solution of ventilation for 27.5 ppm exposure after using five parameters from the optimization from only the second data set and optimizing over τ_r and τ_{Q_2} . The parameter values used in this solution are: $k_0 = 166$, $\tau_{Q_1} = 46.0$, $p = 3.246$, $\alpha = 78035.1$, $K_D = 3.5$, $\tau_r = 4.29$, and $\tau_{Q_2} = 1856.2$. The two-parameter optimization was performed using all data points in the third data set except for the first, fourth, and fifteenth data points.

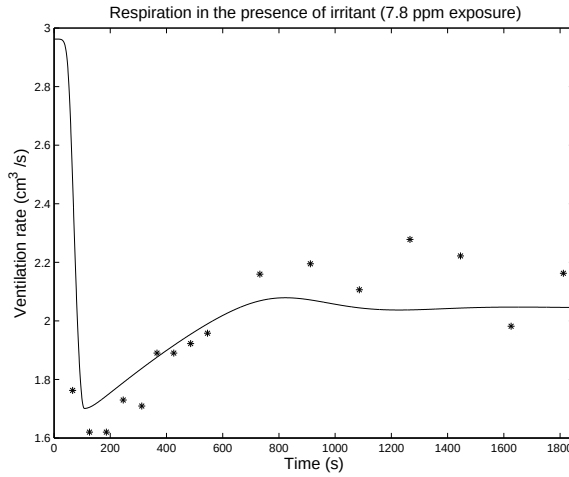


Figure 3.25: Solution of ventilation for the 7.8 ppm exposure after optimizing over only τ_Q with fixed values from an optimization over the second data set and an averaged value of τ_{Q_2} . The parameters used in this solution are: $\tau_r = 10.10$, $k_0 = 166.0$, $\tau_{Q_1} = 46.0$, $\tau_{Q_2} = 1531.6$, $p = 3.246$, $\alpha = 78035.1$, and $K_D = 3.50$. Note that all the data points in the first data set were used in this optimization.

reaction or adaptation times in the system, and it does seem logical that these times could be dose dependent. The values of τ_r for the various exposure levels ($\tau_r = 10.07$ seconds for 7.8 ppm, $\tau_r = 6.70$ seconds for 13.7 ppm, $\tau_r = 4.29$) decrease with the increasing exposure level which seems to support the idea of τ_r being dose-dependent. The parameter τ_{Q_2} , however, does not have such a nice pattern across dosage level ($\tau_{Q_2} = 1688.9$ seconds for 7.8 ppm, $\tau_{Q_2} = 1095.4$ seconds for 13.7 ppm, $\tau_{Q_2} = 1856.2$ seconds for 27.5 ppm). Also, the values of τ_{Q_2} do not vary much across exposure level. Further, since τ_{Q_1} does not seem to vary with dosage, one might not expect τ_{Q_2} to vary either. Moreover, we know that the overall model is not very sensitive to changes in τ_Q as shown in the sensitivity analysis. Hence, the three values of τ_{Q_2} were averaged to get one value ($\tau_{Q_2} = 1531.6$ seconds), and single-parameter optimizations on τ_r were run on all three data sets. The resulting values of τ_r were $\tau_r = 10.10$ for 7.8 ppm, $\tau_r = 6.54$ for 13.7 ppm, and $\tau_r = 4.40$ for 25.7 ppm; and the resulting ventilation curves are contained in Figure 3.25, Figure 3.26, and Figure 3.27.

The comparative overall unweighted cost values for the three different solutions presented (optimizations over each dose, optimization over τ_r and τ_{Q_2} , optimization over τ_r with an average τ_{Q_2}) are contained in Table 3.8. Note that these costs are calculated based on all used data points and not on selective subsets as used in the optimizations.

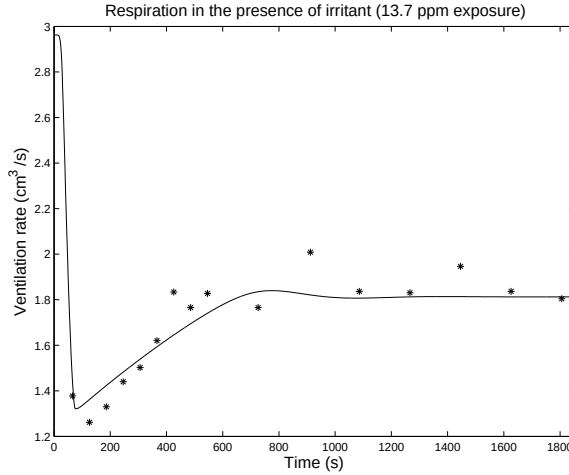


Figure 3.26: Solution of ventilation for the 13.7 ppm exposure after optimizing over only τ_Q with fixed values from an optimization over the second data set and an averaged value of τ_{Q_2} . The parameters used in this solution are: $\tau_r = 6.54$, $k_0 = 166.0$, $\tau_{Q_1} = 46.0$, $\tau_{Q_2} = 1531.6$, $p = 3.246$, $\alpha = 78035.1$, and $K_D = 3.50$. All the data points in the second data set were used in this optimization except for the fourteenth.

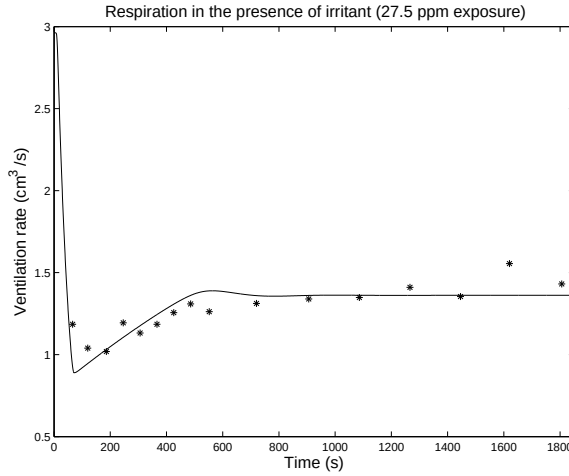


Figure 3.27: Solution of ventilation for the 27.5 ppm exposure after optimizing over only τ_Q with fixed values from an optimization over the second data set and an averaged value of τ_{Q_2} . The parameters used in this solution are: $\tau_r = 4.40$, $k_0 = 166.0$, $\tau_{Q_1} = 46.0$, $\tau_{Q_2} = 1531.6$, $p = 3.246$, $\alpha = 78035.1$, and $K_D = 3.50$. All the data points in the third data set were used in this optimization except for the fifteenth.

3.7 Discussion

The solutions presented in Section 3.6 all seem to fit data well suggesting that the model does reasonably describe the physiological system. The shape and value of the solutions seem reasonable even if we cannot get one set of parameters for all dosage levels. We should note that we lowered the overall cost function when using either five or six parameters in common, and the cost difference between varying two parameters and only varying τ_r was minor. Comparing the cost values shown in Table 3.8, we should note that the major contribution to this small difference between sharing five or six parameters is the worsening of the fit to the third exposure level. The data from the third exposure level may or may not have flattened by the end of the collection period and perhaps further experimental studies could better elucidate if τ_{Q_2} varies with dose. Seeing that the cost function is actually smaller with more parameters in common across dosage suggests that many of the parameters can be the same across exposure level, and the closeness of the two values when fewer parameters differ with dose probably suggests that there is dose-dependence with only one investigated parameter. We should note, however, that the decrease in cost from the individual optimizations to the double-parameter optimizations indicates that we had not found the three global optima in the optimizations over each exposure level. Perhaps more effort in the individual optimizations before incorporating parameter dose-dependence would help improve the results.

The achieved parameter values seem reasonable as well. The parameter τ_r represents a nerve adaptation constant and values of between 4 and 10 seconds seem physiologically within reason since in [69] the original τ_i values were 0.5, 5.0, and 500 seconds. The values of k_0 and α could vary greatly and still be plausible. Specifically, α was expected to be large since the reconstruction of x_{steady} from the original function from [69] results in a minimum for Q_{steady} above the value Q_{min} . Both p and K_D appear reasonable as well since neither is extremely large nor extremely small. A difference in the two values of τ_Q seems

Table 3.8: Total cost function values for each of the optimization results presented.

	7.8 ppm	13.7 ppm	25.7 ppm	Total
Optimization over each dose	0.9583	0.1367	0.0859	1.1809
Varying τ_r and τ_{Q_2}	0.6953	0.1367	0.1323	0.9643
Varying τ_r with fixed average τ_{Q_2}	0.6913	0.1329	0.1586	0.9828

likely according to data, and the time of recovery being much higher makes sense with data as well.

The model does seem to describe the system reasonably well, but we would hope that a single set of parameters would fit regardless of dose. Since the model did not capture the behavior of the data without incorporating some dose-dependence, it is possible the model does not take all of the necessary aspects of the system into account. Perhaps more detail in the model is needed in the differential equations or how we deal with the time of adaptation.

3.7.1 Possible Model Changes

The model in Section 3.2 (and Appendix B) was derived with the idea that a simpler option was a better place to begin from in modeling irritant response. Perhaps more complexity is needed or small changes need to be incorporated in order to capture the system without dose-dependent parameters. Small changes in values chosen based on supportive studies (such as the values of w_i) or arbitrary values (such as δ) might affect the system as well.

The model from [39] was greatly simplified in order to not begin with an overly complicated description. We may, however, need some of the details that we omitted. We used a basic loss term and did not account for layers of tissue into the cavity wall because we considered the response to depend on the irritant presence in the air inside the nasal cavity. Perhaps the receptors actually respond to the presence of irritant in the mucosa. In the model development we considered using a simple one-compartment model for total formaldehyde concentration in the mucosa, to allow for a time-dependence in the build-up and clearance of the chemical activity (tissue concentration) during and after exposure. This additional mucosa compartment for each spacial compartment within the cavity is shown pictorially in Figure 3.3. Ignoring the potential for molecular formaldehyde to reach high enough concentrations in the mucosa to reduce uptake from the gas-phase by "back pressure," we could consider the rate of delivery of formaldehyde to the tissue compartment as equal to the rate of flux across the air:tissue interface from each lumen compartment. Removal could be assumed to simply occur by a first-order mechanism that includes blood perfusion and all chemical reactions. The mass balance on total formaldehyde concentration in mucosa compartment i , could then be described:

$$V_{Mi} \frac{dC_{Mi}}{dt} = K_{gc,i} S_i C_i - \beta_i C_{Mi}, \quad (3.84)$$

where β_i is the first-order loss constant and the factor. If then we based the equations for Δn_i on the concentration of formaldehyde in the mucosa compartments, C_{Mi} , we could possibly better describe the overall physiological system. Alternate models of for formaldehyde in the mucosa compartments could be also be taken from [30] or [41]. We should also note that models of formaldehyde dosimetry usually involve a linear and a nonlinear term (such as $k_f C + \frac{V_M C}{K_M + C}$) [30]. Varying β_i values may remove the need for the dose-dependence on τ_T .

We could also incorporate more complexity into the occupancy function $r(C_i)$. We originally formulated this function

$$r(C) = \begin{cases} \frac{C}{C+K_D} - r_0, & \frac{C}{C+K_D} > r_0 \\ 0, & \frac{C}{C+K_D} \leq r_0. \end{cases}, \quad (3.85)$$

but we made the assumption that $r_0 = 0$. The value r_0 could be defined otherwise or estimated through optimization. Further, we could define the occupancy function in an entirely different way. We could consider r as a differential equation and hence incorporate time dependence into the r function. One way we could do this is to let r be the number of occupied receptors normalized so that it is between 0 and 1. (Note that the r function shown in (3.85) should always be greater than or equal to 0 and less than 1 for any non-negative r_0 .) Hence, $1 - r$ is the number of unoccupied receptors, and

$$\frac{dr}{dt} = k_{on} C (1 - r) - k_{off} r, \quad (3.86)$$

where C represents either the concentration in a specific compartment (C_i) or the total of such concentrations, depending on the way we chose to approach the situation. Note that if we do consider $C = C_i$, at steady-state

$$r = \frac{C}{C + k_{off}/k_{on}},$$

which is identical to the r used in the optimization with $K_D = k_{off}/k_{on}$ and with the addition of time-dependence. By using different rates of increasing and decreasing occupancy, we could perhaps incorporate a difference in ventilation drop and recovery without having changing values for τ_Q . With (3.86) in place we might also be able to remove the weighting coefficient w_i in the equations for Δn_i . We could also change the description of occupancy by considering cooperation among receptor molecules and then raising r to a power in the current equation for n . By describing the occupancy differently, we might better model the dynamics of the response and may be able to describe τ_Q with one value or capture what appears to be dose-dependence in at least one parameter.

In the formulation of the sensory response model, the model from [69] was altered to account for maximum ventilation under normal conditions, i.e., $Q_{max} = Q_0$. The setting of Q_{max} at the normal state for n then forces $N = 0$ because of the nature of our sigmoidal function for Q_{steady} as discussed in Section 3.2.2. With better information about what maximum ventilation exists, perhaps with a lack of nerve activity, Q_{max} could be set differently and changes in the nerve equations such as the addition of the chosen parameter δ would be unnecessary. Incorporating this change into the model may negligibly affect the overall system if Q_{max} is close to Q_0 or if the Δn_i 's are very different from the value of N that would then be necessary in the model. We should further note that the functions for Δn could be eliminated entirely in favor of a direct connection between Q and the C_i values as was briefly discussed in the model formulation in Section 3.2.2. Also briefly mentioned in Section 3.2.2 was that the respiration rate could be divided into the tidal volume and the respiration frequency, and by considering respiration in this manner, we could further improve the accuracy of the model. Yet another option would be to simplify the Δn_i equations by replacing " $(n + \delta)(1 - n)$ " with simply " $(1 - n)$." This replacement would eliminate the need for δ and would have a nontrivial solution with initial value $n = 0$.

In all of the three parameter sets suggested in Section 3.6, the parameter τ_r varied with exposure level. Perhaps we should focus on how to change our consideration of this parameter since we are able to get good fitting solution curves when we allow τ_r to be different values for different dosages. We should recall that in the baroreflex-feedback

model in [69], each equation for $\Delta\dot{n}_i$ had a different time adaptation constant, τ_i . Perhaps by having a different time constant for each compartment, we could describe the model without the need for any dose-dependent parameters. Having five time constants instead of one would allow more freedom in the optimization, but we do not want to have more parameters than we can reasonably optimize over. Since the olfactory tissue is where more of the nerve activity is [79], we could possibly have two time constants, τ_{resp} and τ_{olf} , which allow the time constants from the olfactory compartments ($i = DO1, DO2$) and from the respiratory compartments ($i = VR1, VR2, DR$) to differ. Perhaps changing the values of τ_r in this way could also eliminate the need for the weighting values, w_i , since τ_r and k_0 (and hence the w_i 's) affect the model in a similar way, as was mentioned in the steady state analysis in Section 3.4 and follows from the sensitivity analysis in Section 3.5.

3.7.2 Delay Incorporation

The problem with our results prior to the separation of τ_Q into two distinct values was that we still had not captured the entire behavior of the data. The ventilation solution was recovering much too quickly to truly represent the physical situation. Hence, to better represent the data we must slow this recovery down. One way, other than using (3.83), is to incorporate a delay in the ventilation equation, i.e., alter our differential equation for ventilation to be

$$\frac{dQ}{dt} = \frac{Q_{steady}(n) - Q(t - \tau)}{\tau_Q} \quad (3.87)$$

where τ is the delay in seconds between when the nerve fires and when ventilation actually decreases. Once the firing rate of the receptors in the nasal cavity has been increased, the signal to alter respiration must still travel to the rat's brain and then be processed and sent to the organs and muscles involved in respiration. Although we would expect this time to be short, even a delay in a matter of seconds can affect our system. An attempt was made to incorporate this delay, but the routine used (Matlab's *dde23*) was far too slow to achieve results in any remotely reasonable amount of time. The model is such a stiff system that developing the history needed in the routine was incredibly time consuming and the use of (3.87) was abandoned for this study. Perhaps using another algorithm or software with the

delay in the model would produce a better solution than the ones presented in Section 3.6. The delay, τ , slows changes in respiration but may not produce the asymmetrical behavior of the data. The dynamic receptor model in (3.86) may better handle the differences in the decrease and recovery of ventilation because of the allowance of different rates for the activation and deactivation of receptors.

3.7.3 Extending the Model to Other Irritants

Although the specific results of this investigation involved formaldehyde data, one would expect that the presented model would be easily generalized to other inhaled irritants. The generalization could be as simple as changing the $K_{gc,i}$ values given that the irritant affects the trigeminal system in a similar way. Regardless of what specific parameters would require alteration, the model structure seems likely to be appropriate for other irritants.

Chapter 4

Conclusion

As stated in Chapter 1, the objective of this work was to further the study of physiological modeling. By incorporating different methods of model improvement, we hope to show a definite improvement in the models discussed. Through the use of Bayesian methods and computational optimization, we have increased the scope of the models considered.

In Chapter 2, an established model of benzene metabolism in mice was extended to not only describe the metabolism in humans but to incorporate the variability across the species. Although the resulting model did not capture all of the variability of available data, we showed that variation can be incorporated into a PBPK model, and we can see how the distributions of the investigated parameters narrowed to not overestimate the observed variation. Further, the model reasonably fit the data from two very different studies. By altering the PBPK model for mice very little, we illustrated how existing models can be slightly adjusted to describe not only a different species but also complexity within that species.

In Chapter 3, we formulated a new model based on other related but distinct models. Thorough analysis as well as thoughtful adaptation of the established models led to a sensory response model that fit quite well with experimental data. Not only did the model fit the data quite well, the estimated parameters seemed reasonable biologically. Since the model is in an early stage of development, there is definitely room for improvement. Still, we can see good results from the sensory response model and definite promise with continued work. Although the changes made to existing models were more extensive than those in

Chapter 2, we still illustrate how existing models can be utilized to describe complicated systems and in this case, systems that may initially seem very different from each other.

As is always the case with physiological modeling, one must balance with what is feasible mathematically and what is reasonable biologically. Although the three-zone division of the liver in the model in Chapter 2 and listed in Appendix A may not be a direct representation of the structure of the liver, this *physiologically-based* model formulation of the liver helped Cole *et al.* improve the model from the one in [29] to the one in [28]. Further, in Section 3.2.2, part of the challenge of modeling the nerve response was balancing the mathematics with the biology. Changes needed to be made in the response function (x in the original work [69], Q in the model presented for the sensory response model) so that the model agreed with the consulted biologists' suggestion of maximum ventilation as initial ventilation. Although we could have adapted the model in different ways, the chosen alterations worked well with data, and the formulations in the model development demonstrate the balance necessary to bridge the gap between the two disciplines and further the knowledge of physiology.

Appendix A

The Benzene Model Equations

A.1 The Benzene PBPK Model Symbols

The following symbols and abbreviations are used in the PBPK model given in A.2. Units of the symbols are given in parentheses.

A.1.1 Chemical Abbreviations

<i>BZ</i>	Benzene
<i>BO</i>	Benzene oxide
<i>PH</i>	Phenol
<i>HQ</i>	Hydroquinone
<i>MA</i>	Muconic acid
<i>PMA</i>	Phenylmercapturic acid
<i>PH – Conj</i>	Phenol conjugates
<i>HQ – Conj</i>	Hydroquinone conjugates
<i>Cat</i>	Catechol
<i>THB</i>	Trihydroxy benzene

A.1.2 Compartment Abbreviations:

F	Fat
S	Slowly or Poorly Perfused Tissue
R	Rapidly or Richly Perfused Tissue
K	Kidney
$L1$	Zone 1 of the Liver
$L2$	Zone 2 of the Liver
$L3$	Zone 3 of the Liver
Bl	Blood
$Stom$	Stomach
I	Inhaled air
E	Exhaled air

A.1.3 Primary Symbols

C_j^i	Concentration of chemical i in tissue j ($\mu\text{mol}/L$)
CA^{BZ}	Concentration of BZ in the arterial blood ($\mu\text{mol}/L$)
CV^{BZ}	Concentration of BZ in the venous blood ($\mu\text{mol}/L$)
CV_j^i	Concentration of chemical i in venous blood from tissue j ($\mu\text{mol}/L$)
C_I^{BZ}	Concentration of BZ in inhaled air ($\mu\text{mol}/L$)
C_E^{BZ}	Concentration of BZ in exhaled air ($\mu\text{mol}/L$)
AM^i	Amount of chemical i in urine (μmol)
AM^{Stom}	Amount of BZ in the stomach (μmol)
RM_j^i	Rate of metabolism of chemical i to chemical j ($\mu\text{mol}/h$)
Q_j	Flow in tissue j (L/h)

Q_{AvV}	Alveolar ventilation (L/h)
Q_{Card}	Cardiac blood output (L/h)
P_j^i	Tissue j /blood partition coefficient for chemical i (dimensionless)
$P_{Bl:Air}^{BZ}$	Blood/air partition coefficient for BZ (dimensionless)
BW	Body weight (kg)
V_j	Volume of tissue j (L)
T_L	Total mass of the liver (g)
C^{MP}	Concentration of microsomal protein per gram of tissue in the liver (mg/g)
C^{CP}	Concentration of cytosolic protein per gram of tissue in the liver (mg/g)
V_{2E1}	CYP2E1 specific activity as determined by the oxidation of p-nitrophenol to p-nitrocatechol ($\mu mol/mg/h$)
A^i	Affinity parameter for CYP2E1 for substrate i ($L/\mu mol$)
$k_1, k_5 - k_7$	Efficiencies of CYP2E1 for specific oxidation relative to V_{2E1} ($L/\mu mol$)
$k_2 - k_4$	First-order rates of metabolism ($1/h$)
k_8	Rate of uptake from the stomach to the liver ($1/h$)
k_9, k_{10}	Binding coefficients ($1/h$)
V_{PH1}, V_{PH2}	Maximum rates of metabolism of PH by two sulfate transferases ($\mu mol/mg/h$)
$K_{m,1}^{PH}, K_{m,2}^{PH}$	Concentrations at half-saturation of PH by two sulfate transferases ($\mu mol/L$)
V_{HQ}	Maximum rate of metabolism for HQ ($\mu mol/mg/h$)
K_m^{HQ}	Concentration at half-saturation for HQ ($\mu mol/L$)
k_{Card}	Proportionality constant between BW and Q_{Card} ($L/(h * kg)$)
$k_{Q_{AvV}}$	Proportionality constant between Q_{Card} and Q_{AvV} (dimensionless)

f_{alv} Fraction of each inhaled breath that perfuses the alveolar space
(*dimensionless*)

A.2 The Benzene PBPK Mathematical Model

The following system of ordinary differential equations that was derived in [28] was based on a perfusion-limited model, or equivalently, a flow-limited model of disposition. More specifically, it was assumed that the rate of uptake of benzene into a tissue compartment is limited by the blood flow rate to the tissue rather than the rate of diffusion across the cell membrane. For the sake of completeness the model equations and the differential equations (grouped by chemical) are given below.

A.2.1 Explicit Equations

Concentration of chemical i in venous blood leaving compartment j : $CV_j^i = \frac{C_j^i}{P_j^i}$

Cardiac flow: $Q_{Card} = Q_F + Q_S + Q_R + Q_L + Q_K$

Concentration of BZ in venous blood:

$$CV^{BZ} = \frac{CV_F^{BZ}Q_F + CV_S^{BZ}Q_S + CV_R^{BZ}Q_R + CV_L^{BZ}Q_L + CV_K^{BZ}Q_K}{Q_{Card}} \quad (A.1)$$

Concentration of BZ in the arterial blood:

$$CA^{BZ} = \frac{Q_{AvV}C_I^{BZ} + Q_{Card}CV^{BZ}}{\frac{Q_{AvV}}{P_{Bl:Air}} + Q_{Card}} \quad (A.2)$$

CYP2E1 activity in the liver:

$$RM_{BO,L3}^{BZ} = k_1 \frac{V_{2E1} C_{L3}^{BZ}}{D_L} C^{MP} \frac{T_L}{3} \quad (A.3)$$

$$RM_{HQ,L3}^{PH} = k_5 \frac{V_{2E1} C_{L3}^{PH}}{D_L} C^{MP} \frac{T_L}{3} \quad (A.4)$$

$$RM_{Cat,L3}^{PH} = k_6 \frac{V_{2E1} C_{L3}^{PH}}{D_L} C^{MP} \frac{T_L}{3} \quad (A.5)$$

$$RM_{THB,L3}^{HQ} = k_7 \frac{V_{2E1} C_{L3}^{HQ}}{D_L} C^{MP} \frac{T_L}{3} \quad (A.6)$$

$$D_L = 1 + A^{BZ} C_{L3}^{BZ} + A^{PH} C_{L3}^{PH} + A^{HQ} C_{L3}^{HQ} \quad (A.7)$$

CYP2E1 activity in the kidney:

$$RM_{BO,K}^{BZ} = k_1 \frac{V_{2E1}}{10} \frac{C_K^{BZ}}{D_K} C^{MP} T_K \quad (A.8)$$

$$RM_{HQ,K}^{PH} = k_5 \frac{V_{2E1}}{10} \frac{C_K^{PH}}{D_K} C^{MP} T_K \quad (A.9)$$

$$RM_{Cat,K}^{PH} = k_6 \frac{V_{2E1}}{10} \frac{C_K^{PH}}{D_K} C^{MP} T_K \quad (A.10)$$

$$RM_{THB,K}^{HQ} = k_7 \frac{V_{2E1}}{10} \frac{C_K^{HQ}}{D_K} C^{MP} T_K \quad (A.11)$$

$$D_K = 1 + A^{BZ} C_K^{BZ} + A^{PH} C_K^{PH} + A^{HQ} C_K^{HQ} \quad (A.12)$$

Total mass of j =liver or kidney: $T_j = V_j * \frac{10^3 g}{1L}$

Metabolism of BO to PH in compartment j :

$$RM_{PH,j}^{BO} = k_2 C_j^{BO} V_j \quad (A.13)$$

Metabolism of BO to PMA in compartment j :

$$RM_{PMA,j}^{BO} = k_3 C_j^{BO} V_j \quad (\text{A.14})$$

Metabolism of BO to MA in compartment $L3$:

$$RM_{MA,L3}^{BO} = k_4 C_{L3}^{BO} \frac{V_{L3}}{3} \quad (\text{A.15})$$

Conjugation of PH :

$$RM_{Conj,L1}^{PH} = \left(\frac{V_{PH1} C_{L1}^{PH}}{K_{m,1}^{PH} + C_{L1}^{PH}} + \frac{V_{PH2} C_{L1}^{PH}}{K_{m,2}^{PH} + C_{L1}^{PH}} \right) C^{CP} \frac{T_L}{3} \quad (\text{A.16})$$

Conjugation of HQ :

$$RM_{Conj,L3}^{HQ} = \frac{V_{HQ} C_{L3}^{HQ}}{K_m^{HQ} + C_{L3}^{HQ}} C^{MP} \frac{T_L}{3} \quad (\text{A.17})$$

Concentration of exhaled benzene:

$$C_E^{BZ} = (1 - f_{alv}) \cdot C_I^{BZ} + f_{alv} [Q_{Card} \cdot (C V^{BZ} - C A^{BZ}) + Q_{AvV} \cdot C_I^{BZ}] / Q_{AvV} \quad (\text{A.18})$$

$$(\text{A.19})$$

A.2.2 The Ordinary Differential Equation System

Benzene

$$\text{Fat: } V_F \frac{dC_F^{BZ}}{dt} = Q_F (C A^{BZ} - C V_F^{BZ}) \quad (\text{A.20})$$

$$\text{Slowly: } V_S \frac{dC_S^{BZ}}{dt} = Q_S (C A^{BZ} - C V_S^{BZ}) \quad (\text{A.21})$$

$$\text{Rapidly: } V_R \frac{dC_R^{BZ}}{dt} = Q_R (C A^{BZ} - C V_R^{BZ}) \quad (\text{A.22})$$

$$\text{Kidney: } V_K \frac{dC_K^{BZ}}{dt} = Q_K(CA^{BZ} - CV_K^{BZ}) - RM_{BO,K}^{BZ} \quad (\text{A.23})$$

$$\text{Liver (Zone 1): } \frac{V_L}{3} \frac{dC_{L1}^{BZ}}{dt} = Q_L(CA^{BZ} - C_{L1}^{BZ}) + k_8 AM^{Stom} \quad (\text{A.24})$$

$$\text{Liver (Zone 2): } \frac{V_L}{3} \frac{dC_{L2}^{BZ}}{dt} = Q_L(C_{L1}^{BZ} - C_{L2}^{BZ}) \quad (\text{A.25})$$

$$\text{Liver (Zone 3): } \frac{V_L}{3} \frac{dC_{L3}^{BZ}}{dt} = Q_L(C_{L2}^{BZ} - CV_{L3}^{BZ}) - RM_{BO,L3}^{BZ} \quad (\text{A.26})$$

$$\text{Stomach: } \frac{dAM^{Stom}}{dt} = -k_8 AM^{Stom} \quad (\text{A.27})$$

$$\text{Exhaled: } \frac{dAM_E^{BZ}}{dt} = Q_{Card}(CV^{BZ} - CA^{BZ}) + Q_{AvV} \cdot C_I^{BZ} \quad (\text{A.28})$$

Benzene Oxide

$$\begin{aligned} \text{Blood: } V_{Bl} \frac{dC_{Bl}^{BO}}{dt} = & Q_F CV_F^{BO} + Q_S CV_S^{BO} + Q_R CV_R^{BO} \\ & + Q_K CV_K^{BO} + Q_L CV_{L3}^{BO} - Q_{Card} C_{Bl}^{BO} \\ & - RM_{PMA,Bl}^{BO} - RM_{PH,Bl}^{BO} \end{aligned} \quad (\text{A.29})$$

$$\begin{aligned} \text{Fat: } V_F \frac{dC_F^{BO}}{dt} = & Q_F (C_{Bl}^{BO} - CV_F^{BO}) - RM_{PMA,F}^{BO} \\ & - RM_{PH,F}^{BO} \end{aligned} \quad (\text{A.30})$$

$$\begin{aligned} \text{Slowly: } V_S \frac{dC_S^{BO}}{dt} = & Q_S (C_{Bl}^{BO} - CV_S^{BO}) - RM_{PMA,S}^{BO} \\ & - RM_{PH,S}^{BO} \end{aligned} \quad (\text{A.31})$$

$$\begin{aligned} \text{Rapidly: } V_R \frac{dC_R^{BO}}{dt} = & Q_R (C_{Bl}^{BO} - CV_R^{BO}) - RM_{PMA,R}^{BO} \\ & - RM_{PH,R}^{BO} \end{aligned} \quad (\text{A.32})$$

$$\begin{aligned}
\text{Kidney: } V_K \frac{dC_K^{BO}}{dt} &= Q_K(C_{Bl}^{BO} - CV_K^{BO}) + RM_{BO,K}^{BZ} \\
&\quad - RM_{PH,K}^{BO} - RM_{PMA,K}^{BO}
\end{aligned} \tag{A.33}$$

$$\text{Liver (Zone 1): } \frac{V_L}{3} \frac{dC_{L1}^{BO}}{dt} = Q_L(C_{Bl}^{BO} - C_{L1}^{BO}) - RM_{PH,L1}^{BO} \tag{A.34}$$

$$\text{Liver (Zone 2): } \frac{V_L}{3} \frac{dC_{L2}^{BO}}{dt} = Q_L(C_{L1}^{BO} - C_{L2}^{BO}) - RM_{PH,L2}^{BO} \tag{A.35}$$

$$\begin{aligned}
\text{Liver (Zone 3): } \frac{V_L}{3} \frac{dC_{L3}^{BO}}{dt} &= Q_L(C_{L2}^{BO} - CV_{L3}^{BO}) + RM_{BO,L3}^{BZ} \\
&\quad - RM_{PH,L3}^{BO} - RM_{MA,L3}^{BO} - RM_{PMA,L3}^{BO}
\end{aligned} \tag{A.36}$$

Phenol and Phenol Conjugates

$$\begin{aligned}
\text{Blood: } V_{Bl} \frac{dC_{Bl}^{PH}}{dt} &= Q_F CV_F^{PH} + Q_S CV_S^{PH} + Q_R CV_R^{PH} \\
&\quad + Q_K CV_K^{PH} + Q_L CV_{L3}^{PH} - Q_{Card} C_{Bl}^{PH} \\
&\quad + RM_{PH,Bl}^{BO} - k_9 C_{Bl}^{PH} V_{Bl}
\end{aligned} \tag{A.37}$$

$$\begin{aligned}
\text{Fat: } V_F \frac{dC_F^{PH}}{dt} &= Q_F(C_{Bl}^{PH} - CV_F^{PH}) + RM_{PH,F}^{BO} \\
&\quad - k_9 C_F^{PH} V_F
\end{aligned} \tag{A.38}$$

$$\begin{aligned}
\text{Slowly: } V_S \frac{dC_S^{PH}}{dt} &= Q_S(C_{Bl}^{PH} - CV_S^{PH}) + RM_{PH,S}^{BO} \\
&\quad - k_9 C_S^{PH} V_S
\end{aligned} \tag{A.39}$$

$$\begin{aligned}
\text{Rapidly: } V_R \frac{dC_R^{PH}}{dt} &= Q_R(C_{Bl}^{PH} - CV_R^{PH}) + RM_{PH,R}^{BO} \\
&\quad - k_9 C_R^{PH} V_R
\end{aligned} \tag{A.40}$$

$$\text{Kidney: } V_K \frac{dC_K^{PH}}{dt} = Q_K(C_{Bl}^{PH} - CV_K^{PH}) + RM_{PH,K}^{BO}$$

$$-RM_{HQ,K}^{PH} - RM_{Cat,K}^{PH} - k_9 C_K^{PH} V_K \quad (A.41)$$

$$\begin{aligned} \text{Liver (Zone 1): } \frac{V_L}{3} \frac{dC_{L1}^{PH}}{dt} &= Q_L(C_{Bl}^{PH} - C_{L1}^{PH}) + RM_{PH,L1}^{BO} \\ &\quad - RM_{Conj,L1}^{PH} - k_9 C_{L1}^{PH} \frac{V_L}{3} \end{aligned} \quad (A.42)$$

$$\begin{aligned} \text{Liver (Zone 2): } \frac{V_L}{3} \frac{dC_{L2}^{PH}}{dt} &= Q_L(C_{L1}^{PH} - C_{L2}^{PH}) + RM_{PH,L2}^{BO} \\ &\quad - k_9 C_{L2}^{PH} \frac{V_L}{3} \end{aligned} \quad (A.43)$$

$$\begin{aligned} \text{Liver (Zone 3): } \frac{V_L}{3} \frac{dC_{L3}^{PH}}{dt} &= Q_L(C_{L2}^{PH} - C_{L3}^{PH}) + RM_{PH,L3}^{BO} \\ &\quad - RM_{HQ,L3}^{PH} - RM_{Cat,L3}^{PH} - k_9 C_{L3}^{PH} \frac{V_L}{3} \end{aligned} \quad (A.44)$$

$$\text{Conjugates: } \frac{dAM^{PH-Conj}}{dt} = RM_{Conj,L1}^{PH} \quad (A.45)$$

Hydroquinone and Hydroquinone Conjugates

$$\begin{aligned} \text{Blood: } V_{Bl} \frac{dC_{Bl}^{HQ}}{dt} &= Q_F C V_F^{HQ} + Q_S C V_S^{HQ} + Q_R C V_R^{HQ} \\ &\quad + Q_K C V_K^{HQ} + Q_L C V_{L3}^{HQ} - Q_{Card} C_{Bl}^{HQ} \\ &\quad - k_{10} C_{Bl}^{HQ} V_{Bl} \end{aligned} \quad (A.46)$$

$$\text{Fat: } V_F \frac{dC_F^{HQ}}{dt} = Q_F(C_{Bl}^{HQ} - C V_F^{HQ}) - k_{10} C_F^{HQ} V_F \quad (A.47)$$

$$\text{Slowly: } V_S \frac{dC_S^{HQ}}{dt} = Q_S(C_{Bl}^{HQ} - C V_S^{HQ}) - k_{10} C_S^{HQ} V_S \quad (A.48)$$

$$\text{Rapidly: } V_R \frac{dC_R^{HQ}}{dt} = Q_R(C_{Bl}^{HQ} - C V_R^{HQ}) - k_{10} C_R^{HQ} V_R \quad (A.49)$$

$$\text{Kidney: } V_K \frac{dC_K^{HQ}}{dt} = Q_K(C_{Bl}^{HQ} - C V_K^{HQ}) + RM_{HQ,K}^{PH}$$

$$-RM_{THB,K}^{HQ} - k_{10}C_K^{HQ}V_K \quad (A.50)$$

$$\text{Liver (Zone 1): } \frac{V_L}{3} \frac{dC_{L1}^{HQ}}{dt} = Q_L(C_{Bl}^{HQ} - C_{L1}^{HQ}) - k_{10}C_{L1}^{HQ} \frac{V_L}{3} \quad (A.51)$$

$$\text{Liver (Zone 2): } \frac{V_L}{3} \frac{dC_{L2}^{HQ}}{dt} = Q_L(C_{L1}^{HQ} - C_{L2}^{HQ}) - k_{10}C_{L2}^{HQ} \frac{V_L}{3} \quad (A.52)$$

$$\begin{aligned} \text{Liver (Zone 3): } \frac{V_L}{3} \frac{dC_{L3}^{HQ}}{dt} = & Q_L(C_{L2}^{HQ} - C_{L3}^{HQ}) + RM_{HQ,L3}^{PH} \\ & - RM_{THB,L3}^{HQ} - RM_{Conj,L3}^{HQ} - k_{10}C_{L3}^{HQ} \frac{V_L}{3} \end{aligned} \quad (A.53)$$

$$\text{Conjugates: } \frac{dAM^{HQ-Conj}}{dt} = RM_{Conj,L3}^{HQ} \quad (A.54)$$

Other Metabolites

Muconic Acid

$$\frac{dAM^{MA}}{dt} = RM_{MA,L3}^{BO} \quad (A.55)$$

Phenylmercapturic Acid

$$\begin{aligned} \frac{dAM^{PMA}}{dt} = & RM_{PMA,Bl}^{BO} + RM_{PMA,F}^{BO} + RM_{PMA,S}^{BO} \\ & + RM_{PMA,R}^{BO} + RM_{PMA,K}^{BO} + RM_{PMA,L3}^{BO} \end{aligned} \quad (A.56)$$

Catechol and Trihydroxy benzene

$$\frac{dAM^{Cat/THB}}{dt} = RM_{Cat,L3}^{PH} + RM_{Cat,K}^{PH} + RM_{THB,L3}^{HQ} + RM_{THB,K}^{HQ} \quad (A.57)$$

Appendix B

The Sensory Irritant Equations

B.1 The Sensory Irritant Model Symbols

Compartments:

NV	The nasal vestibule compartment
DR	The respiratory compartment of the dorsal flow
$DO1$	The first olfactory compartment of the dorsal flow
$DO2$	The second olfactory compartment of the dorsal flow
$VR1$	The first respiratory compartment of the ventral flow
$VR2$	The second respiratory compartment of the ventral flow
NP	The nasopharynx compartment
LRC	The lower respiratory compartment

States:

- C_i The concentration of formaldehyde in the air flow through compartment i ($\mu\text{mol}/\text{cm}^3$)
- Q The ventilation rate, i.e., air flow rate through the respiratory tract (cm^3/s)

Parameters:

S_i	The surface area of compartment i (cm^2)
V_i	The volume of the air in compartment i (cm^3)
$K_{gc,i}$	Compartmental mass transfer coefficient for compartment i (cm/s)
C_{inh}	The concentration of formaldehyde being inhaled ($\mu mol/cm^3$)
$r(C_i)$	Function representing the response due to chemical concentration that depends on occupancy chemical receptors on the nerve receptor surface (<i>dimensionless</i>)
K_D	The receptor-chemical dissociation constant ($\mu mol/cm^3$)
r_0	The threshold parameter for $r(C_i)$ (<i>dimensionless</i>)
τ_r	An adaptation time constant for the firing rate n (s)
k_0	The intrinsic sensitivity of the receptor to a chemical (<i>dimensionless</i>)
w_i	A weighting factor for each compartment that will depend on nerve receptors (<i>dimensionless</i>)
δ	Small positive constant in order to achieve a nontrivial solution to the differential equation system (<i>dimensionless</i>)
n	Total firing rate relative to the maximum (<i>dimensionless</i>)
Δn_i	Firing rate addition from receptors in the mucosa of compartment i (<i>dimensionless</i>)
Q_{steady}	Sigmoidal function to represent the nerve change in response to formaldehyde as a function of n (cm^3/h)
τ_Q	Time constant characterizing the time it takes for the nervous response to take effect. The value of τ_Q is denoted τ_{Q_1} during the initial decrease in ventilation and is denoted τ_{Q_2} during the recovery to steady state. (s)
Q_{min}, Q_{max}	the maximum and minimum values of ventilation (cm^3/s)

p	parameter controlling the steepness of the sigmoid Q_{steady} (<i>dimensionless</i>)
α	constant in Q_{steady} dependent on data (<i>dimensionless</i>)

B.2 The Sensory Irritant Model Equations

$$V_{NV} \frac{dC_{NV}}{dt} = Q(C_{inh} - C_{NV}) - K_{gc,NV} S_{NV} C_{NV} \quad (B.1)$$

$$V_{VR1} \frac{dC_{VR1}}{dt} = f_V Q(C_{NV} - C_{VR1}) - K_{gc,VR1} S_{VR1} C_{VR1} \quad (B.2)$$

$$V_{VR2} \frac{dC_{VR2}}{dt} = f_V Q(C_{VR1} - C_{VR2}) - K_{gc,VR2} S_{VR2} C_{VR2} \quad (B.3)$$

$$V_{DR} \frac{dC_{DR}}{dt} = f_D Q(C_{NV} - C_{DR}) - K_{gc,DR} S_{DR} C_{DR} \quad (B.4)$$

$$V_{DO1} \frac{dC_{DO1}}{dt} = f_D Q(C_{DR} - C_{DO1}) - K_{gc,DO1} S_{DO1} C_{DO1} \quad (B.5)$$

$$V_{DO2} \frac{dC_{DO2}}{dt} = f_D Q(C_{DO1} - C_{DO2}) - K_{gc,DO2} S_{DO2} C_{DO2} \quad (B.6)$$

$$V_{NP} \frac{dC_{NP}}{dt} = Q(f_D C_{DO2} + f_V C_{VR2} - C_{NP}) - K_{gc,NP} S_{NP} C_{NP} \quad (B.7)$$

$$V_{LRC} \frac{dC_{LRC}}{dt} = Q(C_{NP} - C_{LRC}) - K_{gc,LRC} S_{LRC} C_{LRC} \quad (B.8)$$

$$r(C) = \begin{cases} \frac{C}{C+K_D} - r_0, & \frac{C}{C+K_D} > r_0 \\ 0, & \frac{C}{C+K_D} \leq r_0 \end{cases} \quad (B.9)$$

$$\Delta \dot{n}_{VR1} = w_{VR1} k_0 r(C_{VR1}) \frac{(n+\delta)(1-n)}{(1+\delta)^2} - \frac{\Delta n_{VR1}}{\tau_r} \quad (B.10)$$

$$\Delta \dot{n}_{VR2} = w_{VR2} k_0 r(C_{VR2}) \frac{(n+\delta)(1-n)}{(1+\delta)^2} - \frac{\Delta n_{VR2}}{\tau_r} \quad (B.11)$$

$$\Delta \dot{n}_{DR} = w_{DR} k_0 r(C_{DR}) \frac{(n+\delta)(1-n)}{(1+\delta)^2} - \frac{\Delta n_{DR}}{\tau_r} \quad (B.12)$$

$$\Delta \dot{n}_{DO1} = w_{DO1} k_0 r(C_{DO1}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO1}}{\tau_r} \quad (\text{B.13})$$

$$\Delta \dot{n}_{DO2} = w_{DO2} k_0 r(C_{DO2}) \frac{(n + \delta)(1 - n)}{(1 + \delta)^2} - \frac{\Delta n_{DO2}}{\tau_r} \quad (\text{B.14})$$

$$n = \Delta n_{VR1} + \Delta n_{VR2} + \Delta n_{DR} + \Delta n_{DO1} + \Delta n_{DO2} \quad (\text{B.15})$$

$$Q_{steady}(n) = \frac{Q_{max} - Q_{min}}{1 + \alpha n^p} + Q_{min} \quad (\text{B.16})$$

$$\frac{dQ}{dt} = \frac{1}{\tau_Q} (Q_{steady}(n) - Q(t)) \quad (\text{B.17})$$

B.3 The Sensory Irritant Model Sensitivity Equations

The following lists the model and the sensitivity equations for each of the six parameters (τ_r , k_0 , τ_Q , p , α , and k_D) being optimized. The complete sensory model, complete with abbreviations that will be used later is listed below.

$$V_{NV} \frac{dC_{NV}}{dt} = Q(C_{inh} - C_{NV}) - K_{gc,NV} S_{NV} C_{NV}$$

$$V_{VR1} \frac{dC_{VR1}}{dt} = f_V Q(C_{NV} - C_{VR1}) - K_{gc,VR1} S_{VR1} C_{VR1}$$

$$V_{VR2} \frac{dC_{VR2}}{dt} = f_V Q(C_{VR1} - C_{VR2}) - K_{gc,VR2} S_{VR2} C_{VR2}$$

$$V_{DR} \frac{dC_{DR}}{dt} = f_D Q(C_{NV} - C_{DR}) - K_{gc,DR} S_{DR} C_{DR}$$

$$V_{DO1} \frac{dC_{DO1}}{dt} = f_D Q(C_{DR} - C_{DO1}) - K_{gc,DO1} S_{DO1} C_{DO1}$$

$$V_{DO2} \frac{dC_{DO2}}{dt} = f_D Q(C_{DO1} - C_{DO2}) - K_{gc,DO2} S_{DO2} C_{DO2}$$

$$V_{NP} \frac{dC_{NP}}{dt} = Q(f_D C_{DO2} + f_V C_{VR2} - C_{NP}) - K_{gc,NP} S_{NP} C_{NP}$$

$$V_{LRC} \frac{dC_{LRC}}{dt} = Q(C_{NP} - C_{LRC}) - K_{gc,LRC} S_{LRC} C_{LRC}$$

$$\Delta \dot{n}_{VR1} = w_{VR1} k_0 r(C_{VR1}) g(n) - \frac{\Delta n_{VR1}}{\tau_r}$$

$$\Delta \dot{n}_{VR2} = w_{VR2} k_0 r(C_{VR2}) g(n) - \frac{\Delta n_{VR2}}{\tau_r}$$

$$\Delta \dot{n}_{DR} = w_{DR} k_0 r(C_{DR}) g(n) - \frac{\Delta n_{DR}}{\tau_r}$$

$$\Delta \dot{n}_{DO1} = w_{DO1} k_0 r(C_{DO1}) g(n) - \frac{\Delta n_{DO1}}{\tau_r}$$

$$\Delta \dot{n}_{DO2} = w_{DO2} k_0 r(C_{DO2}) g(n) - \frac{\Delta n_{DO2}}{\tau_r}$$

$$n = \Delta n_{VR1} + \Delta n_{VR2} + \Delta n_{DR} + \Delta n_{DO1} + \Delta n_{DO2}$$

$$Q_{steady}(n) = \frac{Q_{max} - Q_{min}}{1 + \alpha n^p} + Q_{min}$$

$$\frac{dQ}{dt} = \frac{1}{\tau_Q} (Q_{steady}(n) - Q(t))$$

where

$$g(n) = \frac{(n + \delta)(1 - n)}{(1 + \delta)^2}$$

$$g'(n) = \frac{1 - 2n - \delta}{(1 + \delta)^2}$$

for some small δ . Define r such that

$$r(C) = \frac{C}{C + K_D}.$$

Note that $r(0) = 0$ and is now more considered to follow Michelis-Menton kinetics, and that this is equivalent to an earlier formulation of r with $r_0 = 0$. Further, the following derivatives will be defined first to simplify our calculations:

$$\begin{aligned}
\frac{dQ_{steady}(n)}{dn} &= (Q_{max} - Q_{min}) \left[\frac{-\alpha p n^{p-1}}{(1 + \alpha n^p)^2} \right] \\
\frac{dQ_{steady}(n)}{d\alpha} &= (Q_{max} - Q_{min}) * \\
&\quad \left[\frac{-n^p - \alpha p n^{p-1} \left(\frac{d\Delta n_{VR1}}{d\alpha} + \frac{d\Delta n_{VR2}}{d\alpha} + \frac{d\Delta n_{DR}}{d\alpha} + \frac{d\Delta n_{DO1}}{d\alpha} + \frac{d\Delta n_{DO2}}{d\alpha} \right)}{(1 + \alpha n^p)^2} \right] \\
\frac{dQ_{steady}(n)}{dp} &= (Q_{max} - Q_{min}) * \\
&\quad \left[\frac{-\alpha n^p \left[\frac{p}{n} \left(\frac{d\Delta n_{VR1}}{dp} + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) + \ln(n) \right]}{(1 + \alpha n^p)^2} \right]
\end{aligned}$$

B.3.1 The sensitivity equations for τ_r

$$\begin{aligned}
\frac{d}{d\tau_r} \left[\frac{dC_{NV}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NV}}{d\tau_r} \right] \\
&= \frac{1}{V_{NV}} \left[\frac{dQ}{d\tau_r} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{d\tau_r} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{d\tau_r} \right] \\
&= \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{d\tau_r} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{d\tau_r} - \frac{dC_{VR1}}{d\tau_r} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{d\tau_r} \right] \\
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{d\tau_r} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{d\tau_r} - \frac{dC_{VR2}}{d\tau_r} \right) \right]
\end{aligned}$$

$$\begin{aligned}
& -K_{gc,VR2}S_{VR2}\frac{dC_{VR2}}{d\tau_r} \Big] \\
\frac{d}{d\tau_r} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{d\tau_r} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{d\tau_r} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{d\tau_r} - \frac{dC_{DR}}{d\tau_r} \right) \right. \\
&\quad \left. - K_{gc,DR}S_{DR}\frac{dC_{DR}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{d\tau_r} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{d\tau_r} (C_{DR} - C_{DO1}) + f_D Q \left(\frac{dC_{DR}}{d\tau_r} - \frac{dC_{DO1}}{d\tau_r} \right) \right. \\
&\quad \left. - K_{gc,DO1}S_{DO1}\frac{dC_{DO1}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO2}}{d\tau_r} \right] \\
&= \frac{1}{V_{DO2}} \left[f_D \frac{dQ}{d\tau_r} (C_{DO1} - C_{DO2}) + f_D Q \left(\frac{dC_{DO1}}{d\tau_r} - \frac{dC_{DO2}}{d\tau_r} \right) \right. \\
&\quad \left. - K_{gc,DO2}S_{DO2}\frac{dC_{DO2}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{NP}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NP}}{d\tau_r} \right] \\
&= \frac{1}{V_{NP}} \left[\frac{dQ}{d\tau_r} (f_D C_{DO2} + f_V C_{VR2} - C_{NP}) \right. \\
&\quad \left. + Q \left(f_D \frac{dC_{DO2}}{d\tau_r} + f_V \frac{dC_{VR2}}{d\tau_r} - \frac{dC_{NP}}{d\tau_r} \right) \right. \\
&\quad \left. - K_{gc,NP}S_{NP}\frac{dC_{NP}}{d\tau_r} \right] \\
\frac{d}{d\tau_r} \left[\frac{dC_{LRC}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{LRC}}{d\tau_r} \right] \\
&= \frac{1}{V_{LRC}} \left[\frac{dQ}{d\tau_r} (C_{NP} - C_{LRC}) + Q \left(\frac{dC_{NP}}{d\tau_r} - \frac{dC_{LRC}}{d\tau_r} \right) \right]
\end{aligned}$$

$$\begin{aligned}
& -K_{gc,LRC}S_{LRC}\frac{dC_{LRC}}{d\tau_r}\Big] \\
\frac{d}{d\tau_r}\left[\frac{d\Delta n_{VR1}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{VR1}}{d\tau_r}\right] \\
&= \frac{d}{d\tau_r}\left[w_{VR1}k_0\frac{C_{VR1}}{C_{VR1}+K_D}g(n)-\frac{\Delta n_{VR1}}{\tau_r}\right] \\
&= w_{VR1}k_0\frac{K_D\frac{dC_{VR1}}{d\tau_r}}{(C_{VR1}+K_D)^2}g(n) \\
&\quad +w_{VR1}k_0\frac{C_{VR1}}{C_{VR1}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\tau_r}\right. \\
&\quad \left.+\frac{d\Delta n_{VR2}}{d\tau_r}+\frac{d\Delta n_{DR}}{d\tau_r}+\frac{d\Delta n_{DO1}}{d\tau_r}+\frac{d\Delta n_{DO2}}{d\tau_r}\right) \\
&\quad -\left(\frac{\tau_r\frac{d\Delta n_{VR1}}{d\tau_r}-\Delta n_{VR1}}{\tau_r^2}\right) \\
\frac{d}{d\tau_r}\left[\frac{d\Delta n_{VR2}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{VR2}}{d\tau_r}\right] \\
&= w_{VR2}k_0\frac{K_D\frac{dC_{VR2}}{d\tau_r}}{(C_{VR2}+K_D)^2}g(n) \\
&\quad +w_{VR2}k_0\frac{C_{VR2}}{C_{VR2}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\tau_r}\right. \\
&\quad \left.+\frac{d\Delta n_{VR2}}{d\tau_r}+\frac{d\Delta n_{DR}}{d\tau_r}+\frac{d\Delta n_{DO1}}{d\tau_r}+\frac{d\Delta n_{DO2}}{d\tau_r}\right) \\
&\quad -\left(\frac{\tau_r\frac{d\Delta n_{VR2}}{d\tau_r}-\Delta n_{VR2}}{\tau_r^2}\right) \\
\frac{d}{d\tau_r}\left[\frac{d\Delta n_{DR}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{DR}}{d\tau_r}\right] \\
&= w_{DR}k_0\frac{K_D\frac{dC_{DR}}{d\tau_r}}{(C_{DR}+K_D)^2}g(n) \\
&\quad +w_{DR}k_0\frac{C_{DR}}{C_{DR}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\tau_r}\right.
\end{aligned}$$

$$\begin{aligned}
& + \frac{d\Delta n_{VR2}}{d\tau_r} + \frac{d\Delta n_{DR}}{d\tau_r} + \frac{d\Delta n_{DO1}}{d\tau_r} + \frac{d\Delta n_{DO2}}{d\tau_r} \Bigg) \\
& - \left(\frac{\tau_r \frac{d\Delta n_{DR}}{d\tau_r} - \Delta n_{DR}}{\tau_r^2} \right) \\
\frac{d}{d\tau_r} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{d\tau_r} \right] \\
&= w_{DO1} k_0 \frac{K_D \frac{dC_{DO1}}{d\tau_r}}{(C_{DO1} + K_D)^2} g(n) \\
&+ w_{DO1} k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_r} \right. \\
&+ \frac{d\Delta n_{VR2}}{d\tau_r} + \frac{d\Delta n_{DR}}{d\tau_r} + \frac{d\Delta n_{DO1}}{d\tau_r} + \frac{d\Delta n_{DO2}}{d\tau_r} \Bigg) \\
&- \left(\frac{\tau_r \frac{d\Delta n_{DO1}}{d\tau_r} - \Delta n_{DO1}}{\tau_r^2} \right) \\
\frac{d}{d\tau_r} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{d\tau_r} \right] \\
&= w_{DO2} k_0 \frac{K_D \frac{dC_{DO2}}{d\tau_r}}{(C_{DO2} + K_D)^2} g(n) \\
&+ w_{DO2} k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_r} \right. \\
&+ \frac{d\Delta n_{VR2}}{d\tau_r} + \frac{d\Delta n_{DR}}{d\tau_r} + \frac{d\Delta n_{DO1}}{d\tau_r} + \frac{d\Delta n_{DO2}}{d\tau_r} \Bigg) \\
&- \left(\frac{\tau_r \frac{d\Delta n_{DO2}}{d\tau_r} - \Delta n_{DO2}}{\tau_r^2} \right) \\
\frac{d}{d\tau_r} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{d\tau_r} \right] \\
&= \frac{1}{\tau_Q} \left[\frac{dQ_{steady}(n)}{dn} \left(\frac{d\Delta n_{VR1}}{d\tau_r} + \frac{d\Delta n_{VR2}}{d\tau_r} \right. \right. \\
&+ \frac{d\Delta n_{DR}}{d\tau_r} + \frac{d\Delta n_{DO1}}{d\tau_r} + \frac{d\Delta n_{DO2}}{d\tau_r} \Bigg) - \frac{dQ}{d\tau_r} \Bigg]
\end{aligned}$$

B.3.2 The sensitivity equations for k_0

$$\begin{aligned}
\frac{d}{dk_0} \left[\frac{dC_{NV}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NV}}{dk_0} \right] \\
&= \frac{1}{V_{NV}} \left[\frac{dQ}{dk_0} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{dk_0} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{dk_0} \right] \\
\frac{d}{dk_0} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{dk_0} \right] \\
&= \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{dk_0} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{dk_0} - \frac{dC_{VR1}}{dk_0} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{dk_0} \right] \\
\frac{d}{dk_0} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{dk_0} \right] \\
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{dk_0} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{dk_0} - \frac{dC_{VR2}}{dk_0} \right) \right. \\
&\quad \left. - K_{gc,VR2} S_{VR2} \frac{dC_{VR2}}{dk_0} \right] \\
\frac{d}{dk_0} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{dk_0} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{dk_0} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{dk_0} - \frac{dC_{DR}}{dk_0} \right) \right. \\
&\quad \left. - K_{gc,DR} S_{DR} \frac{dC_{DR}}{dk_0} \right] \\
\frac{d}{dk_0} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{dk_0} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{dk_0} (C_{DR} - C_{DO1}) + f_D Q \left(\frac{dC_{DR}}{dk_0} - \frac{dC_{DO1}}{dk_0} \right) \right]
\end{aligned}$$

$$\begin{aligned}
& -K_{gc,DO1}S_{DO1}\frac{dC_{DO1}}{dk_0}\Big] \\
\frac{d}{dk_0}\left[\frac{dC_{DO2}}{dt}\right] &= \frac{d}{dt}\left[\frac{dC_{DO2}}{dk_0}\right] \\
&= \frac{1}{V_{DO2}}\left[f_D\frac{dQ}{dk_0}(C_{DO1}-C_{DO2})+f_DQ\left(\frac{dC_{DO1}}{dk_0}-\frac{dC_{DO2}}{dk_0}\right)\right. \\
& \quad \left.-K_{gc,DO2}S_{DO2}\frac{dC_{DO2}}{dk_0}\right] \\
\frac{d}{dk_0}\left[\frac{dC_{NP}}{dt}\right] &= \frac{d}{dt}\left[\frac{dC_{NP}}{dk_0}\right] \\
&= \frac{1}{V_{NP}}\left[\frac{dQ}{dk_0}(f_DC_{DO2}+f_VC_{VR2}-C_{NP})\right. \\
& \quad \left.+Q\left(f_D\frac{dC_{DO2}}{dk_0}+f_V\frac{dC_{VR2}}{dk_0}-\frac{dC_{NP}}{dk_0}\right)\right. \\
& \quad \left.-K_{gc,NP}S_{NP}\frac{dC_{NP}}{dk_0}\right] \\
\frac{d}{dk_0}\left[\frac{dC_{LRC}}{dt}\right] &= \frac{d}{dt}\left[\frac{dC_{LRC}}{dk_0}\right] \\
&= \frac{1}{V_{LRC}}\left[\frac{dQ}{dk_0}(C_{NP}-C_{LRC})+Q\left(\frac{dC_{NP}}{dk_0}-\frac{dC_{LRC}}{dk_0}\right)\right. \\
& \quad \left.-K_{gc,LRC}S_{LRC}\frac{dC_{LRC}}{dk_0}\right] \\
\frac{d}{dk_0}\left[\frac{d\Delta n_{VR1}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{VR1}}{dk_0}\right] \\
&= w_{VR1}\frac{C_{VR1}}{C_{VR1}+K_D}g(n)+w_{VR1}k_0\frac{K_D\frac{dC_{VR1}}{dk_0}}{(C_{VR1}+K_D)^2}g(n) \\
& \quad +w_{VR1}k_0\frac{C_{VR1}}{C_{VR1}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{dk_0}\right. \\
& \quad \left.+\frac{d\Delta n_{VR2}}{dk_0}+\frac{d\Delta n_{DR}}{dk_0}+\frac{d\Delta n_{DO1}}{dk_0}+\frac{d\Delta n_{DO2}}{dk_0}\right) \\
& \quad -\frac{1}{\tau_r}\frac{d\Delta n_{VR1}}{dk_0}
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dk_0} \left[\frac{d\Delta n_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR2}}{dk_0} \right] \\
&= w_{VR2} \frac{C_{VR2}}{C_{VR2} + K_D} g(n) + w_{VR2} k_0 \frac{K_D \frac{dC_{VR2}}{dk_0}}{(C_{VR2} + K_D)^2} g(n) \\
&\quad + w_{VR2} k_0 \frac{C_{VR2}}{C_{VR2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dk_0} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dk_0} + \frac{d\Delta n_{DR}}{dk_0} + \frac{d\Delta n_{DO1}}{dk_0} + \frac{d\Delta n_{DO2}}{dk_0} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR2}}{dk_0} \\
\frac{d}{dk_0} \left[\frac{d\Delta n_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DR}}{dk_0} \right] \\
&= w_{DR} \frac{C_{DR}}{C_{DR} + K_D} g(n) + w_{DR} k_0 \frac{K_D \frac{dC_{DR}}{dk_0}}{(C_{DR} + K_D)^2} g(n) \\
&\quad + w_{DR} k_0 \frac{C_{DR}}{C_{DR} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dk_0} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dk_0} + \frac{d\Delta n_{DR}}{dk_0} + \frac{d\Delta n_{DO1}}{dk_0} + \frac{d\Delta n_{DO2}}{dk_0} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DR}}{dk_0} \\
\frac{d}{dk_0} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{dk_0} \right] \\
&= w_{DO1} \frac{C_{DO1}}{C_{DO1} + K_D} g(n) + w_{DO1} k_0 \frac{K_D \frac{dC_{DO1}}{dk_0}}{(C_{DO1} + K_D)^2} g(n) \\
&\quad + w_{DO1} k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dk_0} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dk_0} + \frac{d\Delta n_{DR}}{dk_0} + \frac{d\Delta n_{DO1}}{dk_0} + \frac{d\Delta n_{DO2}}{dk_0} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO1}}{dk_0}
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dk_0} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{dk_0} \right] \\
&= w_{DO2} \frac{C_{DO2}}{C_{DO2} + K_D} g(n) + w_{DO2} k_0 \frac{K_D \frac{dC_{DO2}}{dk_0}}{(C_{DO2} + K_D)^2} g(n) \\
&\quad + w_{DO2} k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dk_0} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dk_0} + \frac{d\Delta n_{DR}}{dk_0} + \frac{d\Delta n_{DO1}}{dk_0} + \frac{d\Delta n_{DO2}}{dk_0} \right) \\
&\quad - \frac{1}{\tau_Q} \frac{d\Delta n_{DO2}}{dk_0} \\
\frac{d}{dk_0} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{dk_0} \right] \\
&= \frac{1}{\tau_r} \left[\frac{dQ_{steady}(n)}{dn} \left(\frac{d\Delta n_{VR1}}{dk_0} + \frac{d\Delta n_{VR2}}{dk_0} \right. \right. \\
&\quad \left. \left. + \frac{d\Delta n_{DR}}{dk_0} + \frac{d\Delta n_{DO1}}{dk_0} + \frac{d\Delta n_{DO2}}{dk_0} \right) - \frac{dQ}{dk_0} \right]
\end{aligned}$$

B.3.3 The sensitivity equations for τ_Q

$$\begin{aligned}
\frac{d}{d\tau_Q} \left[\frac{dC_{NV}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NV}}{d\tau_Q} \right] \\
&= \frac{1}{V_{NV}} \left[\frac{dQ}{d\tau_Q} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{d\tau_Q} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{d\tau_Q} \right] = \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{d\tau_Q} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{d\tau_Q} - \frac{dC_{VR1}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{d\tau_Q} \right]
\end{aligned}$$

$$\begin{aligned}
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{d\tau_Q} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{d\tau_Q} - \frac{dC_{VR2}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,VR2} S_{VR2} \frac{dC_{VR2}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{d\tau_Q} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{d\tau_Q} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{d\tau_Q} - \frac{dC_{DR}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,DR} S_{DR} \frac{dC_{DR}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{d\tau_Q} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{d\tau_Q} (C_{DR} - C_{DO1}) + f_D Q \left(\frac{dC_{DR}}{d\tau_Q} - \frac{dC_{DO1}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,DO1} S_{DO1} \frac{dC_{DO1}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO2}}{d\tau_Q} \right] \\
&= \frac{1}{V_{DO2}} \left[f_D \frac{dQ}{d\tau_Q} (C_{DO1} - C_{DO2}) + f_D Q \left(\frac{dC_{DO1}}{d\tau_Q} - \frac{dC_{DO2}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,DO2} S_{DO2} \frac{dC_{DO2}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{NP}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NP}}{d\tau_Q} \right] \\
&= \frac{1}{V_{NP}} \left[\frac{dQ}{d\tau_Q} (f_D C_{DO2} + f_V C_{VR2} - C_{NP}) \right. \\
&\quad \left. + Q \left(f_D \frac{dC_{DO2}}{d\tau_Q} + f_V \frac{dC_{VR2}}{d\tau_Q} - \frac{dC_{NP}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,NP} S_{NP} \frac{dC_{NP}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{dC_{LRC}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{LRC}}{d\tau_Q} \right]
\end{aligned}$$

$$\begin{aligned}
&= \frac{1}{V_{LRC}} \left[\frac{dQ}{d\tau_Q} (C_{NP} - C_{LRC}) + Q \left(\frac{dC_{NP}}{d\tau_Q} - \frac{dC_{LRC}}{d\tau_Q} \right) \right. \\
&\quad \left. - K_{gc,LRC} S_{LRC} \frac{dC_{LRC}}{d\tau_Q} \right] \\
\frac{d}{d\tau_Q} \left[\frac{d\Delta n_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR1}}{d\tau_Q} \right] \\
&= w_{VR1} k_0 \frac{K_D \frac{dC_{VR1}}{d\tau_Q}}{(C_{VR1} + K_D)^2} g(n) \\
&\quad + w_{VR1} k_0 \frac{C_{VR1}}{C_{VR1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_Q} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{d\tau_Q} + \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR1}}{d\tau_Q} \\
\frac{d}{d\tau_Q} \left[\frac{d\Delta n_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR2}}{d\tau_Q} \right] \\
&= w_{VR2} k_0 \frac{K_D \frac{dC_{VR2}}{d\tau_Q}}{(C_{VR2} + K_D)^2} g(n) \\
&\quad + w_{VR2} k_0 \frac{C_{VR2}}{C_{VR2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_Q} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{d\tau_Q} + \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR2}}{d\tau_Q} \\
\frac{d}{d\tau_Q} \left[\frac{d\Delta n_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DR}}{d\tau_Q} \right] \\
&= w_{DR} k_0 \frac{K_D \frac{dC_{DR}}{d\tau_Q}}{(C_{DR} + K_D)^2} g(n) \\
&\quad + w_{DR} k_0 \frac{C_{DR}}{C_{DR} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_Q} \right.
\end{aligned}$$

$$\begin{aligned}
& + \frac{d\Delta n_{VR2}}{d\tau_Q} + \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \Bigg) \\
& - \frac{1}{\tau_r} \frac{d\Delta n_{DR}}{d\tau_Q} \\
\frac{d}{d\tau_Q} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{d\tau_Q} \right] \\
&= w_{DO1} k_0 \frac{K_D \frac{dC_{DO1}}{d\tau_Q}}{(C_{DO1} + K_D)^2} g(n) \\
&+ w_{DO1} k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_Q} \right. \\
&+ \frac{d\Delta n_{VR2}}{d\tau_Q} + \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \Bigg) \\
&- \frac{1}{\tau_r} \frac{d\Delta n_{DO1}}{d\tau_Q} \\
\frac{d}{d\tau_Q} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{d\tau_Q} \right] \\
&= w_{DO2} k_0 \frac{K_D \frac{dC_{DO2}}{d\tau_Q}}{(C_{DO2} + K_D)^2} g(n) \\
&+ w_{DO2} k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\tau_Q} \right. \\
&+ \frac{d\Delta n_{VR2}}{d\tau_Q} + \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \Bigg) \\
&- \frac{1}{\tau_r} \frac{d\Delta n_{DO2}}{d\tau_Q} \\
\frac{d}{d\tau_Q} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{d\tau_Q} \right] \\
&= \frac{1}{\tau_Q^2} \left(\tau_Q \left[\frac{dQ_{steady}(n)}{dn} \left(\frac{d\Delta n_{VR1}}{d\tau_Q} + \frac{d\Delta n_{VR2}}{d\tau_Q} \right. \right. \right. \\
&+ \frac{d\Delta n_{DR}}{d\tau_Q} + \frac{d\Delta n_{DO1}}{d\tau_Q} + \frac{d\Delta n_{DO2}}{d\tau_Q} \Bigg) - \frac{dQ}{d\tau_Q} \Bigg] \\
&- Q_{steady}(n) + Q)
\end{aligned}$$

B.3.4 The sensitivity equations for p

$$\begin{aligned}
\frac{d}{dp} \left[\frac{dC_{NV}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NV}}{dp} \right] \\
&= \frac{1}{V_{NV}} \left[\frac{dQ}{dp} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{dp} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{dp} \right] \\
\frac{d}{dp} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{dp} \right] \\
&= \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{dp} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{dp} - \frac{dC_{VR1}}{dp} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{dp} \right] \\
\frac{d}{dp} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{dp} \right] \\
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{dp} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{dp} - \frac{dC_{VR2}}{dp} \right) \right. \\
&\quad \left. - K_{gc,VR2} S_{VR2} \frac{dC_{VR2}}{dp} \right] \\
\frac{d}{dp} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{dp} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{dp} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{dp} - \frac{dC_{DR}}{dp} \right) \right. \\
&\quad \left. - K_{gc,DR} S_{DR} \frac{dC_{DR}}{dp} \right] \\
\frac{d}{dp} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{dp} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{dp} (C_{DR} - C_{DO1}) + f_D Q \left(\frac{dC_{DR}}{dp} - \frac{dC_{DO1}}{dp} \right) \right. \\
&\quad \left. - K_{gc,DO1} S_{DO1} \frac{dC_{DO1}}{dp} \right]
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dp} \left[\frac{dC_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO2}}{dp} \right] \\
&= \frac{1}{V_{DO2}} \left[f_D \frac{dQ}{dp} (C_{DO1} - C_{DO2}) + f_D Q \left(\frac{dC_{DO1}}{dp} - \frac{dC_{DO2}}{dp} \right) \right. \\
&\quad \left. - K_{gc,DO2} S_{DO2} \frac{dC_{DO2}}{dp} \right]
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dp} \left[\frac{dC_{NP}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NP}}{dp} \right] \\
&= \frac{1}{V_{NP}} \left[\frac{dQ}{dp} (f_D C_{DO2} + f_V C_{VR2} - C_{NP}) \right. \\
&\quad \left. + Q \left(f_D \frac{dC_{DO2}}{dp} + f_V \frac{dC_{VR2}}{dp} - \frac{dC_{NP}}{dp} \right) \right. \\
&\quad \left. - K_{gc,NP} S_{NP} \frac{dC_{NP}}{dp} \right]
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dp} \left[\frac{dC_{LRC}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{LRC}}{dp} \right] \\
&= \frac{1}{V_{LRC}} \left[\frac{dQ}{dp} (C_{NP} - C_{LRC}) + Q \left(\frac{dC_{NP}}{dp} - \frac{dC_{LRC}}{dp} \right) \right. \\
&\quad \left. - K_{gc,LRC} S_{LRC} \frac{dC_{LRC}}{dp} \right]
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dp} \left[\frac{d\Delta n_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR1}}{dp} \right] \\
&= w_{VR1} k_0 \frac{K_D \frac{dC_{VR1}}{dp}}{(C_{VR1} + K_D)^2} g(n) \\
&\quad + w_{VR1} k_0 \frac{C_{VR1}}{C_{VR1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dp} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR1}}{dp}
\end{aligned}$$

$$\frac{d}{dp} \left[\frac{d\Delta n_{VR2}}{dt} \right] = \frac{d}{dt} \left[\frac{d\Delta n_{VR2}}{dp} \right]$$

$$\begin{aligned}
&= w_{VR2}k_0 \frac{K_D \frac{dC_{VR2}}{dp}}{(C_{VR2} + K_D)^2} g(n) \\
&\quad + w_{VR2}k_0 \frac{C_{VR2}}{C_{VR2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dp} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR2}}{dp} \\
\frac{d}{dp} \left[\frac{d\Delta n_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DR}}{dp} \right] \\
&= w_{DR}k_0 \frac{K_D \frac{dC_{DR}}{dp}}{(C_{DR} + K_D)^2} g(n) \\
&\quad + w_{DR}k_0 \frac{C_{DR}}{C_{DR} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dp} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DR}}{dp} \\
\frac{d}{dp} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{dp} \right] \\
&= w_{DO1}k_0 \frac{K_D \frac{dC_{DO1}}{dp}}{(C_{DO1} + K_D)^2} g(n) \\
&\quad + w_{DO1}k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dp} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO1}}{dp} \\
\frac{d}{dp} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{dp} \right]
\end{aligned}$$

$$\begin{aligned}
&= w_{DO2} k_0 \frac{K_D \frac{dC_{DO2}}{dp}}{(C_{DO2} + K_D)^2} g(n) \\
&\quad + w_{DO2} k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dp} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dp} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{dp} + \frac{d\Delta n_{DO2}}{dp} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO2}}{dp} \\
\frac{d}{dp} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{dp} \right] \\
&= \frac{1}{\tau_Q} \left[\frac{dQ_{steady}(n)}{dp} - \frac{dQ}{dp} \right]
\end{aligned}$$

B.3.5 The sensitivity equations for α

$$\begin{aligned}
\frac{d}{d\alpha} \left[\frac{dC_{NV}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NV}}{d\alpha} \right] \\
&= \frac{1}{V_{NV}} \left[\frac{dQ}{d\alpha} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{d\alpha} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{d\alpha} \right] \\
&= \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{d\alpha} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{d\alpha} - \frac{dC_{VR1}}{d\alpha} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{d\alpha} \right] \\
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{d\alpha} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{d\alpha} - \frac{dC_{VR2}}{d\alpha} \right) \right]
\end{aligned}$$

$$\begin{aligned}
& -K_{gc,VR2}S_{VR2}\frac{dC_{VR2}}{d\alpha} \Big] \\
\frac{d}{d\alpha} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{d\alpha} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{d\alpha} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{d\alpha} - \frac{dC_{DR}}{d\alpha} \right) \right. \\
&\quad \left. - K_{gc,DR}S_{DR}\frac{dC_{DR}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{d\alpha} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{d\alpha} (C_{DR} - C_{DO1}) + f_D Q \left(\frac{dC_{DR}}{d\alpha} - \frac{dC_{DO1}}{d\alpha} \right) \right. \\
&\quad \left. - K_{gc,DO1}S_{DO1}\frac{dC_{DO1}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO2}}{d\alpha} \right] \\
&= \frac{1}{V_{DO2}} \left[f_D \frac{dQ}{d\alpha} (C_{DO1} - C_{DO2}) + f_D Q \left(\frac{dC_{DO1}}{d\alpha} - \frac{dC_{DO2}}{d\alpha} \right) \right. \\
&\quad \left. - K_{gc,DO2}S_{DO2}\frac{dC_{DO2}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{NP}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NP}}{d\alpha} \right] \\
&= \frac{1}{V_{NP}} \left[\frac{dQ}{d\alpha} (f_D C_{DO2} + f_V C_{VR2} - C_{NP}) \right. \\
&\quad + Q \left(f_D \frac{dC_{DO2}}{d\alpha} + f_V \frac{dC_{VR2}}{d\alpha} - \frac{dC_{NP}}{d\alpha} \right) \\
&\quad \left. - K_{gc,NP}S_{NP}\frac{dC_{NP}}{d\alpha} \right] \\
\frac{d}{d\alpha} \left[\frac{dC_{LRC}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{LRC}}{d\alpha} \right] \\
&= \frac{1}{V_{LRC}} \left[\frac{dQ}{d\alpha} (C_{NP} - C_{LRC}) + Q \left(\frac{dC_{NP}}{d\alpha} - \frac{dC_{LRC}}{d\alpha} \right) \right]
\end{aligned}$$

$$\begin{aligned}
& -K_{gc,LRC}S_{LRC}\frac{dC_{LRC}}{d\alpha}\Big] \\
\frac{d}{d\alpha}\left[\frac{d\Delta n_{VR1}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{VR1}}{d\alpha}\right] \\
&= w_{VR1}k_0\frac{K_D\frac{dC_{VR1}}{d\alpha}}{(C_{VR1}+K_D)^2}g(n) \\
&\quad +w_{VR1}k_0\frac{C_{VR1}}{C_{VR1}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\alpha}\right. \\
&\quad \left.+\frac{d\Delta n_{VR2}}{d\alpha}+\frac{d\Delta n_{DR}}{d\alpha}+\frac{d\Delta n_{DO1}}{d\alpha}+\frac{d\Delta n_{DO2}}{d\alpha}\right) \\
&\quad -\frac{1}{\tau_r}\frac{d\Delta n_{VR1}}{d\alpha} \\
\frac{d}{d\alpha}\left[\frac{d\Delta n_{VR2}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{VR2}}{d\alpha}\right] \\
&= w_{VR2}k_0\frac{K_D\frac{dC_{VR2}}{d\alpha}}{(C_{VR2}+K_D)^2}g(n) \\
&\quad +w_{VR2}k_0\frac{C_{VR2}}{C_{VR2}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\alpha}\right. \\
&\quad \left.+\frac{d\Delta n_{VR2}}{d\alpha}+\frac{d\Delta n_{DR}}{d\alpha}+\frac{d\Delta n_{DO1}}{d\alpha}+\frac{d\Delta n_{DO2}}{d\alpha}\right) \\
&\quad -\frac{1}{\tau_r}\frac{d\Delta n_{VR2}}{d\alpha} \\
\frac{d}{d\alpha}\left[\frac{d\Delta n_{DR}}{dt}\right] &= \frac{d}{dt}\left[\frac{d\Delta n_{DR}}{d\alpha}\right] \\
&= w_{DR}k_0\frac{K_D\frac{dC_{DR}}{d\alpha}}{(C_{DR}+K_D)^2}g(n) \\
&\quad +w_{DR}k_0\frac{C_{DR}}{C_{DR}+K_D}g'(n)\left(\frac{d\Delta n_{VR1}}{d\alpha}\right. \\
&\quad \left.+\frac{d\Delta n_{VR2}}{d\alpha}+\frac{d\Delta n_{DR}}{d\alpha}+\frac{d\Delta n_{DO1}}{d\alpha}+\frac{d\Delta n_{DO2}}{d\alpha}\right) \\
&\quad -\frac{1}{\tau_r}\frac{d\Delta n_{DR}}{d\alpha}
\end{aligned}$$

$$\begin{aligned}
\frac{d}{d\alpha} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{d\alpha} \right] \\
&= w_{DO1} k_0 \frac{K_D \frac{dC_{DO1}}{dp}}{(C_{DO1} + K_D)^2} g(n) \\
&\quad + w_{DO1} k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\alpha} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{d\alpha} + \frac{d\Delta n_{DR}}{dp} + \frac{d\Delta n_{DO1}}{d\alpha} + \frac{d\Delta n_{DO2}}{d\alpha} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO1}}{d\alpha} \\
\frac{d}{d\alpha} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{d\alpha} \right] \\
&= w_{DO2} k_0 \frac{K_D \frac{dC_{DO2}}{d\alpha}}{(C_{DO2} + K_D)^2} g(n) \\
&\quad + w_{DO2} k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{d\alpha} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{d\alpha} + \frac{d\Delta n_{DR}}{d\alpha} + \frac{d\Delta n_{DO1}}{d\alpha} + \frac{d\Delta n_{DO2}}{d\alpha} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO2}}{d\alpha} \\
\frac{d}{d\alpha} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{d\alpha} \right] \\
&= \frac{1}{\tau_Q} \left[\frac{dQ_{steady}(n)}{d\alpha} - \frac{dQ}{d\alpha} \right]
\end{aligned}$$

B.3.6 The sensitivity equations for K_D

$$\frac{d}{dK_D} \left[\frac{dC_{NV}}{dt} \right] = \frac{d}{dt} \left[\frac{dC_{NV}}{dK_D} \right]$$

$$\begin{aligned}
&= \frac{1}{V_{NV}} \left[\frac{dQ}{dK_D} (C_{inh} - C_{NV}) - Q \frac{dC_{NV}}{dK_D} - K_{gc,NV} S_{NV} \frac{dC_{NV}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR1}}{dK_D} \right] \\
&= \frac{1}{V_{VR1}} \left[f_V \frac{dQ}{dK_D} (C_{NV} - C_{VR1}) + f_V Q \left(\frac{dC_{NV}}{dK_D} - \frac{dC_{VR1}}{dK_D} \right) \right. \\
&\quad \left. - K_{gc,VR1} S_{VR1} \frac{dC_{VR1}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{VR2}}{dK_D} \right] \\
&= \frac{1}{V_{VR2}} \left[f_V \frac{dQ}{dK_D} (C_{VR1} - C_{VR2}) + f_V Q \left(\frac{dC_{VR1}}{dK_D} - \frac{dC_{VR2}}{dK_D} \right) \right. \\
&\quad \left. - K_{gc,VR2} S_{VR2} \frac{dC_{VR2}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DR}}{dK_D} \right] \\
&= \frac{1}{V_{DR}} \left[f_D \frac{dQ}{dK_D} (C_{NV} - C_{DR}) + f_D Q \left(\frac{dC_{NV}}{dK_D} - \frac{dC_{DR}}{dK_D} \right) \right. \\
&\quad \left. - K_{gc,DR} S_{DR} \frac{dC_{DR}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO1}}{dK_D} \right] \\
&= \frac{1}{V_{DO1}} \left[f_D \frac{dQ}{dK_D} (C_{DR} - C_{DO1}) \right. \\
&\quad \left. + f_D Q \left(\frac{dC_{DR}}{dK_D} - \frac{dC_{DO1}}{dK_D} \right) \right. \\
&\quad \left. - K_{gc,DO1} S_{DO1} \frac{dC_{DO1}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{DO2}}{dK_D} \right] \\
&= \frac{1}{V_{DO2}} \left[f_D \frac{dQ}{dK_D} (C_{DO1} - C_{DO2}) \right]
\end{aligned}$$

$$\begin{aligned}
& +f_D Q \left(\frac{dC_{DO1}}{dK_D} - \frac{dC_{DO2}}{dK_D} \right) \\
& -K_{gc,DO2} S_{DO2} \frac{dC_{DO2}}{dK_D} \Big] \\
\frac{d}{dK_D} \left[\frac{dC_{NP}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{NP}}{dK_D} \right] \\
&= \frac{1}{V_{NP}} \left[\frac{dQ}{dK_D} (f_D C_{DO2} + f_V C_{VR2} - C_{NP}) \right. \\
& \quad + Q \left(f_D \frac{dC_{DO2}}{dK_D} + f_V \frac{dC_{VR2}}{dK_D} - \frac{dC_{NP}}{dK_D} \right) \\
& \quad \left. -K_{gc,NP} S_{NP} \frac{dC_{NP}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{dC_{LRC}}{dt} \right] &= \frac{d}{dt} \left[\frac{dC_{LRC}}{dK_D} \right] \\
&= \frac{1}{V_{LRC}} \left[\frac{dQ}{dK_D} (C_{NP} - C_{LRC}) + Q \left(\frac{dC_{NP}}{dK_D} - \frac{dC_{LRC}}{dK_D} \right) \right. \\
& \quad \left. -K_{gc,LRC} S_{LRC} \frac{dC_{LRC}}{dK_D} \right] \\
\frac{d}{dK_D} \left[\frac{d\Delta n_{VR1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR1}}{dK_D} \right] \\
&= w_{VR1} k_0 \frac{K_D \frac{dC_{VR1}}{dK_D} - C_{VR1}}{(C_{VR1} + K_D)^2} g(n) \\
& \quad + w_{VR1} k_0 \frac{C_{VR1}}{C_{VR1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dK_D} \right. \\
& \quad \left. + \frac{d\Delta n_{VR2}}{dK_D} + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) \\
& \quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR1}}{dK_D} \\
\frac{d}{dK_D} \left[\frac{d\Delta n_{VR2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{VR2}}{dK_D} \right]
\end{aligned}$$

$$\begin{aligned}
&= w_{VR2}k_0 \frac{K_D \frac{dC_{VR2}}{dK_D} - C_{VR2}}{(C_{VR2} + K_D)^2} g(n) \\
&\quad + w_{VR2}k_0 \frac{C_{VR2}}{C_{VR2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dK_D} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dK_D} + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{VR2}}{dK_D} \\
\frac{d}{dK_D} \left[\frac{d\Delta n_{DR}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DR}}{dK_D} \right] \\
&= w_{DR}k_0 \frac{K_D \frac{dC_{DR}}{dK_D} - C_{DR}}{(C_{DR} + K_D)^2} g(n) \\
&\quad + w_{DR}k_0 \frac{C_{DR}}{C_{DR} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dK_D} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dK_D} + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DR}}{dK_D} \\
\frac{d}{dK_D} \left[\frac{d\Delta n_{DO1}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO1}}{dK_D} \right] \\
&= w_{DO1}k_0 \frac{K_D \frac{dC_{DO1}}{dK_D} - C_{DO1}}{(C_{DO1} + K_D)^2} g(n) \\
&\quad + w_{DO1}k_0 \frac{C_{DO1}}{C_{DO1} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dK_D} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dK_D} + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) \\
&\quad - \frac{1}{\tau_r} \frac{d\Delta n_{DO1}}{dK_D} \\
\frac{d}{dK_D} \left[\frac{d\Delta n_{DO2}}{dt} \right] &= \frac{d}{dt} \left[\frac{d\Delta n_{DO2}}{dK_D} \right]
\end{aligned}$$

$$\begin{aligned}
&= w_{DO2}k_0 \frac{K_D \frac{dC_{DO2}}{dK_D} - C_{DO2}}{(C_{DO2} + K_D)^2} g(n) \\
&\quad + w_{DO2}k_0 \frac{C_{DO2}}{C_{DO2} + K_D} g'(n) \left(\frac{d\Delta n_{VR1}}{dK_D} \right. \\
&\quad \left. + \frac{d\Delta n_{VR2}}{dK_D} + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) \\
&\quad - \frac{1}{\tau_Q} \frac{d\Delta n_{DO2}}{dK_D} \\
\frac{d}{dK_D} \left[\frac{dQ}{dt} \right] &= \frac{d}{dt} \left[\frac{dQ}{dK_D} \right] \\
&= \frac{1}{\tau_r} \left[\frac{dQ_{steady}(n)}{dn} \left(\frac{d\Delta n_{VR1}}{dK_D} + \frac{d\Delta n_{VR2}}{dK_D} \right. \right. \\
&\quad \left. \left. + \frac{d\Delta n_{DR}}{dK_D} + \frac{d\Delta n_{DO1}}{dK_D} + \frac{d\Delta n_{DO2}}{dK_D} \right) - \frac{dQ}{dK_D} \right]
\end{aligned}$$

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