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OPTIMAL CONTROL FRAMEWORKS FOR MODELING DYNAMICS AND ANDROGEN DEPRIVATION THERAPIES IN PROSTATE CANCER

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OPTIMAL CONTROL FRAMEWORKS FOR MODELING DYNAMICS AND ANDROGEN DEPRIVATION THERAPIES IN PROSTATE CANCER

by

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ABSTRACT

OPTIMAL CONTROL FRAMEWORKS FOR MODELING DYNAMICS AND ANDROGEN DEPRIVATION THERAPIES IN PROSTATE CANCER

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In this work, we present an optimal control approach for the assessment of treatments in prostate cancer. For this purpose, we use two different approaches, based on differential equations, to model the dynamics of prostate cancer. For the first approach, we use a system of ordinary differential equations (ODE) that model androgen-dependent and independent prostate cancer cell mechanisms. Given some synthetic patient data, we then performed a parameter estimation process by formulating an optimization problem to obtain the coefficients in this model. A second optimal control problem was formulated to obtain optimal androgen suppression therapies. A theoretical analysis of both optimization problems was performed to prove the existence of the minimizers. The numerical implementation of the optimization problems was done using a non-linear conjugate gradient method. Several numerical experiments demonstrate the accuracy and robustness of our proposed ODE framework. The second approach involved extending a reduced version of the aforementioned ODE model to a Liouville partial differential equation model that captures more variabilities and randomness involved in clinical trials and formulating

the corresponding parameter estimation and optimal control problems. The numerical implementation was done using a second-order spatially accurate finite volume scheme. First, the comparison of the ODE and the Liouville framework results of parameter estimation demonstrated that the Liouville modeling framework is more accurate in capturing the cancer cell dynamics. Results of the Liouville optimal control framework demonstrated the effectiveness in obtaining optimal therapies to combat prostate cancer.

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CHAPTER 1

Introduction

1.1 Prostate

The prostate is a small male gland about the size of a walnut that is part of both the male reproductive and endocrine systems. It is located below the bladder. Precisely, deep inside the groin, between the base of the penis and the front of the rectum. It is very important for reproduction because it produces and supplies part of the seminal fluid, which mixes with sperm from the testes and helps it travel, nourish, and survive. During ejaculation, the prostate muscles help push this fluid into the urethra, where it's ejected with sperm as semen. One of the deadliest conditions that affect the prostate is cancer.

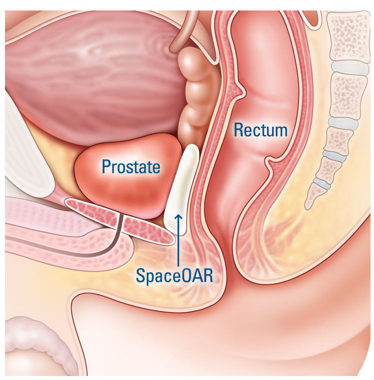

Figure 1.1: prostate gland [79]

1.2 Prostate cancer developments, motivation

Prostate cancer begins when some of the cells in the prostate gland start growing uncontrollably. It usually starts as a tumor without any signs or symptoms in young men, typically between the ages of 20 and 30. However, the problem is that symptoms only become noticeable after a long time, when the disease has already become dangerous. This means that by the time symptoms appear, the available treatment options for the patient are reduced, and the chances of survival are also lower [10, 41]. Although it is difficult to determine the exact causes of prostate cancer, age, race, and inherited factors are the most strongly established risk factors for it. [65].

Prostate cancer is one of the most common and dangerous type of non-skin cancer, and is considered the second leading cause of death among men in the United States [54]. One out of every six men is estimated to be diagnosed with prostate cancer at some point in their life [53]. According to the American Cancer Society, there are around 268,490 new cases of prostate cancer in the United States, with 34,500 deaths in 2022 [92]. There are more than 3.1 million American men currently living with prostate cancer, which is nearly equal to the population of Chicago, Illinois. Therefore, the disease remains a highly discussed and researched topic in cancer studies [96].

Globally, prostate cancer is becoming more common, although it is particularly prevalent in poorer countries [89]. The World Health Organization reported 9.6 million cancer deaths and 18.1 million new cancer cases in 2018. By the year 2040, it is expected that there will be 29.5 million new cases of cancer and 16.5 million deaths [72]. Thus, it is imperative to determine efficient and effective treatment strategies for this disease.

1.3 Prostate cancer models

Doctors and researchers began to study the growth and effects of prostate cancer, and most studies and research were done in clinics. However, there are many challenges exist in clinical prostate cancer research. Some of them require clinical studies to understand the complex mechanisms of cancer and associated treatments. Another significant clinical challenge is obtaining an effective treatment strategy for each patient individually, or at least identifying a subset of patients who could benefit from a particular treatment. In addition, testing even one therapy during clinical trials is costly.

These obstacles show the necessity of continuous research efforts to improve our understanding of prostate cancer and optimize treatment options for better patient results. There is a significant lack of detailed knowledge of the intricate mechanisms behind prostate cancer and the results of different therapies, and it is for this reason that some researchers have found new research methods using mathematical models to more effectively understand how prostate cancer behaves [59].

In the past years, a lot of mathematical models have been created and analyzed through collaborations with doctors to explore various aspects of prostate cancer, such as treatment choices and timetables for those treatments [76]. Through these collaborations, important discoveries have been made about how prostate cancer develops and changes over time. In the most notable of these discoveries, Yorke et al. [76] created a simple model to describe and explain how prostate cancer grows and progresses. Ideta et al. [50] formulated mathematical models to determine prostate cancer growth while on intermittent androgen therapy. Portz and Kuang [78] created a mathematical model of the cancer with the treatment of androgen deprivation therapy, and this is the first clinically validated dynamical model for the disease. Rutter and Kuang [83] built a new population model for vaccination and androgen deprivation therapy. Baez and Kuang [7] introduced a two-subpopulation model for prostate cancer undergoing androgen suppression therapy. For other models, [29, 31, 42, 43, 51, 52, 94, 95].

1.4 Prostate cancer treatment

The success of some previous work [7, 59, 78, 83] led to the development of several models to study the cancer's progression and treatment. One of the frequently used methods for this treatment is androgen deprivation therapy (ADT), which uses drugs to block or lower levels of androgen and starve the prostate cancer cells of androgen. This method was based on the significant cancer research discovery made by Huggins and Hodes [49]. They found that removing the testicles (castration) can help reduce the size of prostate tumors. This discovery highlighted the significant role of androgen, a male sex hormone, in the growth of prostate cancer cells. Their research opened the possibility of treating some cancers using chemical treatments, making this an essential development in the field. As a result, Huggins was awarded the Nobel Prize in Medicine and Physiology in 1966 for this remarkable discovery [70].

Over time, androgen deprivation therapy, a form of hormone therapy, is a typical treatment for localized and locally progressing prostate cancer and has been shown to improve survival significantly. It can be said that mathematical models have made great progress in helping us understand how cancer cells grow and how androgen deprivation affects their growth and response to treatment. These models have made significant contributions to the field of cancer treatment and provided important knowledge and new ways to treat cancer effectively. See, e.g., [7, 29, 31, 42, 43, 46, 50, 52, 78, 83, 91, 94].

Typically, androgen deprivation therapy (ADT) thrives at the beginning of treatment because it targets the primary tumor cells that rely on androgen for their growth. However, in many cases, ADT has some side effects [60]. It is unable to prevent a relapse. This happens because, after a few years, the androgen-dependent (AD) tumor cells resist treatment and transform into androgen-independent (AI) cells. These AI cells can continue multiplying even in an environment with limited androgen availability [20, 38, 85]. Some research indicates that only specific groups of patients may experience benefits from intermittent androgen deprivation therapy, but the determination of those specific groups is still an ongoing process [58, 93].

Although mathematical models have suggested that intermittent androgen deprivation therapy might extend the time until androgen-independent relapse, there is currently no solid proof from clinical trials to support this claim [15, 25, 84, 90]. Moreover, doctors have no agreement about the treatment's duration or intervals [35].

One could say that the results shown in these studies show that prostate cancer can go into near extinction during the on-treatment interval before coming back during the off-treatment break. Also, the mechanism used for the method to incorporate androgen into growth and death rates is ineffective when androgen independence (AI) cells overtake androgen dependence (AD) cells. Thus, developing and assessing the optimal ADT method for prostate cancer is essential.

1.5 Optimal control

Most of the past optimal control models of cancer therapy worked to minimize total tumor volume. Swan and Vincent [88] provide the first cancer treatment applications of optimal control theory. Over time, researchers have applied optimal control theory to explore various cancer treatments, including chemotherapies and radiotherapy [1, 11, 56, 21, 63, 68, 23]. Additionally, in prostate cancer research, some studies use optimal control to find the best schedule of androgen-dependent therapy [45, 47].

The optimal dose schedule is considered good when the goal of the therapy is to reduce the variance in tumor burden over a period of time. In 2009, Gatenby [33] demonstrated how effective this goal is in achieving long-term control of tumors.

Jessica J. Cunningham et al. [27] used optimal control theory to find the best treatment schedule for patients by using nonlinear constrained optimization. The results showed that long-term tumor control is possible with optimized therapy.

The primary motivation of this work is to formulate an optimization problem to find the optimal dose (lowest dose) that will result in the best treatment for the patient. In this context, developing and assessing effective treatment methods for prostate cancer is essential, as it will provide a fast and practical framework for treatment assessments.

1.6 Outline of thesis

This dissertation is organized into six chapters and has the following structure: In Chapter 2, provides the preliminary work and essential definitions necessary for the subsequent parts of this dissertation. In Chapter 3, delves into ODE modeling and the parameter estimation problem, covering and explaining the mathematical ODE model and the non-dimensional modeling approach used. Provided are some theoretical results and formulate an optimality system, in addition to the showcases numerical results obtained from solving the parameter estimation problem. In Chapter 4, formulates optimization problems related to drug treatments, discussing theoretical results and presenting numerical optimal control results from optimal control procedures. In Chapter 5, the focus shifts to the Liouville optimal control problem in PDE. This section introduces the Liouville model for prostate cancer and explores two optimization problems related to parameter estimation and optimal control. It offers theoretical insights, numerical schemes, and outcomes derived from solving the Liouville equations. Finally, Chapter 6 concludes the thesis and summarizes the main findings, contributions, and potential future research directions.

CHAPTER 2

Definitions and preliminaries

This chapter explains some important terms and background knowledge necessary for understanding what follows. This will help us understand the upcoming content more easily. Many definitions and theorems come from this books [14, 16, 67].

2.1 The Nonlinear Conjugate Gradient Method

Nonlinear conjugate gradient method (NCG) [40, 80] are iterative approaches used to solve optimization problems of the form

$$u_{k+1} = u_k + \alpha_k d_k,$$

Where d_k is a search direction, and α_k is a stepsize usually computed using a line search. We will use the Armijo line search because it effectively tackles non-convex regression problems [22]. A conjugate gradient approach combines information about the negative gradient at the current point with the direction from the previous step. This helps us make progress in the right direction. Consequently, an NCG method chooses

$$\begin{cases} d_0 = -\nabla f\left(u_0\right) \\ d_{k+1} = -\nabla f\left(u_{k+1}\right) + \beta_{k+1} d_k \quad \forall k \in \mathbb{N} \end{cases}$$

Where β_{k+1} is the NCG update parameter is chosen according to the formula proposed by Hager and Zhang [39] given by

$$\beta_{k+1}^{HZ} = \frac{1}{d_k^T y_k} \left(y_k - 2 d_k \frac{\left\| y_k \right\|^2}{d_k^T y_k} \right)^T \nabla f\left(u_{k+1}\right),$$

where $y_k = \nabla f\left(u_{k+1}\right) - \nabla f\left(u_k\right)$.

Algorithm 2.1 Projected NCG Scheme

Input: initial approx. $\boldsymbol{u}_0$. Evaluate $d_0 = -\nabla f(u_0)$, index $k = 0$, maximum $k = k_{\max}$, tolerance $=$ tol .
While $(k < k_{\max})$ do
Set $u_{k+1} = u_k + \alpha_k d_k$, where α_k is obtained using a line-search algorithm.
Compute $y_k = \nabla f(u_{k+1}) - \nabla f(u_k)$.
Compute β_k^{HZ} using $\beta_{k+1}^{HZ} = \frac{1}{d_k^T y_k}\left(y_k - 2d_k \frac{\|y_k\|^2}{d_k^T y_k}\right)^T \nabla f(u_{k+1})$.
Set $d_{k+1} = -\nabla f(u_{k+1}) + \beta_{k+1} d_k \quad \forall k \in \mathbb{N}$.
If $\|\boldsymbol{u}_{k+1} - \boldsymbol{u}_k\| <$ tol, terminate.
Set $k = k + 1$.
End while.

Definition 2.1.1 (Vector Space)**.** Let V be a non-empty set, and suppose $u, v \in V \implies u + v \in V$, and let a, b be scalars. Then V is called a vector if the following properties hold:

(1) $u + v = v + u$,

(2) $u + (v + w) = (u + v) + w$ for all $u, v, w \in V$,

(3) $\exists\ 0 \in V,\ \forall\ u \in V\ \ u + 0 = 0 + u = u$,

(4) $\forall u \in V \exists (-u) \in V$ such that $u + (-u) = 0 = (-u) + u$,

(5) $\forall u \in V, a(u + v) = a \cdot u + a \cdot v$,

(6) $(a + b)u = a \cdot u + b \cdot v$,

(7) $(ab)u = a(bu)$,

(8) $1 \cdot u = u$.

Definition 2.1.2 (Norm)**.** Let V be a vector space. Let $\|u\|$ be a non-negative number associated with each $u \in V$ such that if $u, v \in V$, which has the following properties:

(1) $\|u\| = 0 \Longleftrightarrow u = 0$,

(2) $\|au\| = |a|\|u\|$,

(3) $\|u + v\| \leq \|u\| + \|v\|$.

Then $\|\cdot\|$ is referred to as a norm and V is called a norm vector space.

Theorem 2.1.1 (Grönwall's Inequality)**.** Let $x(\cdot)$ be a nonnegative, absolutely continuous function on $[0, T]$, which satisfies the almost everywhere (a.e.) inequality

$$x'(t) \leq \beta(t)x(t) + \alpha(t)$$

where β, α are nonnegative, summable functions on $[0, T]$. Then

$$x(t) \leq \left[x(0) + \int_0^t \alpha(s)\mathrm{d}s\right] e^{\int_0^t \beta(s)\mathrm{d}s}$$

for all $0 \leq t \leq T$.

Definition 2.1.3 (Strongly convergence)**.** A sequence $\{u_n\}_{n=1}^{\infty}$ in a vector space V is said to converge strongly to some $u \in V$, written as

$$u_n \to u$$

if

$$\lim_{n\to\infty} \|u_n - u\| = 0$$

Definition 2.1.4 (Weakly convergence)**.** A sequence $\{u_n\}$ in a Banach space V weakly convergence to $u \in V$, written as

$$u_k \rightharpoonup u$$

if

$$\lim_{n\to\infty} f(u_n) = f(u), \forall f \in V^*$$

Definition 2.1.5 (Sobolev space)**.** The Sobolev space $W^{k,p}(\Omega)$ is defined as

$$W^{k,p}(\Omega) = \left\{u \in W^k(\Omega) : D^\alpha u \in L^p, \forall |\alpha| \leq k\right\}$$

Definition 2.1.6 (norm Sobolev space)**.** If $u \in W^{k,p}(U)$, we define its norm to be

$$\|u\|_{W^{k,p}(U)} := \begin{cases} \left(\sum_{|\alpha|\leq k} \int_U |D^\alpha u|^p \, dx\right)^{\frac{1}{p}} & (1 \leq p < \infty) \\ \sum_{|\alpha|\leq k} \operatorname{ess\,sup}_U |D^\alpha u| & (p = \infty) \end{cases}$$

Definition 2.1.7 (coerciveness)**.** Let $f : \mathbb{R}^n \to \mathbb{R}$ be a continuous function defined over $\mathbb{R}^n$. The function f is called coercive if

$$\lim_{\|\mathbf{x}\|\to\infty} f(\mathbf{x}) = \infty$$

Let V be a Banach space and K be a non-empty subset of V. Let $J : V \to \mathbb{R}$, and we consider

$$\inf_{v\in K\subset V} J(v)$$

Definition 2.1.8. An element u is called a local minimizer of J on K if $u \in K$ and $\exists\ \delta > 0$ such that $\forall\ v \in K$

$$\|v - u\| < \delta \Longrightarrow J(v) \geq J(u)$$

An element u is called a global minimizer of J on K if $u \in K$ and

$$J(v) \geq J(u) \quad \forall\ v \in K$$

Definition 2.1.9. A minimizing sequence of a function J on the set K is a sequence $(u^n)_{n\in\mathbb{N}}$ such that

$$u^n \in K \forall n \text{ and } \lim_{n\to+\infty} J(u^n) = \inf_{v\in K} J(v)$$

Definition 2.1.10 (convex)**.** A set $K \subset V$ is said to be convex if, for any $u, v \in K$ and for any $\theta \in [0, 1]$,

$$\theta u + (1 - \theta)v \in K$$

Definition 2.1.11. Let K be convex subset of V, then a function $J : K \to \mathbb{R}$, is said to be convex on K if

$$J(\theta u + (1-\theta)v) \leq \theta J(u) + (1-\theta)J(y), \forall u, v \in K, \forall \theta \in [0,1].$$

Definition 2.1.12. Definition 9.2 The functional J is called (sequential) lower semi-continuous (lsc) at $y \in V$ if

$$J(y) \leq \liminf_{k\to\infty} J(y_k) \tag{2.1.1}$$

for all sequences $(y_k) \subset V$ converging strongly to $y, y_k \to y$. The functional J is (sequential) weakly lower semi-continuous (wlsc) if (2.1.1) holds for all sequences $(y_k) \subset V$ converging weakly to $y, y_k \rightharpoonup y$.

Theorem 2.1.2 (Cauchy, Lipschitz, Picard)**.** Let E be a Banach space and let F : $E \to E$ be a Lipschitz map, i.e., there is a constant L such that

$$\|Fu - Fv\| \leq L\|u - v\| \quad \forall u, v \in E.$$

Then given any $u_0 \in E$, there exists a unique solution $u \in C^1([0,+\infty); E)$ of the problem

$$\begin{cases} \frac{du}{dt}(t) = Fu(t) & \text{on } [0,+\infty), \\ u(0) = u_0. \end{cases}$$

u_0 is called the initial data.

Definition 2.1.13 (Gâteaux derivative)**.** F is said to be Gâteaux differentiable at z if its is directional derivative exists and $F'(z;h) = F'(z)h$ for $F'(z) \in \mathcal{L}(Z;V)$. We refer to $F'(z)$ as the Gâteaux derivative at z.

Definition 2.1.14 (Fréchet derivative)**.** F is said to be Fréchet differentiable at z if and only if F is Gâteaux differentiable at z and the following holds:

$$F(z+h) = F(z) + F'(z)h + r(z,h) \text{ with } \frac{\|r(z,h)\|_V}{\|h\|_Z} \to 0 \text{ as } \|h\|_Z \to 0$$

CHAPTER 3

ODE modeling: Parameter estimation problem

3.1 Introduction

We formulated a prostate cancer dynamics model to determine optimal ADT dosage using an ordinary differential equation (ODE) model. These ODE models contain numerous parameters usually estimated from disparate sources, posing a significant challenge in devising personalized treatments. Some parameters have similar values across patients, while others are more patient-specific, called unknown parameters. Our goal is to find the unknown parameters of the ODE model from measured data. That is known as the parameter estimation method.

Olufsen and Ottesen [74] studied three methods to estimate parameters. Their methods involved lengthy computations. In the work of Yoshito Hirata et al., [48], seven methods for parameter estimation were studied. They concluded that these methods are only sometimes feasible due to numerous disadvantages, e.g., huge computational costs associated with the bootstrapping method. Suzuki and Aihara [87] discussed two methods: the variational Bayes method, which is slightly more effective for long-term predictions, whereas the Gaussian method is better for short-term predictions. The SVD-QR and the sub-space selection methods for estimating parameters contained correlated parameters that gave rise to more significant errors in the predicted parameter estimates. E J Her et al. [44] studied the clinical outcomes data between 1995 and 2012 using parameter estimation performed with a maximum likelihood estimation method. However, with this approach, fitting all the parameters was impossible. Roberta Coletti et al. [24] use parameter estimates from the literature related to human patients.

In the aforementioned parameter estimation methods, correlated parameters and huge computational expenses are significant challenges. To address these issues, we will use a new method for parameter estimation that is robust and accurate. Our parameter estimation method is based on an optimization framework numerically implemented using a robust and accurate optimization scheme.

3.2 Mathematical ODE model

Portz et al.[78] created a model that uses cell quotas to study the relationship between androgen levels and prostate cancer cells. According to this model, they assumed that the tumor consists of two types of cells: androgen-dependent (AD) and androgen-independent (AI) cancer cells. Each cell type needs a certain amount of androgen called the cell quota (Q). When the available androgen drops below this threshold, the specific type of cells that depend on it decreases. This model helps us understand how prostate cancer cells react to different androgen levels.

We describe an ODE-based mathematical cell quota model to describe the dynamics of prostate cancer, where the model variables are as follows

$X_1(t)$: Androgen dependent (AD) - cells

$X_2(t)$: Androgen independent (AI) -cells

$Q(t)$: The cell quota for androgen -nM

t : Time - /day

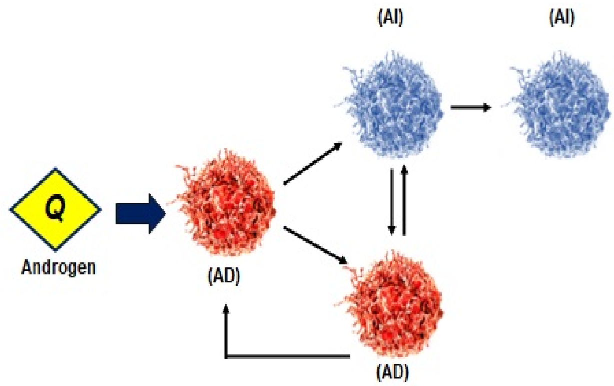

Figure 3.1: Schematic of the processes that occur in the model

The AD and AI cell populations are modeled by

$$\begin{aligned}\frac{dX_1}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2,\\ \frac{dX_2}{dt} &= \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1.\end{aligned} \tag{3.2.1}$$

The proliferation rate of the AD cell population is zero when $Q(t)$ is at the minimum cell quota q. As $Q(t)$ increases, the growth rate approaches its maximum value μ_m. The AD cell population's apoptosis rate and the AI population's net growth rate, excluding mutation, are constant. We also have the following expressions for the AD to AI mutation rate, $m_1(Q)$, and the AI to AD mutation rate $m_2(Q)$

$$\begin{aligned}m_1(Q) &= c_1\frac{k_1^n}{Q^n + k_1^n},\\ m_2(Q) &= c_2\frac{Q^n}{Q^n + k_2^n}.\end{aligned} \tag{3.2.2}$$

We remark that $m_1(Q)$ is low for normal androgen levels and high for low androgen levels. In contrast, $m_2(Q)$ is high for normal androgen levels and low for low androgen levels. Where n is a hill coefficient, which describes the cell switching sensitivity to the cell quota level, we considered $n = 1$ for ultrasensitivity [31]. The cell quota for androgen within the AD cells is modeled by

$$\frac{dQ}{dt} = v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ \tag{3.2.3}$$

3.2.1 The non-dimensional modeling

This section will convert the system from its current form with specific values to a non-dimensional form. That has two purposes: First, it helps simplify our equations by grouping parameters, making them cleaner and easier to handle. Second, non-dimensionalization is often done to reduce the computational cost of solving the system and guarantee the numerical algorithms' stability. We non-dimensionalize the ODE system using the following non-dimensionalized states, time variables, and parameters:

$$\begin{aligned} &{X_1}^* = l_1 X_1 \;\rightarrow\; X_1 = \frac{{X_1}^*}{l_1}, \quad {X_2}^* = l_2 X_2 \;\rightarrow\; X_2 = \frac{{X_2}^*}{l_2} \\ &Q^* = l_3 Q \;\rightarrow\; Q = \frac{Q^*}{l_3}, \qquad\quad t^* = l_4 t \;\rightarrow\; t = \frac{t^*}{l_4} \end{aligned} \tag{3.2.4}$$

The non-dimensionalized parameters will be:

$$\begin{aligned} &{\mu_m}^* = \frac{\mu_m}{l_4},\; d_1^* = \frac{d_1}{l_4},\; {d_2}^* = \frac{d_2}{l_4},\; {q_1}^* = l_3 q_1,\; {q_2}^* = l_3 q_2,\; {k_1}^* = l_3 k_1,\; {k_2}^* = l_3 k_2, \\ &c_1^* = \frac{c_1}{l_4},\; c_2^* = \frac{c_2}{l_4},\; {v_m}^* = \frac{l_3}{l_4} v_m,\; {q_m}^* = l_3 q_m,\; q^* = l_3 q,\; {v_h}^* = l_3 v_h,\; b^* = \frac{b}{l_4},\; A^* = l_3 A. \end{aligned} \tag{3.2.5}$$

Then (3.2.1) can be transformed in the following way:

$$\frac{d\frac{{X_1}^*}{l_1}}{d\frac{t^*}{l_4}} = \mu_m \left(1 - \frac{q_1}{\frac{Q^*}{l_3}}\right) \frac{{X_1}^*}{l_1} - d_1 \frac{{X_1}^*}{l_1} - c_1 \frac{k_1^n}{\left(\frac{Q^*}{l_3}\right)^n + k_1^n} \frac{{X_1}^*}{l_1} + c_2 \frac{\left(\frac{Q^*}{l_3}\right)^n}{\left(\frac{Q^*}{l_3}\right)^n + k_2^n} \frac{{X_2}^*}{l_2},$$

Which gives us

$$\frac{d{X_1}^*}{dt^*} = \frac{\mu_m}{l_4} \left(1 - \frac{l_3 q_1}{Q^*}\right) {X_1}^* - \frac{d_1}{l_4} {X_1}^* - \frac{c_1}{l_4} \frac{(l_3 k_1)^n}{Q^{*n} + (l_3 k_1)^n} {X_1}^* + \frac{l_1}{l_4 l_2} c_2 \frac{Q^{*n}}{Q^{*n} + (l_3 k_2)^n} {X_2}^*$$

Using the non-dimensional parameters, we have

$$\frac{dX_1^*}{dt^*} = {\mu_m}^* \left(1 - \frac{{q_1}^*}{Q^*}\right) {X_1}^* - {d_1}^* {X_1}^* - {c_1}^* \frac{k_1^{*n}}{Q^{*n} + k_1^{*n}} {X_1}^* + {c_2}^* \frac{Q^{*n}}{Q^{*n} + k_2^{*n}} {X_2}^*.$$

Using similar computations, we have

$$\begin{aligned} \frac{d{X_2}^*}{dt^*} &= {\mu_m}^* \left(1 - \frac{{q_2}^*}{Q^*}\right) {X_1}^* - {d_2}^* {X_2}^* - {c_2}^* \frac{Q^{*n}}{Q^{*n} + {k_2}^{*n}} {X_2}^* + {c_1}^* \frac{k_1^{*n}}{Q^{*n} + k_1^{*n}} {X_1}^*, \\ \frac{dQ^*}{dt^*} &= {v_m}^* \frac{{q_m}^* - Q^*}{{q_m}^* - q^*} \frac{A^*}{A^* + {v_h}^*} - {\mu_m}^* \left(Q^* - q^*\right) - b^* Q^*. \end{aligned}$$

Without loss of generality, we can remove the $*$ and rewrite the non-dimensional ODEs as follows

$$\begin{aligned} \frac{dX_1}{dt} &= \left(\mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2\right) = F_1(X_1, X_2, Q, \theta), \quad X_1(0) = 1 \\ \frac{dX_2}{dt} &= \left(\mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1\right) = F_2(X_1, X_2, Q, \theta), \quad X_2(0) = 1 \\ \frac{dQ}{dt} &= v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ = F_3(X_1, X_2, Q, \theta), \quad Q(0) = 1 \end{aligned} \tag{3.2.6}$$

3.3 Parameter estimation optimization problem

Let $\theta = (\mu_m, q_1, q_2, d_1, d_2, A)$ be the vector of the unknown patient specific parameters in (3.2.6). The reason for this choice is because these parameters show wide variability amongst different patients. The other parameters in (3.2.6) are more specific to the cancer type and, thus, can be considered fixed and known across patients.

Parameter	Meaning	Value and units	Reference
μ_m	Maximum proliferation rate	0.025-0.045/day	[13]
q	Minimum AD cell quota	0.175-0.45 nM	[18]
q_1	Minimum AD cell quota	0.175-0.45 nM	[18]
q_2	Minimum AI cell quota	0.1-0.3 nM	[18]
k_1	AD to AI mutation half-saturation level	0.08 nM	[78]
k_2	AI to AD mutation half-saturation level	1.7 nM	[78]
d_1	AD cell apoptosis rate	0.015-0.02/day	[13]
d_2	AI cell apoptosis rate	0.015-0.02/day	[13]
c_1	Maximum AD to AI mutation rate	0.00015/day	[50]
c_2	Maximum AI to AD mutation rate	0.0001/day	[78]
b	Cell quota degradation rate	0.09/day	[50]
q_m	Maximum cell quota	5 nM	[78]
v_m	Maximum cell quota uptake rate	0.275 nM/day	[78]
v_h	Uptake rate half-saturation level	4 nM	[78]
A	Maximum serum androgen level	27-35 nM	[77]

Table 3.1: Biological reference range for the parameters

Our goal is to estimate θ given some data about X_1, X_2, Q. For this purpose, we solve the following constrained optimization problem:

$$\min_{\theta \in T_{ad}} J\left(X_1, X_2, Q, \theta\right) = \frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^d(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^d(t)\right)^2 dt + \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^d(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2_{\ell^2} \tag{3.3.1}$$

subject to the system (3.2.6). Here ${X_1}^d(t), {X_2}^d(t), Q^d(t)$ are given data functions constructed using observations of these variables from an individual patient. The first three terms in the functional J, given in (3.3.1), are data-fitting terms with weights $\alpha_1, \alpha_2, \alpha_3$. The last term in J is a l^2 regularization term for the parameter set θ, with $\|\cdot\|_{l^2}$ representing the standard l^2 Euclidean norm. The set T_{ad} is the admissible set of θ defined as

$$T_{ad} = \{\theta \in \mathbb{R}^6 : \theta(i) \in [0, M_i],\ M_i > 0\},$$

with M_i chosen based on the observed biological reference range of the parameters, as given in Table 3.1.

3.4 Theoretical results

This section will present some theoretical results for the optimization problem stated in (3.3.1). We begin with the positivity of the solutions of (3.2.6)

Theorem 3.4.1. Given $X_1(0) \geq 0, X_2(0) \geq 0, Q(0) \geq 0$, the solutions $(X_1(t), X_2(t), Q(t))$ of (3.2.6) are non-negative for all $t \geq 0$.

Proof. From the first equation of (3.2.6), we have

$$\begin{aligned}\frac{dX_1}{dt} &= \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2, \\ &= -\left(-\mu_m \left(1 - \frac{q_1}{Q}\right) + d_1 + c_1 \frac{k_1^n}{Q^n + k_1^n}\right) X_1 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2\end{aligned} \tag{3.4.1}$$

We consider the following integrating factor

$$I_f^1 = \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)}\right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n}\right) ds \tag{3.4.2}$$

Multiplying (3.4.1) by the integrating factor I_f^1, we obtain

$$\begin{aligned}&\frac{dX_1}{dt} \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)}\right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n}\right) ds \\ &\quad = c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)}\right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n}\right) ds\end{aligned} \tag{3.4.3}$$

This gives us

$$\begin{aligned}&X_1(t) \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)}\right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n}\right) ds - X_1(0) \\ &\quad = \int_0^t c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^z \left(-\mu_m \left(1 - \frac{q_1}{Q(z)}\right) + d_1 + c_1 \frac{k_1^n}{Q(z)^n + k_1^n}\right) dz\end{aligned}$$

which implies

$$X_1(t) = X_1(0) \exp \int_0^t - \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds$$
$$+ \exp \int_0^t - \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds$$
$$\int_0^t c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^z \left(-\mu_m \left(1 - \frac{q_1}{Q(z)} \right) + d_1 + c_1 \frac{k_1^n}{Q(z)^n + k_1^n} \right) dz \geq 0$$

Thus, $X_1(t) \geq 0$.

For the second equation in (3.2.6)

$$\begin{aligned} \frac{dX_2}{dt} &= \mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - c_2 \frac{Q^n}{Q^n + k_2^n} X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 \\ &= - \left(-\mu_m \left(1 - \frac{q_2}{Q} \right) + d_2 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \right) X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1, \end{aligned} \tag{3.4.4}$$

we consider the following integrating factor

$$I_f^2 = \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds \tag{3.4.5}$$

Multiplying (3.4.4) by the integrating factor I_f^2, we obtain

$$\frac{dX_2}{dt} \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds$$
$$= c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds,$$

Which again gives us

$$X_2(t) = X_2(0) \exp - \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds + \exp$$
$$- \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds \int_0^t c_1 \frac{k_1^n}{Q^n + k_1^n} X_1$$
$$\exp \int_0^z \left(-\mu_m \left(1 - \frac{q_2}{Q(z)} \right) + d_2 + c_2 \frac{Q(z)^n}{Q(z)^n + k_2^n} X_2 \right) dz \geq 0$$

Thus, $X_2(t) \geq 0$.

From the third equation in (3.2.6)

$$\begin{aligned}\frac{dQ}{dt} &= v_m \frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ \\ &= \frac{v_m q_m A - v_m Q A}{(q_m - q)(A+v_h)} - \mu_m Q + \mu_m q - bQ \\ &= \frac{v_m q_m A}{(q_m - q)(A+v_h)} - \frac{v_m Q A}{(q_m - q)(A+v_h)} - \mu_m Q + \mu_m q - bQ \\ &= \frac{v_m q_m A}{(q_m - q)(A+v_h)} + \mu_m q - \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) Q,\end{aligned} \tag{3.4.6}$$

we consider the integrating factor

$$I_f^3 = \exp\int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) ds \tag{3.4.7}$$

Multiplying (3.4.6) by the integrating factor I_f^3, we obtain

$$\begin{aligned}&\frac{dQ}{dt}\exp\int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) ds \\ &\quad = \left(\frac{v_m q_m A}{(q_m - q)(A+v_h)} + \mu_m q\right)\exp\int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) ds\end{aligned} \tag{3.4.8}$$

Solving this equation, we obtain

$$\begin{aligned}Q(t) = Q(0)\exp - \int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) ds + \exp \\ - \int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) ds \int_0^t \left(\frac{v_m q_m A}{(q_m - q)(A+v_h)}\right. \\ \left. + \mu_m q\right) dt \exp\int_0^t \left(\frac{v_m A}{(q_m - q)(A+v_h)} + \mu_m + b\right) dz \geq 0\end{aligned}$$

This gives us $Q(t) \geq 0$. □

Proposition 3.4.1. The solution of the system (3.2.6), satisfies the following stability estimate

$$Q(t) \leq \alpha|Q(0)| + \beta \quad \text{where } \alpha, \beta \geq 0,$$

$$(X_1 + X_2) \leq |(X_1 + X_2)(0)|\, e^{\mu_m T}$$

Proof. We have

$$\begin{aligned}\frac{dQ}{dt} &= v_m \frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ \quad , Q(0)=0\\ &= \frac{-v_m A Q}{(q_m-q)(A+v_h)} - \mu_m Q - bQ + \frac{v_m q_m A}{(q_m-q)(A+v_h)} + \mu_m q\\ &= \left(\frac{-v_m A}{(q_m-q)(A+v_h)} - \mu_m - b\right)Q + \frac{v_m q_m A}{(q_m-q)(A+v_h)} + \mu_m q\end{aligned}$$

Let

$$C_1 = \frac{-v_m A}{(q_m-q)(A+v_h)} - \mu_m - b$$

and

$$C_2 = \frac{v_m q_m A}{(q_m-q)(A+v_h)} + \mu_m q.$$

Then we have

$$\frac{dQ}{dt} = C_1 Q + C_2$$

Using Gronwall's inequality, we obtain the following

$$\begin{aligned}Q(t) &\le e^{-\int_0^t C_1 dt}\left(Q(0) + 2\int_0^t C_2 e^{-\int_0^s C_1 ds} ds\right)\\ &\le e^{-C_1 t}\left(Q(0) + 2C_2\int_0^t e^{-C_1 s} ds\right)\\ &\le e^{-C_1 t}\left(Q(0) + 2C_2\left[\frac{e^{-C_1 t}-1}{C_1}\right]\right)\end{aligned}$$

Now if $C_1 \ge 0, e^{-C_1 t} \le 1$ and if $C_1 < 0, e^{-C_1 t} \le e^{-C_1 T}$. Thus, we have

$$Q(t) \le \begin{cases} |Q(0)| & \text{if } C_1 \ge 0\\ e^{-C_1 T}|Q(0)| + 2\,|C_2|\,e^{-C_1 T}\left|\left[\frac{e^{-C_1 T}-1}{C_1}\right]\right|, & \text{if } C_1 < 0\end{cases}$$

$$Q(t) \le \alpha|Q(0)| + \beta \quad \text{where } \alpha, \beta \ge 0 \tag{3.4.9}$$

Next, we consider the first two equations of (3.2.6)

$$\begin{aligned}\frac{dX_1}{dt} &= \mu_m\left(1 - \frac{q_1}{Q}\right)X_1 - d_1 X_1 - c_1\frac{k_1^n}{Q^n + k_1^n}X_1 + c_2\frac{Q^n}{Q^n + k_2^n}X_2\\ \frac{dX_2}{dt} &= \mu_m\left(1 - \frac{q_2}{Q}\right)X_2 - d_2 X_2 - c_2\frac{Q^n}{Q^n + k_2^n}X_2 + c_1\frac{k_1^n}{Q^n + k_1^n}X_1\end{aligned}$$

Adding these two equations, we have

$$\begin{aligned}
\frac{d\left(X_1+X_2\right)}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \\
&+ \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1 \\
&= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \\
&+ \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1 \\
&= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 + \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 \\
&= \mu_mX_1 - \frac{\mu_m q_1}{Q}X_1 - d_1X_1 + \mu_mX_2 - \frac{\mu_m q_2}{Q}X_2 - d_2X_2 \\
&= \mu_m\left(X_1+X_2\right) - \frac{\mu_m}{Q}\left(q_1X_1+q_2X_2\right) - \left(d_1X_1+d_2X_2\right)
\end{aligned}$$

Let $d=\max\left\{d_1,d_2\right\}$ and $q=\max\left\{q_1,q_2\right\}$. Then, we have

$$\begin{aligned}
\frac{d\left(X_1+X_2\right)}{dt} &\le \mu_m\left(X_1+X_2\right) - \frac{q}{Q}\left(X_1+X_2\right) - d\left(X_1+X_2\right) \\
&\le \left[\mu_m - \frac{q\mu_m}{Q} - d\right]\left(X_1+X_2\right)
\end{aligned}$$

Let $a(t)=\mu_m-\frac{q\mu_m}{Q}-d$. Then, we have

$$\frac{d\left(X_1+X_2\right)}{dt} \le a(t)\left(X_1+X_2\right)(t)$$

By Gronwall's inequality, we have

$$\begin{aligned}
\left(X_1+X_2\right)(t) &\le \left(X_1+X_2\right)(0)e^{\int_0^T a(s)ds} \\
&\le \left(X_1+X_2\right)(0)e^{\int_0^T\left(\mu_m-\frac{q\mu_m}{Q(s)}-d\right)ds}, \\
&\le \left(X_1+X_2\right)(0)e^{\int_0^T\left(\mu_m-\frac{q\mu_m}{\alpha|Q(0)|+\beta}-d\right)ds}, \quad \text{(since } Q(s)\le\alpha|Q(0)|+\beta\text{)} \\
&\le \left(X_1+X_2\right)(0)e^{\left(\mu_m-\frac{q\mu_m}{\alpha|Q(0)|+\beta}-d\right)T}, \\
&\le \left|\left(X_1+X_2\right)(0)\right|e^{\mu_m T},
\end{aligned}$$

Which gives us the desired result. □

We next state and prove the existence and uniqueness of the solutions of (3.2.6).

Proposition 3.4.2. The solution $(X_1(t), X_2(t), Q(t))$ of (3.2.6) exists in $C^1([0,T])^3$ and is unique.

Proof. To prove the existence and uniqueness result, we will verify all the conditions of Picard's theorem. For this purpose, let

$$F(X_1, X_2, Q) = \begin{bmatrix} f_1(X_1, X_2, Q) \\ f_2(X_1, X_2, Q) \\ f_3(X_1, X_2, Q) \end{bmatrix} = \begin{bmatrix} \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \\ \mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - c_2 \frac{Q^n}{Q^n + k_2^n} X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 \\ v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ \end{bmatrix}.$$

Now F is continuous in (X_1, X_2, Q), since each $f_i(X_1, X_2, Q)$ is continuous as $i = 1, 2, 3$. Next, we investigate the differentiability of F. For this purpose, we have the following partial derivatives of f_1, f_2, f_3

$$\frac{df_1}{dX_1} = \mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1 \frac{k_1^n}{Q^n + k_1^n}$$
$$\frac{df_1}{dX_2} = c_2 \frac{Q^n}{Q^n + k_2^n}$$
$$\frac{df_1}{dQ} = \frac{\mu_m q_1 X_1}{Q^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{(Q^n + k_1^n)^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{(Q^n + k_2^n)^2}$$

$$\frac{df_2}{dX_1} = c_1 \frac{k_1^n}{Q^n + k_1^n}$$
$$\frac{df_2}{dX_2} = \mu_m - \frac{\mu_m q_2}{Q} - d_2 - c_2 \frac{Q^n}{Q^n + k_2^n}$$
$$\frac{df_2}{dQ} = \frac{\mu_m q_2 X_2}{Q^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{(Q^n + k_2^n)^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{(Q^n + k_1^n)^2}$$

$$\frac{df_3}{dX_1} = 0$$
$$\frac{df_3}{dX_2} = 0$$
$$\frac{df_3}{dQ} = -\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b.$$

Thus

$F'(X_1, X_2, Q)$

$$= \begin{bmatrix} \frac{df_1}{dX_1} & \frac{df_1}{dX_2} & \frac{df_1}{dQ} \\ \frac{df_2}{dX_1} & \frac{df_2}{dX_2} & \frac{df_2}{dQ} \\ \frac{df_3}{dX_1} & \frac{df_3}{dX_2} & \frac{df_3}{dQ} \end{bmatrix}$$

$$= \begin{bmatrix} \mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1 \frac{k_1^n}{Q^n + k_1^n} & c_2 \frac{Q^n}{Q^n + k_2^n} & \frac{\mu_m q_1 X_1}{Q^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2} \\ c_1 \frac{k_1^n}{Q^n + k_1^n} & \mu_m - \frac{\mu_m q_2}{Q} - d_2 - c_2 \frac{Q^n}{Q^n + k_2^n} & \frac{\mu_m q_2 X_2}{Q^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2} \\ 0 & 0 & -\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b \end{bmatrix}$$

Now, $F'(X_1, X_2, Q)$ is continuous, since each $f_i'(X_1, X_2, Q)$ is continuous. Thus, $F(X_1, X_2, Q) \in C^1([0, T])^3$.

Next, we will show that F is locally Lipschitz. From Proposition 4.3.1, we have that Q is bounded. We will show that X_1 and X_2 are also bounded. We have

$$\frac{d(X_1 + X_2)}{dt} = \mu_m (X_1 + X_2) - \frac{\mu_m}{Q}(q_1 X_1 + q_2 X_2) - (d_1 X_1 + d_2 X_2)$$

From Theorem 3.4.1, since $X_1, X_2, Q \geq 0$, this gives us

$$\frac{\mu_m}{Q}(q_1 X_1 + q_2 X_2) \geq 0, \quad (d_1 X_1 + d_2 X_2) \geq 0$$

Thus,

$$\frac{d(X_1 + X_2)}{dt} \leq \mu_m (X_1 + X_2)$$

By Gronwall's inequality, we have

$$\begin{aligned} (X_1 + X_2)(t) &\leq (X_1 + X_2)(0) e^{\int_0^T \mu_m ds} \\ &\leq e^{\mu_m T}(X_1 + X_2)(0) \end{aligned}$$

So, $X_1 + X_2$ is bounded. Since,

$$(X_1)(t) \leq (X_1 + X_2)(t), \quad X_1, X_2 \geq 0$$

$$(X_1)(t) \leq e^{\mu_m T}(X_1 + X_2)(0),$$

and

$$\begin{aligned} (X_2)(t) &\le (X_1+X_2)(t), \quad X_1, X_2 \ge 0 \\ (X_2)(t) &\le e^{\mu_m T}(X_1+X_2)(0), \end{aligned} \tag{3.4.10}$$

we have that $(X_1)(t)$ and $(X_2)(t)$ are also bounded.

Now,

$$\begin{aligned} \|\nabla f_1\|_\infty = \sup\Bigg\{ &\left|\mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1\frac{k_1^n}{Q^n+k_1^n}\right|, \left|c_2\frac{Q^n}{Q^n+k_2^n}\right|, \\ &\left|\frac{\mu_m q_1 X_1}{Q^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right|\Bigg\}. \end{aligned}$$

Now,

$$\begin{aligned} \left|\mu_m\left(1-\frac{q_1}{Q}\right) - d_1 - \frac{c_1k_1^n}{Q^n+k_1^n}\right| &\le \left|\mu_m\left(1-\frac{q_1}{Q}\right)\right| + |d_1| + \left|\frac{c_1k_1^n}{Q^n+k_1^n}\right|, \\ &\le |\mu_m| + |d_1| + |c_1|, \quad (\text{since } q_1 \le Q). \end{aligned}$$

Again,

$$\left|c_2\frac{Q^n}{Q^n+k_2^n}\right| \le \left|c_2\frac{Q^n}{Q^n}\right| \le |c_2|$$

Also,

$$\begin{aligned} &\left|\frac{\mu_m q_1 X_1}{Q^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \\ &\le \left|\frac{\mu_m q_1 X_1}{Q^2}\right| + \left|\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right| + \left|\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \\ &\le \left|\frac{\mu_m}{q_1}\left(\frac{q_1}{Q}\right)^2 X_1\right| + \left|\frac{nc_1k_1^nX_1Q^{n-1}}{(k_1^n)^2}\right| + \left|\frac{nc_2k_2^nX_2Q^{n-1}}{(k_2^n)^2}\right| \\ &\le \left|\frac{\mu_m}{q_1}\right||X_1| + \left|\frac{nc_1X_1Q^{n-1}}{k_1^n}\right| + \left|\frac{nc_2X_2Q^{n-1}}{k_2^n}\right| \\ &\le \left|\frac{\mu_m}{q_1}\right||X_1| + \left|\frac{nc_1}{k_1^n}\right||X_1|\left|Q^{n-1}\right| + \left|\frac{nc_2}{k_2^n}\right||X_2|\left|Q^{n-1}\right| \end{aligned}$$

Since X_1, X_2, Q are bounded.

$$\left|\frac{\mu_m q_1 X_1}{Q^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \le K_3 \tag{3.4.11}$$

Denoting $|\mu_m| + |d_1| + |c_1| = K_1,\ |c_2| = K_2$, we have

$$\|\nabla f_1\|_\infty \leq \max\{K_1, K_2, K_3\} = K$$

So, f_1 is locally Lipschitz. Next, we have

$$\|\nabla f_2\|_\infty = \sup\left\{\left|c_1\frac{k_1^n}{Q^n + k_1^n}\right|, \left|\mu_m - \frac{\mu_m q_2}{Q} - d_2 - c_2\frac{Q^n}{Q^n + k_2^n}\right|,\right.$$
$$\left.\left|\frac{\mu_m q_2 X_2}{Q^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n + k_2^n)^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n + k_1^n)^2}\right|\right.$$

Now,

$$\left|c_1\frac{k_1^n}{Q^n + k_1^n}\right| \leq \left|c_1\frac{k_1^n}{k_1^n}\right| \leq |c_1|, \quad \text{(since } Q \text{ is bounded)}$$

Again,

$$\begin{aligned}\left|\mu_m\left(1 - \frac{q_2}{Q}\right) - d_2 - \frac{c_2Q^n}{Q^n + k_2^n}\right| &\leq \left|\mu_m\left(1 - \frac{q_2}{Q}\right)\right| + |d_2| + \left|\frac{c_2Q^n}{Q^n + k_2^n}\right|, \\ &\leq |\mu_m| + |d_2| + \left|\frac{c_2Q^n}{Q^n}\right| \quad \text{(since } q_2 \leq Q\text{)} \\ &\leq |\mu_m| + |d_2| + |c_2|\end{aligned}$$

Also,

$$\begin{aligned}&\left|\frac{\mu_m q_2 X_2}{Q^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n + k_2^n)^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n + k_1^n)^2}\right| \\ &\leq \left|\frac{\mu_m q_2 X_2}{Q^2}\right| + \left|\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n + k_2^n)^2}\right| + \left|\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n + k_1^n)^2}\right| \\ &\leq \left|\frac{\mu_m}{q_2}\left(\frac{q_2}{Q}\right)^2 X_2\right| + \left|\frac{nc_2k_2^nX_2Q^{n-1}}{(k_2^n)^2}\right| + \left|\frac{nc_1k_1^nX_1Q^{n-1}}{(k_1^n)^2}\right| \\ &\leq \left|\frac{\mu_m}{q_2}\right||X_2| + \left|\frac{nc_2X_2Q^{n-1}}{k_2^n}\right| + \left|\frac{nc_1X_1Q^{n-1}}{k_1^n}\right| \\ &\leq \left|\frac{\mu_m}{q_2}\right||X_2| + \left|\frac{nc_2}{k_2^n}\right||X_2|\left|Q^{n-1}\right| + \left|\frac{nc_1}{k_1^n}\right||X_1|\left|Q^{n-1}\right|\end{aligned}$$

Let $|c_1| = L_1,\ |\mu_m| + |d_2| + |c_2| = L_2$. Since X_1, X_2, Q are bounded

$$\left|\frac{\mu_m q_2 X_2}{Q^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n + k_2^n)^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n + k_1^n)^2}\right| \leq L_3$$

Then

$$\|\nabla f_2\|_\infty \leq \max\{L_2, L_2, L_3\} = L$$

So, f_2 is locally Lipschitz. Finally, we have

$$\|\nabla f_3\|_\infty = \sup\left\{|0|, |0|, \left|-\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b\right|\right.$$

We have

$$\left|-\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b\right| \leq \left|\frac{v_m A}{(q_m - q)(A + v_h)}\right| + |\mu_m| + |b|$$

Let

$$\left|\frac{v_m A}{(q_m - q)(A + v_h)}\right| + |\mu_m| + |b| = M$$

Then,

$$\left|-\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b\right| \leq M$$

Thus,

$$\|\nabla f_3\|_\infty \leq M,$$

and so f_3 is locally Lipschitz. Since f_1, f_2, f_3 Lipschitz, we have F is locally Lipschitz. Thus, by Picard's theorem, (3.2.6) has an unique solution in $C^1([0,T])^3$. □

We next state and prove some properties of the objective functional J.

Proposition 3.4.3. The objective functional J is sequentially weakly lower semi-continuous (w.l.s.c.), bounded from below, coercive on T_{ad} and is Fréchet differentiable.

Proof. The functional J is said to be weakly lower semi-continuous in $\theta \in T_{ad}$ if

$$J(\theta) \leq \lim_{n\to\infty} \inf J(\theta_n), \text{ for all } \theta_n \in T_{ad} \text{ s.t. } \theta_n \to u.$$

It can be easily verified that J, given in (3.3.1), is w.l.s.c due to being continuous in θ. We also note that J for every sequence $\theta_n \subset T_{ad}$ with $\|\theta_n\|_{T_{ad}} \to \infty$, we have $J(\theta_n) \to \infty$. To show that J is bounded from below, assume it is not true. Then there exists a sequence $\theta_n \subset T_{ad}$ with $J(\theta_n) \to -\infty$. The coercivity of J implies that this sequence is bounded. Otherwise we would have $J(\theta_n) \to \infty$. Then, we have the existence of a weakly convergent subsequence (θ_{n_k}) where $k \in \mathbb{N}$, whose limit $\theta \in T_{ad}$ satisfies, by weak lower semi-continuity, $J(\theta) \leq \lim_{k\to\infty} \inf J(\theta_{n_k}) = -\infty$. However, this is a contradiction since the range of J lies in $\mathbb{R}$. Finally, Fréchet differentiability of J follows from the Fréchet differentiability of (X_1, X_2, Q) as a function of θ. □

We finally conclude the theoretical results with the existence of an optimal parameter set.

Theorem 3.4.2. There exists a minimizer $\theta^* \in T_{ad}$ of J, given in (3.3.1).

Proof. Boundedness from below of J implies there exists a minimizing sequence $(\theta^m) \in T_{ad}$. With J being in T_{ad}, this sequence is bounded and, thus, contains a convergent subsequence (θ^{m_l}) in T_{ad} with $\theta^{m_l} \to \theta^*$. Correspondingly, the sequence $(X_1^{m_l}, X_2^{m_l}, Q^{m_l})$, obtained by solving (3.2.6) with θ^{m_l}, is bounded in $(C^1(0,T))^3$ while the sequence of the time derivatives, $(\partial_t X_1^{m_l}, \partial_t X_2^{m_l}, \partial_t Q^{m_l})$, is bounded in $(C^0(0,T))^3$. Therefore, both the sequences converge to (X_1^*, X_2^*, Q^*) and $(\partial_t X_1^*, \partial_t X_2^*, \partial_t Q^*)$, respectively. This implies that θ^* minimizes J, with $(X_1^*, X_2^*, Q^*, \theta^*)$ solving (3.2.6). □

3.5 Optimality system

We now describe the characterization of the minimizer of J, given in (3.3.1), through the first-order necessary optimality system.

Theorem 3.5.1. The minimizer of (3.3.1) is obtained by solving the following optimality system

$$\frac{dX_1}{dt} = \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right) = F_1(X_1, X_2, Q, \theta), \quad X_1(0) = 1$$
$$\frac{dX_2}{dt} = \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right) = F_2(X_1, X_2, Q, \theta), \quad X_2(0) = 1$$
$$\frac{dQ}{dt} = v_m\frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ = F_3(X_1, X_2, Q, \theta), \quad Q(0) = 1 \tag{FOR:ODE}$$

$$\frac{d\tilde{X}_1}{dt} = \left(X_1(t) - X_1^d(t)\right)\alpha_1 - \left[\mu_m\left(1-\frac{q_1}{Q}\right) - d_1 - m_1(Q)\right]\tilde{X}_1 + m_1(Q)\tilde{X}_2, \ \tilde{X}_1(T) = 0$$
$$\frac{d\tilde{X}_2}{dt} = \left(X_2(t) - {X_2}^d(t)\right)\alpha_2 - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\tilde{X}_2 - d_2\tilde{X}_2 - m_2(Q)\tilde{X}_2\right) + m_2(Q)\tilde{X}_1 dt, \ \tilde{X}_2(T) = 0$$
$$\frac{d\tilde{Q}}{dt} = \alpha_3\left(Q(t) - Q^d\right) - \left(\frac{\mu_m}{Q^2}\right)\left(q_1X_1\tilde{X}_1 + q_2X_2\tilde{X}_2\right) - \left(\frac{c_1k_1X_1}{(Q+k_1)^2}\right)\left(\tilde{X}_1 - \tilde{X}_2\right)$$
$$+ \left(\frac{c_2X_2k_2}{(Q+k_2)^2}\right)\left(\tilde{X}_2 - \tilde{X}_1\right) + v_m\frac{\tilde{Q}}{q_m - q}\frac{A}{A+v_h} + \mu_m\tilde{Q} + b\tilde{Q}, \ \tilde{Q}(T) = 0 \tag{ADJ:ODE}$$

$$\left(\beta\mu_m + \int_0^T\left[-\left(1-\frac{q_1}{Q}\right)X_1\tilde{X}_1 - \left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2 + (Q-q)\tilde{Q}\right]dt\right)\cdot(v_1 - \mu_m) \geq 0,$$
$$\left(\beta q_1 + \int_0^T -\mu_m\frac{1}{Q}X_1\tilde{X}_1 dt\right)\cdot(v_2 - q_1) \geq 0$$
$$\left(\beta q_2 + \int_0^T -\mu_m\frac{1}{Q}X_2\tilde{X}_2 dt\right)\cdot(v_3 - q_2) \geq 0$$
$$\left(\beta d_1 + \int_0^T X_1\tilde{X}_1 dt\right)\cdot(v_4 - d_1) \geq 0$$
$$\left(\beta d_2 + \int_0^T X_2\tilde{X}_2 dt\right)\cdot(v_5 - d_2) \geq 0,$$
$$\left(\beta A + \int_0^T v_m\frac{q_m - Q}{q_m - q}\frac{v_h}{(A+v_h)^2}\tilde{Q}dt\right)\cdot(v_6 - A) \geq 0, \tag{OPT:ODE}$$

for all $v = (v_1, \ldots, v_6) \in T_{ad}$.

Proof. To derive the optimality system, we start with the continuous Lagrangian defined as follows:

$$\begin{aligned} L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right) = J\left(X_1, X_2, Q, \theta\right) + \int_0^T \left(\frac{dX_1}{dt} - F_1\right)\tilde{X}_1 dt \\ + \int_0^T \left(\frac{dX_2}{dt} - F_2\right)\tilde{X}_2 dt + \int_0^T \left(\frac{dQ}{dt} - F_3\right)\tilde{Q} dt \end{aligned} \tag{3.5.1}$$

Define the Gateaux derivative (or directional derivative) of L with respect to a generic variable V in the direction $\tilde{V}$ as

$$\frac{\partial L}{\partial V}(\tilde{V}) = \lim_{\varepsilon \to 0} \frac{L(V + \epsilon \tilde{V}) - L(V)}{\epsilon}.$$

By Riesz's representation theorem, one can write.

$$\frac{\partial L}{\partial V}(\tilde{V}) = \langle L_V, \tilde{V} \rangle_{\mathcal{B}_V},$$

where $\langle \cdot, \cdot \rangle_{\mathcal{B}_V}$ is an inner product in a suitable Banach space $\mathcal{B}_V$. For $X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}$, we choose $\langle \cdot, \cdot \rangle_{\mathcal{B}_V}$ as the $L^2([0,T])$ inner product, i.e.,

$$\langle f, g \rangle_{\mathcal{B}_V} = \int_0^T fg \; dt,$$

whereas for each element of θ, we choose $\langle \cdot, \cdot \rangle_{\mathcal{B}_V}$ as the product between two real numbers, i.e.,

$$\langle f, g \rangle_{\mathcal{B}_V} = fg.$$

Then

$$\frac{\partial L}{\partial V} \equiv L_V.$$

For the L defined in (3.5.1), we compute the Gateaux derivatives $\left(\frac{\partial L}{\partial X_1}, \frac{\partial L}{\partial X_2}, \frac{\partial L}{\partial Q}\right)$, which gives the forward equations (FOR:ODE); the Gateaux derivatives $\left(\frac{\partial L}{\partial \tilde{X}_1}, \frac{\partial L}{\partial \tilde{X}_2}, \frac{\partial L}{\partial \tilde{Q}}\right)$, which gives the adjoint equations (ADJ:ODE); and the Gateaux derivatives $\frac{\partial L}{\partial \theta_i}$, $i = 1, \cdots, 6$, which gives the optimality condition (OPT:ODE). The derivation is presented in Appendix A. □

3.6 Numerical results

We now present the numerical results of our non-linear optimization framework for estimating the unknown parameters for the prostate cancer model using noisy synthetic patient data. We choose the final time $T = 1000$, the regularization weights in the functional J, given in (3.3.1) to be $\alpha_1 = 1,\ \alpha_2 = 1,\ \alpha_3 = 1,\ \beta = 0.5$. Our time domain $[0, T]$ is divided into a mesh of 100,000 equally spaced subintervals. The non-dimensionalization scaling factors are $l_1 = 1/60,\ l_2 = 1/60,\ l_3 = 2.5,\ l_4 = 0.01$.

To generate the data, we simulate the forward ODE system (FOR:ODE) on a coarse mesh of 1000 subintervals, interpolate the numerical solution over the actual finer mesh, and add 5% additive Gaussian noise to the interpolated resolution that gives the final form of the data. The forward and the adjoint ODE systems were solved using the forward Euler method. The optimality system (FOR:ODE)-(OPT:ODE) was numerically solved by using the iterative non-linear conjugate gradient (NCG) method. We choose different initial guesses for the NCG algorithm from the biological reference intervals, given in Table 3.1.

Test Case 1: In the first test case, we generate the patient data using the true parameters given in Table 3.2. The initial guess for the parameters are chosen to be 0. The obtained parameters are shown in the third column. We observe that even though the initial guess is far away from the true parameters, some of our estimated parameters are very close to the true parameters, whereas the others are not.

True parameters (θ_t)	Initial guess (θ_0)	Estimated parameters (θ)
$\mu_m = 3.5$	$\mu_m = 0$	$\mu_m = 2.5$
$q_1 = 1$	$q_1 = 0$	$q_1 = 0.4375$
$q_2 = 0.6$	$q_2 = 0$	$q_2 = 0.4156$
$d_1 = 1.9$	$d_1 = 0$	$d_1 = 2$
$d_2 = 1.8$	$d_2 = 0$	$d_2 = 2$
$A = 4$	$A = 0$	$A = 3.375$

Table 3.2: Test case 1: Patient-specific parameter values

We also solve (FOR:ODE) with the estimated parameters; we plot and compare the solutions of X_1, X_2, Q with the data. The plots are shown in Figure 3.2. We observe that the fit for X_1, Q are very good, whereas the fit for X_2 is not as good.

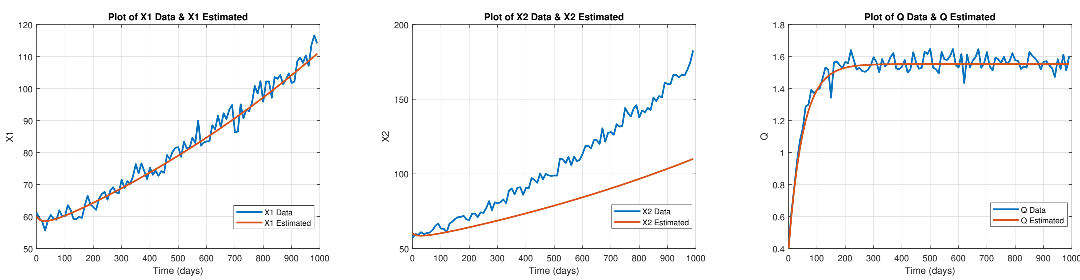

Figure 3.2: Test Case 1: mean trajectories of X_1, X_2, Q with the true and optimal parameter set.

Test Case 2: In test case 2, we choose the same true parameters, but the initial guesses are chosen to be different from test case 1. They are actually chosen to be the maximum possible attainable values in the set T_{ad}. The estimated parameters are again shown in the third column. We again observe a similar behavior as in test case 1, i.e., some of the estimated parameters are close to the true parameters, whereas the others are far away.

True parameters (θ_t)	Initial guess (θ_0)	Estimated parameters (θ)
$\mu_m = 3.5$	$\mu_m = 7$	$\mu_m = 4.36$
$q_1 = 1$	$q_1 = 5$	$q_1 = 1.098$
$q_2 = 0.6$	$q_2 = 1$	$q_2 = 0.636$
$d_1 = 1.9$	$d_1 = 8$	$d_1 = 1.99$
$d_2 = 1.8$	$d_2 = 6$	$d_2 = 1.98$
$A = 4$	$A = 10$	$A = 4.57$

Table 3.3: Test case 2: Patient-specific parameter values

The resulting plots of the solution of (FOR:ODE) with the estimated parameters and the data are compared in Figure 3.3. We now observe that there is a mismatch in the fits of X_1, X_2, whereas the fit of Q is still good.

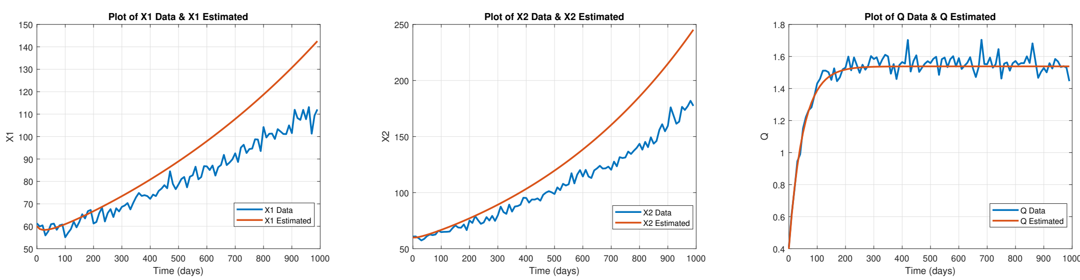

Figure 3.3: Test Case 2: mean trajectories of X_1, X_2, Q with the true and optimal parameter set

Test Case 3: In the final test case, we choose the same true parameters but initial guesses are chosen a bit closer to the true parameters. The results of the estimated parameters in Table 3.4 show that all the estimated parameters are now close to the true parameters.

True parameters (θ_t)	Initial guess (θ_0)	Estimated parameters (θ)
$\mu_m = 3.5$	$\mu_m = 3$	$\mu_m = 3.12$
$q_1 = 1$	$q_1 = 0.5$	$q_1 = 0.7$
$q_2 = 0.6$	$q_2 = 1$	$q_2 = 0.47$
$d_1 = 1.9$	$d_1 = 1.5$	$d_1 = 1.79$
$d_2 = 1.8$	$d_2 = 1.5$	$d_2 = 1.76$
$A = 4$	$A = 3$	$A = 3.51$

Table 3.4: Test case 3: Patient-specific parameter values

The plots of the solution of (FOR:ODE) and the data, presented in Figure 3.4, now show very good fits for all the three variables X_1, X_2, Q, which demonstrates the robustness and accuracy of our proposed parameter estimation framework.

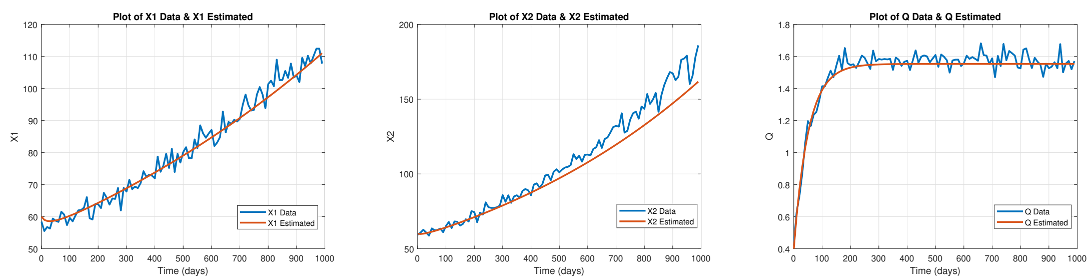

Figure 3.4: Test Case 3: mean trajectories of X_1, X_2, Q with the true and optimal parameter set.

We also compute the respective relative L^2 errors for the 2 test cases. The relative L^2 error between 2 functions $X(t)$ and $X^d(t)$ is defined as

$$Err(X, X^d) = \frac{\|X - X^d\|_{L_2([0,T])}}{\|X^d\|_{L_2([0,T])}}$$

Test Case	$Err(X_1, X_1^d)$	$Err(X_2, X_2^d)$	$Err(Q, Q^d)$
1	0.0981	0.2207	0.0314
2	0.3286	0.2342	0.0319
3	0.1614	0.1789	0.0302

Table 3.5: L^2 error table

The error measurement provides a quantitative way to assess how close the estimated and true values are. When the error is close to zero, it suggests that the estimated values closely align with the true ones. Also, a low error value indicates that the estimates are accurate and that the two sets of values are indeed very close to each other. This helps provide confidence in the reliability of the estimation or modeling process. But if the error is big, it indicates a significant discrepancy between the estimated values and the true values. What we observe from Table 3.5 is that for all the three test cases, the estimated Q is very close to the data. However, either X^1 or X^2 are not very close to their respective datasets. This suggests that even though the ODE parameter estimation framework yields good results, these results are not the most accurate, which motivates the development of the Liouville framework in Chapter 5.

CHAPTER 4

Formulate the optimization problems with drugs

4.1 Introduction

Many mathematical models have been created, most of them aim to achieve results that are very close to the results of clinical trials, and others are only interested in studying the effectiveness of treatments. We found a significant deficiency in this field and therefore need more study. The circulating level of androgen significantly impacts the growth, division, and atrophy of healthy and cancerous prostate cells [30]. When androgen levels are low, it slows down the growth of cancer cells, which is the natural process of prostate cancer cell death [13]. In the field of mathematical oncology, researchers are working on finding the most effective dosing strategies for cancer treatment. They determine that using lower doses and treatment breaks can lead to better long-term control of the disease [12]. One explored approach is metronomic therapy, which involves giving low doses of medication at specific intervals. This alternative strategy has been mathematically studied as a potential option to replace high dose strategies [6, 32, 55, 57, 62, 64, 73, 75].

Chemotherapy is a way to control cancer by directly impacting its growth. To reduce the level of androgen. There are three strategies of treatment [19]:

- **Maximum tolerable dose:** This strategy uses a high dose of medication determined by considering the side effects.
- **Adaptive:** This strategy determines the start and end of treatment based on the patient's biomarkers. It involves stopping treatment before it becomes ineffective, earlier than intermittent strategies. The clinical trial data from

Zhang et al. [34] show that the adaptive treatment is effective at less than 20% of the maximum dose.

- **Intermittent:** This strategy involves taking medication periodically with scheduled breaks in treatment. It is a commonly used approach [2].In the context of modeling intermittent androgen deprivation therapy, the variable $u(t)$ determines the treatment dose. The patients go on and off of therapy according to a fixed interval of time. When $u(t)$ is equal to 1, it signifies the on-treatment period, while $u(t)$ being 0 represents the off-treatment period [83]. The on-off cycles are repeated until the treatment becomes ineffective.

Although initial treatment for prostate cancer often yields positive results, the development of androgen-independent prostate cancer eventually occurs, which is highly lethal in almost all cases [69]. Recent studies and clinical trials have raised concerns about whether intermittent androgen deprivation (IAD) therapy could be increased the comfort and effectiveness of this treatment.[26, 52, 36]. This indicates that the previous methods were not effective treatments. So, we will use a new method to find the optimal dose for treatment using optimal control.

4.2 Optimal control problem for treatment

We first formulate a mathematical deterministic ODE system with an androgen receptor blocker $u(t)$ as a function of time in order to obtain the optimal dosage.

$$\begin{aligned}
\frac{dX_1}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{k_2^n}{Q^n+k_2^n}X_2, \quad X_1(0)=1 \\
\frac{dX_2}{dt} &= \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{k_2^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1, \quad X_2(0)=1 \\
\frac{dQ}{dt} &= v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu(t), \quad Q(0)=1
\end{aligned} \tag{4.2.1}$$

The term $-\gamma Q u(t)$ denotes a decrease in androgen in the presence of the treatment, where γ is the androgen clearance rate 0.08 /day [50]. Our goal is to estimate the best dose of $u(t)$ to control the androgen level Q in a cell close to a normal level $(0.11 - 0.96)$ nM [86]. For this purpose, we solve the following constrained optimization problem:

$$\min_u J_u(Q,u) = \frac{\alpha_0}{2}\int_0^T (Q(t)-Q_m)^2\,dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_4}{2}(Q(T)-Q_m)^2 \quad (4.2.2)$$

subject to the system (4.2.1). Here we will consider Q_m as the middle of the normal androgen level. The first and last terms in the functional J_u, given in (4.2.2), are data-fitting terms with weights α_0, α_4. The second term in J_u is a regularization term for $u(t)$ with weight β_0. We look for u in the set

$$U_{ad} = \{u(t) \in L^2([0,T]) : 0 \le u(t) \le u_r,\ \forall t \in [0,T]\}.$$

where u_r is the maximum tolerable dose.

4.3 Theoretical results

In this section, we present some theoretical results for the optimization problem stated in (4.2.2). We begin with the positivity of the solutions of (4.2.1). The proof follows the same steps that were presented in the previous chapter.

Theorem 4.3.1. Given $X_1(0) \ge 0, X_2(0) \ge 0, Q(0) \ge 0$, the solutions $(X_1(t), X_2(t), Q(t))$ of (4.2.1) are non-negative for all $t \ge 0$.

Proof. From the first equation of (4.2.1), we have

$$\begin{aligned} \frac{dX_1}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2, \\ &= -\left(-\mu_m\left(1-\frac{q_1}{Q}\right) + d_1 + c_1\frac{k_1^n}{Q^n+k_1^n}\right)X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \end{aligned} \quad (4.3.1)$$

We consider the following integrating factor

$$I_f^1 = \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds \tag{4.3.2}$$

Multiplying (4.3.1) by the integrating factor I_f^1, we obtain

$$\begin{aligned} &\frac{dX_1}{dt} \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds \\ &\quad = c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds \end{aligned} \tag{4.3.3}$$

That gives us

$$\begin{aligned} &X_1(t) \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds - X_1(0) \\ &\quad = \int_0^t c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^z \left(-\mu_m \left(1 - \frac{q_1}{Q(z)} \right) + d_1 + c_1 \frac{k_1^n}{Q(z)^n + k_1^n} \right) dz \end{aligned}$$

which implies

$$\begin{aligned} X_1(t) = X_1(0) &\exp \int_0^t - \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds \\ &+ \exp \int_0^t - \left(-\mu_m \left(1 - \frac{q_1}{Q(s)} \right) + d_1 + c_1 \frac{k_1^n}{Q(s)^n + k_1^n} \right) ds \\ &\int_0^t c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \exp \int_0^z \left(-\mu_m \left(1 - \frac{q_1}{Q(z)} \right) + d_1 + c_1 \frac{k_1^n}{Q(z)^n + k_1^n} \right) dz \geq 0 \end{aligned}$$

Thus, $X_1(t) \geq 0$.

For the second equation in (4.2.1)

$$\begin{aligned} \frac{dX_2}{dt} &= \mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - c_2 \frac{Q^n}{Q^n + k_2^n} X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 \\ &= - \left(-\mu_m \left(1 - \frac{q_2}{Q} \right) + d_2 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \right) X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1, \end{aligned} \tag{4.3.4}$$

we consider the following integrating factor

$$I_f^2 = \exp \int_0^t \left(-\mu_m \left(1 - \frac{q_2}{Q(s)} \right) + d_2 + c_2 \frac{Q(s)^n}{Q(s)^n + k_2^n} X_2 \right) ds \tag{4.3.5}$$

Multiplying (4.3.4) by the integrating factor I_f^2, we obtain

$$\begin{aligned}\frac{dX_2}{dt}\exp\int_0^t\left(-\mu_m\left(1-\frac{q_2}{Q(s)}\right)+d_2+c_2\frac{Q(s)^n}{Q(s)^n+k_2^n}X_2\right)ds\\=c_1\frac{k_1^n}{Q^n+k_1^n}X_1\exp\int_0^t\left(-\mu_m\left(1-\frac{q_2}{Q(s)}\right)+d_2+c_2\frac{Q(s)^n}{Q(s)^n+k_2^n}X_2\right)ds,\end{aligned}$$

Which again gives us

$$\begin{aligned}X_2(t)=X_2(0)\exp-\int_0^t\left(-\mu_m\left(1-\frac{q_2}{Q(s)}\right)+d_2+c_2\frac{Q(s)^n}{Q(s)^n+k_2^n}X_2\right)ds+\exp\\-\int_0^t\left(-\mu_m\left(1-\frac{q_2}{Q(s)}\right)+d_2+c_2\frac{Q(s)^n}{Q(s)^n+k_2^n}X_2\right)ds\int_0^t c_1\frac{k_1^n}{Q^n+k_1^n}X_1\\\exp\int_0^z\left(-\mu_m\left(1-\frac{q_2}{Q(z)}\right)+d_2+c_2\frac{Q(z)^n}{Q(z)^n+k_2^n}X_2\right)dz\geq 0\end{aligned}$$

Thus, $X_2(t)\geq 0$.

From the third equation in (4.2.1)

$$\begin{aligned}\frac{dQ}{dt}&=v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ-\gamma Qu\\&=\frac{v_mq_mA-v_mQA}{(q_m-q)(A+v_h)}-\mu_mQ+\mu_mq-bQ-\gamma Qu\\&=\frac{v_mq_mA}{(q_m-q)(A+v_h)}-\frac{v_mQA}{(q_m-q)(A+v_h)}-\mu_mQ+\mu_mq-bQ-\gamma Qu\\&=\frac{v_mq_mA}{(q_m-q)(A+v_h)}+\mu_mq-\left(\frac{v_mA}{(q_m-q)(A+v_h)}+\mu_m+b-\gamma u\right)Q,\end{aligned}\tag{4.3.6}$$

we consider the integrating factor

$$I_f^3=\exp\int_0^t\left(\frac{v_mA}{(q_m-q)(A+v_h)}+\mu_m+b-\gamma u\right)ds\tag{4.3.7}$$

Multiplying (4.3.6) by the integrating factor I_f^3, we obtain

$$\begin{aligned}\frac{dQ}{dt}\exp\int_0^t\left(\frac{v_mA}{(q_m-q)(A+v_h)}+\mu_m+b-\gamma u\right)ds\\=\left(\frac{v_mq_mA}{(q_m-q)(A+v_h)}+\mu_mq\right)\exp\int_0^t\left(\frac{v_mA}{(q_m-q)(A+v_h)}+\mu_m+b-\gamma u\right)ds\end{aligned}\tag{4.3.8}$$

Solving this equation, we obtain

$$\begin{aligned}Q(t) = Q(0)\exp - \int_0^t \left(\frac{v_m A}{(q_m - q)(A + v_h)} + \mu_m + b - \gamma u\right) ds + \exp \\ - \int_0^t \left(\frac{v_m A}{(q_m - q)(A + v_h)} + \mu_m + b - \gamma u\right) ds \int_0^t \left(\frac{v_m q_m A}{(q_m - q)(A + v_h)}\right. \\ \left. + \mu_m q\right) dt \exp \int_0^t \left(\frac{v_m A}{(q_m - q)(A + v_h)} + \mu_m + b - \gamma u\right) dz \geq 0\end{aligned}$$

That gives us $Q(t) \geq 0$. □

Proposition 4.3.1. The solution of the system (4.2.1), satisfies the following stability estimate

$$Q(t) \leq \alpha |Q(0)| + \beta \quad \text{where } \alpha, \beta \geq 0,$$
$$(X_1 + X_2) \leq |(X_1 + X_2)(0)|\, e^{\mu_m T}$$

Proof. We have

$$\begin{aligned}\frac{dQ}{dt} &= v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ - \gamma Q u \quad , Q(0) = 0 \\ &= \frac{-v_m A Q}{(q_m - q)(A + v_h)} - \mu_m Q - bQ - \gamma Q u + \frac{v_m q_m A}{(q_m - q)(A + v_h)} + \mu_m q \\ &= \left(\frac{-v_m A}{(q_m - q)(A + v_h)} - \mu_m - b - \gamma u\right) Q + \frac{v_m q_m A}{(q_m - q)(A + v_h)} + \mu_m q\end{aligned}$$

Let

$$C_1 = \frac{-v_m A}{(q_m - q)(A + v_h)} - \mu_m - b - \gamma u$$

and

$$C_2 = \frac{v_m q_m A}{(q_m - q)(A + v_h)} + \mu_m q.$$

Then we have

$$\frac{dQ}{dt} = C_1 Q + C_2$$

Using Gronwall's inequality, we obtain the following

$$
\begin{aligned}
Q(t) &\leq e^{-\int_0^t C_1 dt}\left(Q(0)+2\int_0^t C_2 e^{-\int_0^s C_1 ds} ds\right) \\
&\leq e^{-C_1 t}\left(Q(0)+2C_2\int_0^t e^{-C_1 s} ds\right) \\
&\leq e^{-C_1 t}\left(Q(0)+2C_2\left[\frac{e^{-C_1 t}-1}{C_1}\right]\right)
\end{aligned}
$$

Now if $C_1 \geq 0, e^{-C_1 t} \leq 1$ and if $C_1 < 0, e^{-C_1 t} \leq e^{-C_1 T}$. Thus, we have

$$
Q(t) \leq \begin{cases} |Q(0)| & \text{if } C_1 \geq 0 \\ e^{-C_1 T}|Q(0)| + 2\,|C_2|\,e^{-C_1 T}\left|\left[\frac{e^{-C_1 T}-1}{C_1}\right]\right|, & \text{if } C_1 < 0 \end{cases}
$$

$$
Q(t) \leq \alpha|Q(0)| + \beta \quad \text{where } \alpha, \beta \geq 0 \tag{4.3.9}
$$

Next, we consider the first two equations of (4.2.1)

$$
\begin{aligned}
\frac{dX_1}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \\
\frac{dX_2}{dt} &= \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1
\end{aligned}
$$

Adding these two equations, we have

$$
\begin{aligned}
\frac{d\left(X_1+X_2\right)}{dt} &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \\
&+ \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1 \\
&= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2 \\
&+ \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1 \\
&= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 + \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 \\
&= \mu_mX_1 - \frac{\mu_m q_1}{Q}X_1 - d_1X_1 + \mu_mX_2 - \frac{\mu_m q_2}{Q}X_2 - d_2X_2 \\
&= \mu_m\left(X_1+X_2\right) - \frac{\mu_m}{Q}\left(q_1X_1+q_2X_2\right) - \left(d_1X_1+d_2X_2\right)
\end{aligned}
$$

Let $d = \max\{d_1, d_2\}$ and $q = \max\{q_1, q_2\}$. Then, we have

$$\begin{aligned}\frac{d(X_1+X_2)}{dt} &\le \mu_m(X_1+X_2) - \frac{q}{Q}(X_1+X_2) - d(X_1+X_2)\\ &\le \left[\mu_m - \frac{q\mu_m}{Q} - d\right](X_1+X_2)\end{aligned}$$

Let $a(t) = \mu_m - \frac{q\mu_m}{Q} - d$. Then, we have

$$\frac{d(X_1+X_2)}{dt} \le a(t)(X_1+X_2)(t)$$

By Gronwall's inequality, we have

$$\begin{aligned}(X_1+X_2)(t) &\le (X_1+X_2)(0)e^{\int_0^T a(s)ds}\\ &\le (X_1+X_2)(0)e^{\int_0^T \left(\mu_m - \frac{q\mu_m}{Q(s)} - d\right)ds},\\ &\le (X_1+X_2)(0)e^{\int_0^T \left(\mu_m - \frac{q\mu_m}{\alpha|Q(0)|+\beta} - d\right)ds}, \quad (\text{since } Q(s) \le \alpha|Q(0)|+\beta)\\ &\le (X_1+X_2)(0)e^{\left(\mu_m - \frac{q\mu_m}{\alpha|Q(0)|+\beta} - d\right)T},\\ &\le |(X_1+X_2)(0)|\, e^{\mu_m T},\end{aligned}$$

Which gives us the desired result. □

We next state and prove the existence and uniqueness of the solutions of (4.2.1).

Proposition 4.3.2. The solution $(X_1(t), X_2(t), Q(t))$ of (4.2.1) exists in $C^1([0,T])^3$ and is unique.

Proof. To prove the existence and uniqueness result, we will verify all the conditions of Picard's theorem. For this purpose, let

$$F(X_1,X_2,Q) = \begin{bmatrix} f_1(X_1,X_2,Q)\\ f_2(X_1,X_2,Q)\\ f_3(X_1,X_2,Q)\end{bmatrix} = \begin{bmatrix} \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{Q^n}{Q^n+k_2^n}X_2\\ \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{Q^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1\\ v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\end{bmatrix}.$$

Now F is continuous in (X_1, X_2, Q), since each $f_i(X_1, X_2, Q)$ is continuous as $i = 1, 2, 3$. Next, we investigate the differentiability of F. For this purpose, we have the following partial derivatives of f_1, f_2, f_3

$$\frac{df_1}{dX_1} = \mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1 \frac{k_1^n}{Q^n + k_1^n}$$

$$\frac{df_1}{dX_2} = c_2 \frac{Q^n}{Q^n + k_2^n}$$

$$\frac{df_1}{dQ} = \frac{\mu_m q_1 X_1}{Q^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2}$$

$$\frac{df_2}{dX_1} = c_1 \frac{k_1^n}{Q^n + k_1^n}$$

$$\frac{df_2}{dX_2} = \mu_m - \frac{\mu_m q_2}{Q} - d_2 - c_2 \frac{Q^n}{Q^n + k_2^n}$$

$$\frac{df_2}{dQ} = \frac{\mu_m q_2 X_2}{Q^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2}$$

$$\frac{df_3}{dX_1} = 0$$

$$\frac{df_3}{dX_2} = 0$$

$$\frac{df_3}{dQ} = -\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b - \gamma u.$$

Thus

$$F'(X_1, X_2, Q) = \begin{bmatrix} \frac{df_1}{dX_1} & \frac{df_1}{dX_2} & \frac{df_1}{dQ} \\ \frac{df_2}{dX_1} & \frac{df_2}{dX_2} & \frac{df_2}{dQ} \\ \frac{df_3}{dX_1} & \frac{df_3}{dX_2} & \frac{df_3}{dQ} \end{bmatrix}$$

$$= \begin{bmatrix} \mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1 \frac{k_1^n}{Q^n + k_1^n} & c_2 \frac{Q^n}{Q^n + k_2^n} & \frac{\mu_m q_1 X_1}{Q^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2} \\ c_1 \frac{k_1^n}{Q^n + k_1^n} & \mu_m - \frac{\mu_m q_2}{Q} - d_2 - c_2 \frac{Q^n}{Q^n + k_2^n} & \frac{\mu_m q_2 X_2}{Q^2} + \frac{n c_2 k_2^n X_2 Q^{n-1}}{\left(Q^n + k_2^n\right)^2} + \frac{n c_1 k_1^n X_1 Q^{n-1}}{\left(Q^n + k_1^n\right)^2} \\ 0 & 0 & -\frac{v_m A}{(q_m - q)(A + v_h)} - \mu_m - b - \gamma u \end{bmatrix}$$

Now, $F'(X_1, X_2, Q)$ is continuous, since each $f_i'(X_1, X_2, Q)$ is continuous. Thus, $F(X_1, X_2, Q) \in C^1([0, T])^3$.

Next, we will show that F is locally Lipschitz. From Proposition 4.3.1, we have that Q is bounded. We will show that X_1 and X_2 are also bounded. We have

$$\frac{d\left(X_1+X_2\right)}{dt} = \mu_m\left(X_1+X_2\right) - \frac{\mu_m}{Q}\left(q_1X_1+q_2X_2\right) - \left(d_1X_1+d_2X_2\right)$$

From Theorem 3.4.1, since $X_1, X_2, Q \geq 0$, this gives us

$$\frac{\mu_m}{Q}\left(q_1X_1+q_2X_2\right) \geq 0, \quad \left(d_1X_1+d_2X_2\right) \geq 0$$

Thus,

$$\frac{d\left(X_1+X_2\right)}{dt} \leq \mu_m\left(X_1+X_2\right)$$

By Gronwall's inequality, we have

$$\begin{aligned}\left(X_1+X_2\right)(t) &\leq \left(X_1+X_2\right)(0)e^{\int_0^T \mu_m ds}\\ &\leq e^{\mu_m T}\left(X_1+X_2\right)(0)\end{aligned}$$

So, X_1+X_2 is bounded. Since,

$$\begin{aligned}&\left(X_1\right)(t) \leq \left(X_1+X_2\right)(t), \quad X_1, X_2 \geq 0\\ &\left(X_1\right)(t) \leq e^{\mu_m T}\left(X_1+X_2\right)(0),\end{aligned}$$

and

$$\begin{aligned}&\left(X_2\right)(t) \leq \left(X_1+X_2\right)(t), \quad X_1, X_2 \geq 0\\ &\left(X_2\right)(t) \leq e^{\mu_m T}\left(X_1+X_2\right)(0),\end{aligned} \tag{4.3.10}$$

we have that $\left(X_1\right)(t)$ and $\left(X_2\right)(t)$ are also bounded.

Now,

$$\begin{aligned}\left\|\nabla f_1\right\|_\infty = \sup\Bigg\{&\left|\mu_m - \frac{\mu_m q_1}{Q} - d_1 - c_1\frac{k_1^n}{Q^n+k_1^n}\right|, \left|c_2\frac{Q^n}{Q^n+k_2^n}\right|,\\ &\left|\frac{\mu_m q_1 X_1}{Q^2} + \frac{nc_1k_1^nX_1Q^{n-1}}{\left(Q^n+k_1^n\right)^2} + \frac{nc_2k_2^nX_2Q^{n-1}}{\left(Q^n+k_2^n\right)^2}\right|\Bigg\}.\end{aligned}$$

Now,

$$\left|\mu_m\left(1-\frac{q_1}{Q}\right)-d_1-\frac{c_1k_1^n}{Q^n+k_1^n}\right| \leq \left|\mu_m\left(1-\frac{q_1}{Q}\right)\right|+|d_1|+\left|\frac{c_1k_1^n}{Q^n+k_1^n}\right|,$$
$$\leq |\mu_m|+|d_1|+|c_1|, \quad (\text{since } q_1\leq Q).$$

Again,

$$\left|c_2\frac{Q^n}{Q^n+k_2^n}\right| \leq \left|c_2\frac{Q^n}{Q^n}\right| \leq |c_2|$$

Also,

$$\begin{aligned}
&\left|\frac{\mu_m q_1 X_1}{Q^2}+\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}+\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \\
&\qquad \leq \left|\frac{\mu_m q_1 X_1}{Q^2}\right|+\left|\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right|+\left|\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \\
&\qquad \leq \left|\frac{\mu_m}{q_1}\left(\frac{q_1}{Q}\right)^2X_1\right|+\left|\frac{nc_1k_1^nX_1Q^{n-1}}{(k_1^n)^2}\right|+\left|\frac{nc_2k_2^nX_2Q^{n-1}}{(k_2^n)^2}\right| \\
&\qquad \leq \left|\frac{\mu_m}{q_1}\right||X_1|+\left|\frac{nc_1X_1Q^{n-1}}{k_1^n}\right|+\left|\frac{nc_2X_2Q^{n-1}}{k_2^n}\right| \\
&\qquad \leq \left|\frac{\mu_m}{q_1}\right||X_1|+\left|\frac{nc_1}{k_1^n}\right||X_1|\left|Q^{n-1}\right|+\left|\frac{nc_2}{k_2^n}\right||X_2|\left|Q^{n-1}\right|
\end{aligned}$$

Since X_1, X_2, Q are bounded.

$$\left|\frac{\mu_m q_1 X_1}{Q^2}+\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}+\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right| \leq K_3 \tag{4.3.11}$$

Denoting $|\mu_m|+|d_1|+|c_1| = K_1,\ |c_2| = K_2$, we have

$$\|\nabla f_1\|_\infty \leq \max\{K_1, K_2, K_3\} = K$$

So, f_1 is locally Lipschitz. Next, we have

$$\begin{aligned}
\|\nabla f_2\|_\infty = \sup\Bigg\{&\left|c_1\frac{k_1^n}{Q^n+k_1^n}\right|, \left|\mu_m-\frac{\mu_m q_2}{Q}-d_2-c_2\frac{Q^n}{Q^n+k_2^n}\right|, \\
&\left|\frac{\mu_m q_2 X_2}{Q^2}+\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}+\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right|
\end{aligned}$$

Now,

$$\left|c_1\frac{k_1^n}{Q^n+k_1^n}\right| \le \left|c_1\frac{k_1^n}{k_1^n}\right| \le |c_1|, \quad \text{(since } Q \text{ is bounded)}$$

Again,

$$\begin{aligned}\left|\mu_m\left(1-\frac{q_2}{Q}\right)-d_2-\frac{c_2Q^n}{Q^n+k_2^n}\right| &\le \left|\mu_m\left(1-\frac{q_2}{Q}\right)\right|+|d_2|+\left|\frac{c_2Q^n}{Q^n+k_2^n}\right|,\\ &\le |\mu_m|+|d_2|+\left|\frac{c_2Q^n}{Q^n}\right| \quad \text{(since } q_2\le Q)\\ &\le |\mu_m|+|d_2|+|c_2|\end{aligned}$$

Also,

$$\begin{aligned}&\left|\frac{\mu_m q_2 X_2}{Q^2}+\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}+\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right|\\ &\le \left|\frac{\mu_m q_2 X_2}{Q^2}\right|+\left|\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}\right|+\left|\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right|\\ &\le \left|\frac{\mu_m}{q_2}\left(\frac{q_2}{Q}\right)^2X_2\right|+\left|\frac{nc_2k_2^nX_2Q^{n-1}}{(k_2^n)^2}\right|+\left|\frac{nc_1k_1^nX_1Q^{n-1}}{(k_1^n)^2}\right|\\ &\le \left|\frac{\mu_m}{q_2}\right||X_2|+\left|\frac{nc_2X_2Q^{n-1}}{k_2^n}\right|+\left|\frac{nc_1X_1Q^{n-1}}{k_1^n}\right|\\ &\le \left|\frac{\mu_m}{q_2}\right||X_2|+\left|\frac{nc_2}{k_2^n}\right||X_2|\left|Q^{n-1}\right|+\left|\frac{nc_1}{k_1^n}\right||X_1|\left|Q^{n-1}\right|\end{aligned}$$

Let $|c_1|=L_1,\ |\mu_m|+|d_2|+|c_2|=L_2$. Since X_1, X_2, Q are bounded

$$\left|\frac{\mu_m q_2 X_2}{Q^2}+\frac{nc_2k_2^nX_2Q^{n-1}}{(Q^n+k_2^n)^2}+\frac{nc_1k_1^nX_1Q^{n-1}}{(Q^n+k_1^n)^2}\right|\le L_3$$

Then

$$\|\nabla f_2\|_\infty \le \max\{L_2, L_2, L_3\}=L$$

So, f_2 is locally Lipschitz. Finally, we have

$$\|\nabla f_3\|_\infty=\sup\left\{|0|,|0|,\left|-\frac{v_mA}{(q_m-q)(A+v_h)}-\mu_m-b-\gamma u\right|\right.$$

We have

$$\left|-\frac{v_mA}{(q_m-q)(A+v_h)}-\mu_m-b-\gamma u\right|\le\left|\frac{v_mA}{(q_m-q)(A+v_h)}\right|+|\mu_m|+|b|-|\gamma u|$$

Let

$$\left|\frac{v_m A}{(q_m - q)\,(A + v_h)}\right| + |\mu_m| + |b| - |\gamma u| = M$$

Then,

$$\left|-\frac{v_m A}{(q_m - q)\,(A + v_h)} - \mu_m - b - \gamma u\right| \le M$$

Thus,

$$\|\nabla f_3\|_\infty \le M,$$

and so f_3 is locally Lipschitz. Since f_1, f_2, f_3 Lipschitz, we have F is locally Lipschitz. Thus, by Picard's theorem, (3.2.6) has an unique solution in $C^1([0,T])^3$. □

We next state and prove some properties of the objective functional J_u.

Proposition 4.3.3. The objective functional J_u is sequentially weakly lower semi-continuous (w.l.s.c.), bounded from below, coercive on U_{ad} and is Fréchet differentiable.

We finally conclude the theoretical results with the existence of an optimal parameter set.

Theorem 4.3.2. There exists a minimizer $u \in U_{ad}$ of J_u, given in (4.2.2).

Proof. For proving the existence of a minimizer of J_u, given in (4.2.2), we can follow the same arguments as given in Theorem 4.3.2, due to the fact that U_{ad} is a closed subspace of a Hilbert space and J_u is coercive in U_{ad}, which yields a convergent subsequence (u_{m_l}) of a minimizing sequence (u_m) for J_u. The compactness result of Aubin-Lions [66] yields strong convergence of a subsequence $(X_1^{m_k}, X_2^{m_k}, Q^{m_k})$ of a sequence $(X_1^{m_l}, X_2^{m_k}, Q^{m_k}) \equiv (X_1^{m_l}(u_{m_l}), X_2^{m_l}(u_{m_l}), Q^{m_l}(u_{m_l}))$ in $(H^1(0,T))^3$. □

4.4 Optimality system

We now describe the characterization of the minimizer of J_u, given in (4.2.2), through the first order necessary optimality system.

Theorem 4.4.1. The minimizer of (4.2.2) is obtained by solving the following optimality system

$$
\begin{aligned}
\frac{dX_1}{dt} &= \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right) = M_1(X_1,X_2,Q,u), \quad X_1(0)=1\\
\frac{dX_2}{dt} &= \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right) = M_2(X_1,X_2,Q,u), \quad X_2(0)=1\\
\frac{dQ}{dt} &= v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu = M_3(X_1,X_2,Q,u), \quad Q(0)=1
\end{aligned}
\tag{FORU:ODE}
$$

$$
\begin{aligned}
\frac{d\tilde{X}_1}{dt} &= -\left[\mu_m\left(1-\frac{q_1}{Q}\right) - d_1 - m_1(Q)\right]\tilde{X}_1 + m_1(Q)\tilde{X}_2, \ \tilde{X}_1(T)=0\\
\frac{d\tilde{X}_2}{dt} &= -\left[\mu_m\left(1-\frac{q_2}{Q}\right) - d_2 - m_2(Q)\right]\tilde{X}_2 + m_2(Q)\tilde{X}_1, \ \tilde{X}_2(T)=0\\
\frac{d\tilde{Q}}{dt} &= \alpha_0(Q(t)-Q_m) - \left(\frac{\mu_m}{Q^2}\right)\left(q_1X_1\tilde{X}_1 + q_2X_2\tilde{X}_2\right) - \left(\frac{c_1k_1X_1}{(Q+k_1)^2}\right)\left(\tilde{X}_1-\tilde{X}_2\right)\\
&\quad + \left(\frac{c_2X_2k_2}{(Q+k_2)^2}\right)\left(\tilde{X}_2-\tilde{X}_1\right) + v_m\frac{\tilde{Q}}{q_m-q}\frac{A}{A+v_h} + \mu_m\tilde{Q} + b\tilde{Q} + \gamma u\tilde{Q},\\
&\quad \tilde{Q}(T) = \alpha_4(Q(T)-Q_m)
\end{aligned}
\tag{ADJU:ODE}
$$

$$
\int_0^T \left(\beta u - \gamma Q\tilde{Q}\right)[v(t)-u(t)]dt \geq 0, \ \forall v \in U_{ad}. \tag{OPTU:ODE}
$$

Proof. The proof follows the same lines as given in Theorem 3.5.1, starting from the following Lagrangian

$$
\begin{aligned}
L\left(X_1,X_2,Q,\tilde{X}_1,\tilde{X}_2,\tilde{Q},u\right) = J_u(Q,u) &+ \int_0^T\left(\frac{dX_1}{dt}-M_1\right)\tilde{X}_1dt + \int_0^T\left(\frac{dX_2}{dt}-M_2\right)\tilde{X}_2dt\\
&+ \int_0^T\left(\frac{dQ}{dt}-M_3\right)\tilde{Q}dt,
\end{aligned}
\tag{4.4.1}
$$

where

$$
\begin{aligned}
M_1(X_1,X_2,Q,u) &= \mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - c_1\frac{k_1^n}{Q^n+k_1^n}X_1 + c_2\frac{k_2^n}{Q^n+k_2^n}X_2,\\
M_2(X_1,X_2,Q,u) &= \mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - c_2\frac{k_2^n}{Q^n+k_2^n}X_2 + c_1\frac{k_1^n}{Q^n+k_1^n}X_1,\\
M_3(X_1,X_2,Q,u) &= v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu(t).
\end{aligned}
$$

□

4.5 Numerical optimal control results

We now present the numerical results of our non-linear optimization framework for estimating treatment for the prostate cancer model (4.2.1) using noisy synthetic data. We choose the final time $T = 1000$, the regularization weights in the functional J_u, given in (4.2.2) to be $\alpha_0 = 1,\ \alpha_4 = 1,\ \beta_0 = 0.5$. Our time domain $[0, T]$ is divided into a mesh of 100,000 equally spaced subintervals. The non-dimensionalization scaling factors are $l_1 = 1/60,\ l_2 = 1/60,\ l_3 = 2.5,\ l_4 = 0.01$.

To generate the data, we simulate the forward ODE system (FORU:ODE) on a coarse mesh of 1000 subintervals, interpolate the numerical solution over the actual finer mesh, and add 3% additive Gaussian noise to the interpolated solution that gives the final form of the data. The forward and the adjoint ODE systems were solved using the forward Euler method. The optimality system (FORU:ODE)-(OPTU:ODE) was numerically solved by using the iterative non-linear conjugate gradient (NCG) method. We choose different initial guesses for the NCG algorithm from the biological reference intervals, given in Table 3.1.

Test Case 1: In this test case, we determined the optimal dose using the same unknown parameters as those estimated in Test Case 3 of Chapter 3, which gave the best parameter estimation results. The determined values are as follows: $\mu_m = 3.12, q_1 = 0.7, q_2 = 0.47, d_1 = 1.79, d_2 = 1.76, A = 3.51$.

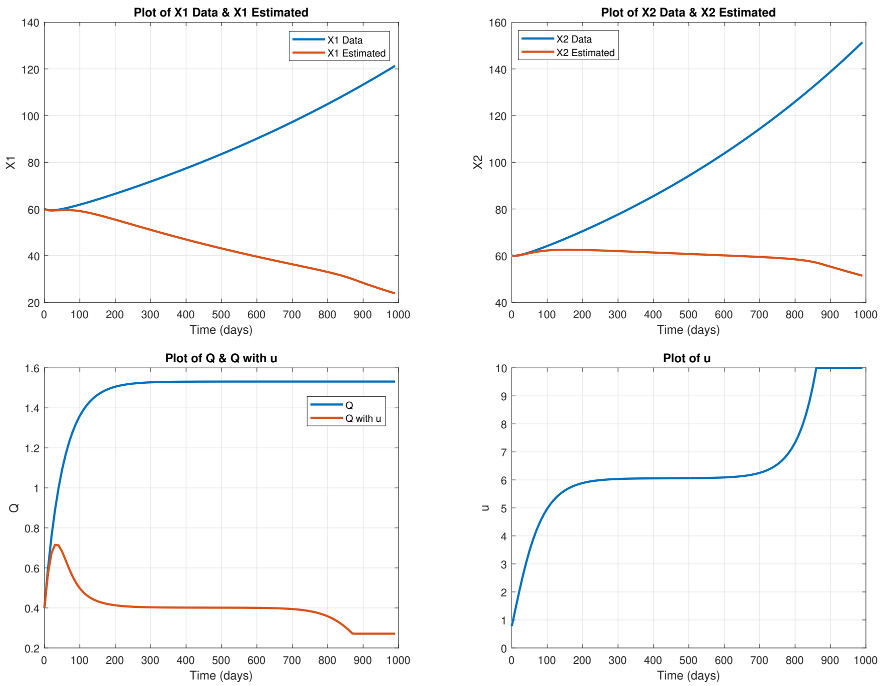

Figure 4.1: The plots of X_1, X_2, Q, u with treatment

The plots of the solution of figure (4.1) make it easy to see that the number of cancer cells X_1, X_2 for both types is decreasing with treatment and increasing with out treatment. We also note that androgen level Q decreases with treatment until it reaches the normal level. while that androgen level Q without treatment is high. Finally,we notice that the value of u in the last figure is changing with time, which means that we do not need to give the patient the same amount of medicine every time. This will increase the efficiency of treatment and survival as well as reduce the cost of treatment.

Test Case 2: To make sure our findings were correct, we used a different set of values that we estimated using our method. These values were $\mu_m = 4.2, q_1 = 1.125, q_2 = 0.6, d_1 = 2, d_2 = 2, A = 4.4$. This helped us be sure our results were consistent and dependable. The best dose we found during this check supported the accuracy of our earlier estimates and gave us more confidence in our research.

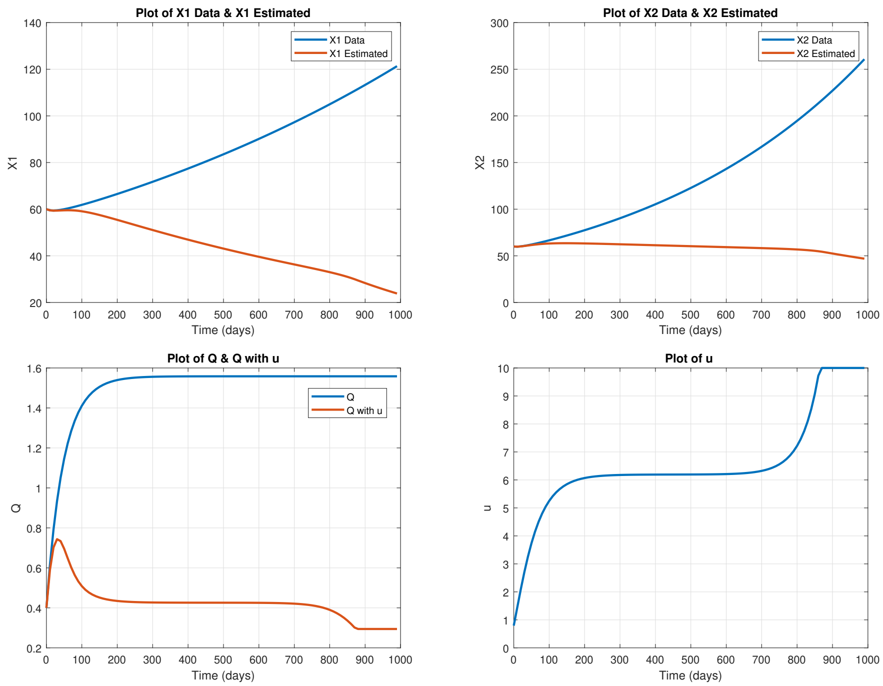

Figure 4.2: The plots of X_1, X_2, Q, u with treatment

The solution plots of (4.2) show the decreasing trend in the number of both type X_1 and X_2 cancer cells with treatment and increasing with out treatment. Additionally, the androgen level Q with treatment decreases until it reaches the normal range. Furthermore, the plot of variable u indicates a changing pattern over time, suggesting that administering the exact medication dosage every time may not be necessary. This dynamic approach could enhance treatment effectiveness, improve survival rates, and potentially reduce treatment costs.

Test Case 3: To double-check about our results, we used another set of unknown values that we estimated using our method. We found these values: $\mu_m = 3.3, q_1 = 0.9, q_2 = 0.5, d_1 = 1.7, d_2 = 1.7, A = 3.9$. This way, we wanted to make sure our findings were reliable and consistent. The best dose we find out during this double-checking process supported the accuracy of our previous estimates and gave us feel more confident in our research.

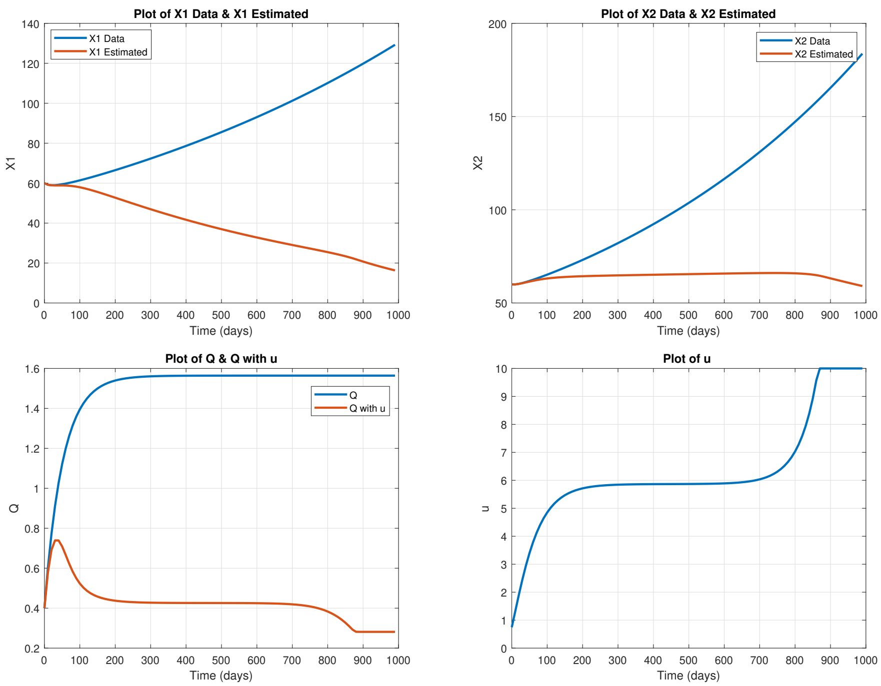

Figure 4.3: The plots of X_1, X_2, Q, u with treatment

The plots of the solution derived from the optimization problem stated in (4.2.2) and the corresponding to the parameters estimated and the data presented in Table 3.1 provide important information regarding the dynamics of cancer cells. It is clear that the number of cancer cells, both types X_1 and X_2, is consistently decreasing over time with treatment and increasing with out treatment. This observation indicates a positive response to the treatment, suggesting the potential effectiveness of the therapeutic approach.

Moreover, the analysis of the androgen level Q with treatment shows that it is decreasing until it eventually stabilizes within the normal range, while the level of androgen without treatment increases. This is an encouraging finding, as reducing androgen levels is a desired outcome in prostate cancer treatment given its influence on the growth and proliferation of cancer cells.

Additionally, the changing values of variable u in the last figure imply that administering the exact medicine dosage at each interval may not be necessary. This dynamic pattern suggests the possibility of adjusting the medication amount according to the patient's condition, which could lead to improved treatment efficacy, enhanced patient survival rates, and potentially reduced treatment costs. Such personalized treatment strategies can potentially optimize the therapeutic outcome and minimize unnecessary medication taken.

CHAPTER 5

Liouville optimal control problem

5.1 Introduction

The parameter estimation results we estimated in Chapter 3 are not very accurate. The primary reason was the use of deterministic modeling of cancer dynamics. We will use a stochastic model for cancer dynamics based on the Liouville equation to address this issue.

In this chapter, we will develop optimization algorithms to solve the unknown patient-specific parameters based on patient data and identify effective androgen suppression methods in prostate cancer using Liouville dynamical models for cancer. These optimization algorithms are important because they let us personalize cancer treatments for each patient. By understanding the specific parameters for each person, we can design treatments that fit their needs. This personalized approach could lead to better outcomes and improve the quality of life for people with prostate cancer.

The Liouville equations are used in different fields like biology, finance, mechanics, and physics to describe how density functions change over time. These equations help us understand the behavior of multiple trials or non-interacting systems [82]. While the focus on control problems governed by Liouville equations has been limited, there are advantages to using the Liouville framework [3, 17]. It allows us to extend optimal control problems from ordinary differential equations (ODE) to partial differential equations (PDE), considering not just one trajectory but a group of trajectories. This perspective is helpful for modeling systems with uncertain initial data and exploring robust control strategies and feedback mechanisms, potentially leading to new successful outcomes [81]. Liouville dynamic models will help us simulate and study how cancer cells grow and how treatments work on them. By doing this, we can understand how best to treat prostate cancer and the most effective methods for each person's situation. It is important to note that the analysis of the Liouville equation is an important topic in modern partial differential equations theory, e.g., [4, 5, 28].

Javier Baez and Yang Kuang found that although the model (3.2.6) is more realistic. However, they reduced the model to make it simple, and they obtained results that better matched the clinical data [7]. Using this method, the model becomes a good balance between being not too complicated and still useful in real-life medical situations.

By the end of this chapter, we hope to find new and effective ways to treat prostate cancer. This will help improve the field of cancer treatment and bring us closer to finding personalized and targeted therapies for people with this disease. Our main goal is to make a difference in patients lives by providing better care and advancing our knowledge in the fight against prostate cancer.

5.2 A Liouville model for prostate cancer

We start off with the non-dimensional ODE model (3.2.6), governing the dynamics of prostate cancer cells that was described in Chapter 3 as follows

$$\begin{aligned}
\frac{dX_1}{dt} &= \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 + c_2 \frac{Q^n}{Q^n + k_2^n} X_2 \\
\frac{dX_2}{dt} &= \mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - c_2 \frac{Q^n}{Q^n + k_2^n} X_2 + c_1 \frac{k_1^n}{Q^n + k_1^n} X_1 \\
\frac{dQ}{dt} &= v_m \frac{q_m - Q}{q_m - s} \frac{A}{A + v_h} - \mu_m (Q - s) - bQ
\end{aligned}$$

We consider a reduced model wherein the AD and AI prostate cancer cells are combined together as a single cell type X. The dynamics of prostate cancer is then described through the following set of equations

$$\begin{aligned}\frac{dX}{dt} &= \mu_m\left(1-\frac{s}{Q}\right)X - dX - c\frac{k^n}{Q^n+k^n}X\\ \frac{dQ}{dt} &= v_m\frac{q_m-Q}{q_m-s}\frac{A}{A+v_h} - \mu_m(Q-s) - bQ.\end{aligned} \tag{5.2.1}$$

In clinical trials, experiments are performed using varying setups, which leads to randomness in the initial conditions. To model this behavior accurately, the aforementioned deterministic setup is inappropriate. Rather, one needs to consider $X(0), Q(0)$ to be random and drawn from some appropriate distribution. This renders X, Q to be random variables. Correspondingly, the ODE system (5.2.1) represents the ensemble dynamics of prostate cancer, initiating from different initial conditions.

Let $p(x,q,t)$ be the joint probability density function associated to X, Q, i.e., $\mathbb{P}(X(t)=x, Q(t)=q) = p(x,q,t)$. Then the ensemble dynamics of (5.2.1) can be represented by the following Liouville equation

$$\begin{aligned}&\frac{dp}{dt} + \nabla\cdot(b(x,q)p(x,q,t)) = 0,\\ &p(x,q,0) = p_0(x,q)\end{aligned} \tag{5.2.2}$$

where

$$b(x,q) = (b_1(x,q), b_2(x,q))$$

with the initial condition at $t=0$ given by $p(x,q,0) = p_0(x,q)$, $(x,q) \in \mathbb{R}^+ \cup \{0\} \times \mathbb{R}^+ \cup \{0\}$, $\nabla \equiv (\frac{\partial}{\partial x}, \frac{\partial}{\partial q})$, and

$$\begin{aligned}b_1(x,q) &= \mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x\\ b_2(x,q) &= v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq,\end{aligned} \tag{5.2.3}$$

Note that b_1, b_2 are essentially the right hand sides of the ODE (5.2.1), replacing X with x and Q with q.

5.3 Liouville optimization problems

5.3.1 Parameter estimation

Let $\theta = \{\mu_m, s, d, A\}$ be the vector of the unknown patient specific parameters in (5.2.1). The reason for this choice is because these parameters show wide variability amongst different patients. The other parameters in (5.2.1) are more specific to the cancer type and, thus, can be considered fixed and known across patients.

Parameter	Meaning	Value and units	Reference
μ_m	Maximum proliferation rate	0.025-0.045/day	[13]
s	Minimum AD cell quota	0.175-0.45 nM	[18]
k	AD to AI mutation half-saturation level	0.08 nM	[78]
d	AD cell apoptosis rate	0.015-0.02/day	[13]
c	Maximum AD to AI mutation rate	0.00015/day	[50]
b	Cell quota degradation rate	0.09/day	[50]
q_m	Maximum cell quota	5 nM	[78]
v_m	Maximum cell quota uptake rate	0.275 nM/day	[78]
v_h	Uptake rate half-saturation level	4 nM	[78]
A	Maximum serum androgen level	27-35 nM	[77]

Table 5.1: Biological reference range for the parameters

Our goal is to estimate θ, given some data about x, q. For this purpose, we solve the following constrained optimization problem for finding θ

$$\min_{\theta} J(p,\theta) = \frac{\alpha}{2}\int_0^T \int_\Omega \left(p(x,q,t) - p^d(x,q,t)\right)^2 dxdqdt + \frac{\beta}{2}\|\theta\|^2 \qquad (5.3.1)$$

subject to the Liouville equations (5.2.2) where $\Omega = \mathbb{R}^+ \cup \{0\} \times \mathbb{R}^+ \cup \{0\}$, $p(x_1, x_2, q, 0) = p_0(x_1, x_2, q)$ in Ω and $p^d(x,q,t)$ is the probability density function of given data observations from the patient. The set T_{ad} is the admissible set of θ defined as

$$T_{ad} = \{\theta \in \mathbb{R}^4 : \theta(i) \in [0, M_i],\ M_i > 0\},$$

with M_i chosen based on the observed biological reference range of the parameters, as given in Table 5.1.

5.3.2 Optimal control problem

We next consider the second optimization problem to control the Liouville prostate cancer dynamics. For this purpose, we consider a controlled Liouville equation

$$\begin{aligned} &\frac{dp}{dt} + \nabla \cdot (b(x,q,u)p(x,q,t)) = 0, \\ &p(x,q,0) = p_0(x,q) \end{aligned} \tag{5.3.2}$$

where

$$b(x,q,u) = (b_1(x,q), b_2(x,q,u))$$

with the initial condition at $t = 0$ given by $p(x,q,0) = p_0(x,q)$, $(x,q) \in \mathbb{R}^+ \cup \{0\} \times \mathbb{R}^+ \cup \{0\}$, $\nabla \equiv (\frac{\partial}{\partial x}, \frac{\partial}{\partial q})$, and

$$\begin{aligned} b_1(x,q) &= \mu_m \left(1 - \frac{s}{q}\right) x - dx - c\frac{k^n}{q^n + k^n}x \\ b_2(x,q) &= v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m(q - s) - bq - \gamma uq. \end{aligned} \tag{5.3.3}$$

Here, $u(t)$ is a function that represents an androgen receptor blocker drug to control the androgen level Q and γ is the androgen clearance rate, as given in Chapter 4. Our goal is to determine the optimal dosage of $u(t)$ that can control the androgen production in cancer cells. We look for u in the admissible set

$$U_{ad} = \{u(t) \in L^2([0,T]) : 0 \leq u(t) \leq u_r\}, \ \forall t \in [0,T],$$

where u_r is the maximum tolerable dose. This can be formulated through the following optimal control problem

$$\min_u J_u(p,u) = \frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d(x,q,t)\right)^2 dxdqdt + \frac{\beta}{2} \int_0^T (u(t))^2 dt \tag{5.3.4}$$

subject to the controlled Liouville equations (5.3.2), where $p^d(x,q,t)$ is the desired distribution of the dynamics that represents a successful treatment regime.

5.4 Theory of the optimization problems

In this section, we present some theoretical results related to the two optimization problems (5.3.1) and (5.3.4). We start with the existence and uniqueness of the solutions of (5.2.2) and (5.3.2), whose proof can be found in [8].

Proposition 5.4.1. Let $p_0 \in H^1(\Omega)$ with $p_0 \geq 0$, $\theta \in T_{ad}$, and $u \in U_{ad}$. Then, there exists an unique non-negative solution of (5.2.2) and (5.3.2) given by $C([0,T]; H^1(\Omega))$.

We also have the following conservativeness property of the Liouville equations (5.2.2) and (5.3.2).

Proposition 5.4.2. The Liouville equations (5.2.2) and (5.3.2) are conservative.

Proof. Multiplying (5.2.2) and (5.3.2) by $\psi \in H^1(\Omega)$ and integrating by parts, we obtain the following

$$\int_\Omega \frac{\partial p}{\partial t} \psi dx = \int_\Omega (bp) \cdot \nabla \psi \, dx. \tag{5.4.1}$$

Choosing $\psi = 1$, we obtain $\int_\Omega p(x,q,t)dx = \int_\Omega p_0(x)dx$ for all $t \in (0,T]$ and this proves the result. □

We also have the following stability estimate of the Liouville equations (5.2.2) and (5.3.2) from [8].

Proposition 5.4.3. The solutions p_1, p_2 of (5.2.2) and (5.3.2), respectively, satisfies the following stability estimate

$$\|p_i(t)\|_{H^1(\Omega)} \leq C_i(\theta) \|p_0\|_{H^1(\Omega)} \exp\left(\int_0^T \|\nabla b\|_{L^\infty(\Omega)} \, dt \right), \; i = 1, 2. \tag{5.4.2}$$

where C is independent of p, p_0, T, b.

The aforementioned results implies that p as functions of θ and u is continuous. Furthermore, it can also be shown that these functions are Fréchet differentiable. We now state some properties of the functionals J, J_u, given in (5.3.1) and (5.3.4), respectively, that can be proved using the fact that the PDF p is non-negative.

Proposition 5.4.4. The objective functionals J, J_u, given in (5.3.1) and (5.3.4), are sequentially weakly lower semi-continuous (w.l.s.c.), bounded from below, coercive on T_{ad}, U_{ad}. respectively, and are Fréchet differentiable.

We finally state and prove the existence of the optimal parameter set θ^* and the optimal drug dosage concentration vector u^* in the following theorem.

Theorem 5.4.1. Let $p_0 \in H^1(\Omega)$ and let J, J_u be given as in (5.3.1) and (5.3.4). Then, there exists pairs $(p_1^*, \theta^*) \in C([0,T]; H^1(\Omega)) \times T_{ad}$ and $(p_2^*, u^*) \in C([0,T]; H^1(\Omega)) \times U_{ad}$ such that p_1^*, p_2^* are solutions of (5.2.2) and (5.3.2), respectively, and θ^*, u^* minimize J, J_u in T_{ad}, U_{ad}, respectively.

Proof. First, we prove the existence of minimizer of J, given in (5.3.1). Due to the fact that J_1 is bounded below, there exists a minimizing sequence $(\theta^m) \in T_{ad}$. Furthermore, J being coercive in T_{ad}, this sequence is bounded, and, thus, it contains a convergent subsequence (θ^{m_l}) in T_{ad} with $\theta^{m_l} \to \theta^*$. Correspondingly, the sequence $(p^{m_l}) = p(\theta^{m_l})$ is bounded in $L^2(0,T; H^1(\Omega))$ by (5.4.2), while the sequence of the time derivatives, $(\partial_t p^{m_l})$, is bounded in $L^2(0,T; H^{-1}(\Omega))$. Therefore, both the sequences converge weakly to p_1^* and $\partial_t p_1^*$, respectively. We, thus, obtain weak convergence of the sequence $(b(\theta^{m_k}))$ in $L^2(0,T,L^2(\Omega))$. This implies that the pair (p_1^*, θ^*) minimizes J.

The existence of a minimizer of J_u, given in (5.3.4), can be proved following the same arguments as above noting the fact that since U_{ad} is a closed subspace of a Hilbert space and J_u being coercive in U_{ad}, there exists a convergent subsequence (u_{m_l}) of a minimizing sequence (u_m) for J_u, and the compactness result of Aubin-Lions [66] yields strong convergence of a subsequence (p^{m_k}) of a sequence (p^{m_l}) in $L^2(0,T,L^2(\Omega))$. □

The differentiability of J, J_u, given in (5.3.1) and (5.3.4), respectively, gives the following optimality systems:

1. Optimality system for parameter estimation:

$$\begin{aligned} &\frac{dp}{dt} - \nabla \cdot (b(x,q)p(x,q,t)) = 0, \\ &p(x,q,0) = p_0(x,q). \end{aligned} \tag{FOR:LIOUV}$$

$$\begin{aligned} &\frac{dw}{dt} + b(x,q) \cdot \nabla w(x,q,t) = \alpha \left(p - p^d\right), \\ &w(x,q,T) = 0. \end{aligned} \tag{ADJ:LIOUV}$$

$$\begin{aligned} &(\beta\mu_m - \int_0^T \int_\Omega \left\{ \left[\left(1 - \frac{s}{q}\right) x \cdot \frac{\partial \omega}{\partial x}, -(q-s) \cdot \frac{\partial \omega}{\partial q} \right] p(x,q,t) \right\} \; dxdqdt) \cdot [v_1 - \mu_m] \geq 0, \\ &(\beta s - \int_0^T \int_\Omega \left(\frac{\mu_m x}{q} p(x,q,t) \cdot \frac{\partial \omega}{\partial x} \right) dxdqdt) \cdot [v_2 - s] \geq 0, \\ &(\beta d + \int_0^T \int_\Omega \left(xp(x,q,t) \cdot \frac{\partial \omega}{\partial x} \right) dxdqdt) \cdot [v_3 - d] \geq 0, \\ &(\beta A - \int_0^T \int_\Omega \left(v_m \frac{q_m - q}{q_m - s} \frac{v_n}{(A + v_n)^2} p(x,q,t) \cdot \frac{\partial \omega}{\partial q} \right) dxdqdt) \cdot [v_4 - A] \geq 0, \end{aligned} \tag{OPT:LIOUV}$$

for all $v = (v_1, v_2, v_3, v_4) \in T_{ad}$.

2. Optimality system for optimal drug control:

$$\begin{aligned} &\frac{dp}{dt} - \nabla \cdot (b(x,q,u)p(x,q,t)) = 0, \\ &p(x,q,0) = p_0(x,q). \end{aligned} \tag{FORU:LIOUV}$$

$$\begin{aligned} &\frac{dw}{dt} + b(x,q,u) \cdot \nabla w(x,q,t) = \alpha \left(p - p^d\right), \\ &w(x,q,T) = 0. \end{aligned} \tag{ADJU:LIOUV}$$

$$\int_0^T \left(\beta u(t) - \int\limits_\Omega \left(-\gamma q p(x,q,t) \frac{dw}{dq} \right) dxdq \right) [v(t) - u(t)] \; dt \geq 0, \;\; \forall v \in U_{ad}. \tag{OPTU:LIOUV}$$

5.5 Numerical schemes for solving the optimality systems

In this section, we present and analyze some numerical schemes to solve the two optimality systems (FOR:LIOUV)-(OPTU:LIOUV). We first note that even though the Liouville equations (5.2.2) and (5.3.2) are theoretically setup in an unobunded domain, for practical implementation, we need to consider a large but bounded domain $\Omega = (-B, B) \times (-B, B) \subset \mathbb{R}^2$. For the initial PDF p_0, we choose a smooth density that is numerically compactly supported in Ω. We then solve (5.2.2) and (5.3.2) in $\Omega \times [0, T]$, choosing homogeneous Dirichlet boundary conditions on $\partial\Omega$. Using the results and techniques proposed in [8, 9], one can prove existence and uniqueness of smooth solutions of (5.2.2) and (5.3.2) in $\Omega \times [0, T]$. We also choose the final time T such that the solutions of the Liouville equations (5.2.2) and (5.3.2) are still contained in Ω away from its boundary.

We now consider a numerical grid that partitions Ω in $N_x \times N_x$, with $N_x > 1$, equally-spaced non-overlapping square cells of side length $h = 2B/N_x$. On this grid, we develop a cell-centered finite-volume scheme with the PDF p and its adjoint w defined at the centers of the square cells. These nodal points are given by

$$x^i := \left(i - \frac{1}{2}\right) h - B, \qquad\qquad q^j := \left(j - \frac{1}{2}\right) h - B.$$

Therefore, the elementary cell is defined as

$$\omega_h^{ij} := \left\{ (x, q) \in \Omega \quad \middle| \quad x \in \left[x^i - \frac{h}{2}, x^i + \frac{h}{2}\right], \quad q \in \left[q^j - \frac{h}{2}, q^j + \frac{h}{2}\right] \right\}.$$

This results in the computational domain as given below

$$\Omega_h = \bigcup_{i,j=1}^{N_x} \omega_h^{ij}.$$

In a similar way, the time interval $[0, T]$ is divided in $N_t > 1$ subintervals of length $\Delta t = \frac{T}{N_t}$ and the points t^k are given by

$$t^k := k\Delta t, \qquad k = 0, \ldots, N_t.$$

Then the time grid is given by $\Gamma_{\Delta t} := \{t^k \ \in \ [0,T],\ k = 0,\ldots,N_t\}$. Thus, corresponding to the space-time cylinder $Q := \Omega \times [0,T]$ we have the numerical grid as $Q_{h,\Delta t} := \Omega_h \times \Gamma_{\Delta t}$.

We now define the cell average of the PDF p (and any other integrable function) on the cell with centre (x^i, q^j) at time t^k as follows

$$\bar{p}^k_{i,j} = \frac{1}{h^2} \int_{x^{i-1/2}}^{x^{i+1/2}} \int_{q^{j-1/2}}^{q^{j+1/2}} p(x,q,t^k)\, dq\, dx. \tag{5.5.1}$$

The initial condition is then given by

$$\bar{p}^0_{i,j} = p^0_{i,j} = \frac{1}{h^2} \int_{x^{i-1/2}}^{x^{i+1/2}} \int_{q^{j-1/2}}^{q^{j+1/2}} p_0(x,q)\, dq\, dx.$$

In the aforementioned finite-volume setting, the unknown variables are the cell-average values $\bar{p}$. Thus, we will formulate numerical schemes to determine these unknown cell-averages as the numerical approximations to the solutions of the Liouville equations and its adjoints. Without loss of generality, we denote the cell-averages without the bars.

For the control function u, we use a piecewise constant approximation, where we denote with $u^{k+1/2}$ the value of the control in the time interval $[t^k, t^{k+1})$. We then project the continuous u to the corresponding numerical grid by setting $u^{k+1/2} = u(t^k)$. For a function g defined on $Q_{h,\Delta t}$, we also define the discrete norms $\|\cdot\|_{1,h}$ and $\|\cdot\|_{\infty,h}$ as follows:

$$\|g(\cdot,\cdot,t^k)\|_{1,h} = h^2 \sum_{i,j}^{N_x} \left|g^k_{i,j}\right|, \qquad \|g(\cdot,\cdot,t^k)\|_{\infty,h} = \max_{i,j=1,\ldots,N_x} \left|g^k_{i,j}\right|,$$

where $g^k_{i,j} = g(x^i, q^j, t^k)$, and (x^i, q^j, t^k) denotes a grid point in $\Omega \times [0,T]$.

5.5.1 A Euler-Kurganov-Tadmor scheme for solving the Liouville equations

In this section, we discuss a numerical scheme for solving the Liouville equations (5.2.2) and (5.3.2) in $\Omega \times [0, T]$. For the spatial discretization, we consider a finite-volume scheme proposed by Kurganov-Tadmor (KT) in [61], combined with a generalized MUSCL flux. To describe this scheme, the flux in the Liouville equations can be considered as a function of p and is denoted by $\mathcal{H}(p) = bp$. Then the KT scheme for the Liouville equation in semi-discretized form is given as follows

$$\frac{\mathrm{d}}{\mathrm{dt}} p_{i,j}(t) = -\frac{F^x_{i+1/2,j}(p^+, p^-; t) - F^x_{i-1/2,j}(p^+, p^-; t)}{h} - \frac{F^q_{i,j+1/2}(p^+, p^-; t) - F^q_{i,j-1/2}(p^+, p^-; t)}{h}, \qquad i, j = 1, \ldots, N_x - 1, \tag{5.5.2}$$

where the $F^x_{\cdot,\cdot}(p^+, p^-; t)$, $F^q_{\cdot,\cdot}(p^+, p^-; t)$ are the numerical fluxes in the x and q directions, respectively. These numerical fluxes are defined as follows:

$$F^x_{i+1/2,j}(p^+, p^-; t) := \frac{h^1(p^+_{i+1/2,j}(t)) + h^1(\rho^-_{i+1/2,j}(t))}{2} - \frac{\mathcal{V}^x_{i+1/2,j}(t)}{2}\Big[p^+_{i+1/2,j}(t) - p^-_{i+1/2,j}(t))\Big], \tag{5.5.3}$$

$$F^q_{i,j+1/2}(p^+, p^-; t) := \frac{h^2(p^+_{i,j+1/2}(t)) + h^2(\rho^-_{i,j+1/2}(t))}{2} - \frac{\mathcal{V}^q_{i,j+1/2}(t)}{2}\Big[p^+_{i,j+1/2}(t) - p^-_{i,j+1/2}(t))\Big], \tag{5.5.4}$$

where $\mathcal{H} = (h^1, h^2) = (b^1 p, b^2 p)$. In the aforementioned formulae, the so-called local speeds $\mathcal{V}^x(t)$, $\mathcal{V}^q(t)$ are given by

$$\mathcal{V}^x_{i+1/2,j}(t) = \left| \, b^1(x^{i+1/2}, q^j, t; u(t)) \, \right|, \; \mathcal{V}^q_{i,j+1/2}(t) = \left| \, b^2(x^i, q^{j+1/2}, t; u(t)) \, \right|, \tag{5.5.5}$$

since $\mathcal{H}(p) = bp$ is linear in p.

The approximation of p at the cell edges in (5.5.4) is given by following intermediate values

$$p^+_{i+1/2,j}(t) := p_{i+1,j}(t) - \frac{h}{2}(p_x)_{i+1,j}(t), \qquad p^-_{i+1/2,j}(t) := p_{i,j}(t) + \frac{h}{2}(p_x)_{i,j}(t). \tag{5.5.6}$$

The partial derivatives of p are approximated using the minmod function as follows: In direction x, we have

$$(p_x)_{i,j}(t) = \text{minmod}\Big(\frac{p_{i,j}(t) - p_{i-1,j}(t)}{h}, \frac{p_{i+1,j}(t) - p_{i-1,j}(t)}{2h}, \frac{p_{i+1,j}(t) - p_{i,j}(t)}{h}\Big). \tag{5.5.7}$$

An analogous expression holds in the direction q. Here the multivariable minmod function for vectors $x \in \mathbb{R}^d$ is given by

$$\text{minmod}(x_1, x_2, \ldots, x_d) := \begin{cases} \min_j\{x_j\} & \text{if } x_j > 0,\ \forall j \in [1, d] \\ \max_j\{x_j\} & \text{if } x_j < 0,\ \forall j \in [1, d] \\ 0 & \text{otherwise.} \end{cases}$$

For the time discretization of the Liouville equations (5.2.2) and (5.3.2), we use the standard first order Euler finite differencing scheme. Together with the the KT flux discretization in the spatial variables, we obtain the fully discrete approximation of the Liouville equations that we call as the Euler-KT (EKT) scheme. This scheme is implemented as follows: Given initial condition $p^k_{i,j}$, in (t^k, t^{k+1}), we have

$$p^{k+1}_{i,j} = p^k_{i,j} + \Delta t\, G(\rho^k_{i,j}). \tag{5.5.8}$$

Here, we use the following definition of the fully discrete fluxes

$$G(p^k_{i,j}) = -\frac{F^{x,k}_{i+1/2,j} - F^{x,k}_{i-1/2,j}}{h} - \frac{F^{q,k}_{i,j+1/2} - F^{q,k}_{i,j-1/2}}{h}. \tag{5.5.9}$$

where $F^{x,k}_{\cdot,\cdot}$, $F^{q,k}_{\cdot,\cdot}$ denotes $F^x_{\cdot,\cdot}$, $F^q_{\cdot,\cdot}$, as given in (5.5.4), corresponding to the time step t^k.

We now analyze some properties of the EKT scheme, given in (5.5.8). We begin with a strong stability property of the EKT scheme that can be proved using arguments given in [37, Lemma 2.1]

Proposition 5.5.1. The EKT scheme has the following strong stability property

$$\|p^{k+1}\|_{\infty,h} \leq \|p^k\|_{\infty,h}, \qquad k = 0, \ldots, N_t - 1.$$

We next show the conservativeness property of the EKT scheme.

Lemma 5.5.1 (Conservativeness)**.** The EKT scheme is conservative, in the sense that

$$\sum_{i,j=1}^{N_x} p_{i,j}^k = \sum_{i,j=1}^{N_x} p_{i,j}^0, \qquad k = 1, \ldots, N_t.$$

Proof. For a fixed $k \in \{0, \ldots, N_t\}$, summing up both the sides in (5.5.8) over all indices $i, j \in \{1, \ldots, N_x\}$ and using the fact that the solution has zero flux on the boundary (since it has compact support in Ω), we get

$$\sum_{i,j=1}^{N_x} p_{i,j}^{k+1} = \sum_{i,j=1}^{N_x} p_{i,j}^k.$$

Iterating over k, we have

$$\sum_{i,j=1}^{N_x} p_{i,j}^k = \sum_{i,j=1}^{N_x} p_{i,j}^0, \qquad k = 1, \ldots, N_t.$$

□

We next show that, under some restriction on Δt, the EKT scheme is positive, i.e., starting with $p_0 \geq 0$, we obtain $p^k \geq 0$ for all k. For this purpose, we define the CFL-number as

$$\lambda \coloneqq \frac{\Delta t}{h}, \tag{5.5.10}$$

We then impose that the function b satisfies the following conditions

$$\lambda \left\|b^1\right\|_{L_T^\infty(L^\infty(\Omega))} \leq \frac{1}{4}, \qquad \lambda \left\|b^2\right\|_{L_T^\infty(L^\infty(\Omega))} \leq \frac{1}{4}. \tag{5.5.11}$$

Under the CFL condition (5.5.11), we can prove the following lemma on the positivity of the EKT scheme.

Lemma 5.5.2 (Positivity)**.** Under the CFL-condition (5.5.11), the numerical solutions to the Liouville equations (5.2.2) and (5.3.2), computed with the EKT scheme, given in (5.5.8) is non-negative, that is,

$$p^0_{i,j} \geq 0 \implies p^k_{i,j} \geq 0, \qquad i,j = 1,\dots,N_x, \qquad k = 1,\dots,N_t. \tag{5.5.12}$$

Proof. Let $p^k_{i,j} \geq 0$ for fixed $0 \leq k < N_t$. We will show that $p^{k+1}_{i,j} \geq 0$ for all $i,j = 1,\dots,N_x$. For this purpose, notice that the EKT scheme can be written as follows

$$\begin{aligned} p^{k+1}_{i,j} = &\frac{\lambda}{2}\big(|b^1_{i+1/2,j}| - b^1_{i+1/2,j}\big)p^+_{i+1/2,j} + \frac{\lambda}{2}\big(|b^1_{i-1/2,j}| + b^1_{i-1/2,j}\big)p^-_{i-1/2,j} \\ &+\frac{\lambda}{2}\big(|b^2_{i,j+1/2}| - b^2_{i,j+1/2}\big)p^+_{i,j+1/2} + \frac{\lambda}{2}\big(|b^2_{i,j-1/2}| + b^2_{i,j-1/2}\big)p^-_{i,j-1/2} \\ &+\Big[\frac{1}{4} - \frac{\lambda}{2}\big(|b^1_{i+1/2,j}| + b^1_{i+1/2,j}\big)\Big]p^-_{i+1/2,j} + \Big[\frac{1}{4} - \frac{\lambda}{2}\big(|b^1_{i-1/2,j}| - b^1_{i-1/2,j}\big)\Big]p^+_{i-1/2,j} \\ &+\Big[\frac{1}{4} - \frac{\lambda}{2}\big(|b^2_{i,j+1/2}| + b^2_{i,j+1/2}\big)\Big]p^-_{i,j+1/2} + \Big[\frac{1}{4} - \frac{\lambda}{2}\big(|b^2_{i,j-1/2}| - b^2_{i,j-1/2}\big)\Big]p^+_{i,j-1/2} \end{aligned}, \tag{5.5.13}$$

where all discrete quantities on the right are considered at the timestep t^k. We note that if $\rho^{\pm}_{i\pm1/2,j},\ \rho^{\pm}_{i,j\pm1/2} \geq 0$, then the first four terms on the right hand side in (5.5.13) are always non-negative. The other terms are non-negative under the CFL-condition (5.5.11). Thus, we only need to show that $p^{\pm}_{i+1/2,j}, p^{\pm}_{i,j+1/2} \geq 0$ for all $i,j = 1,\dots,N_x$, where $p^{\pm}_{i,j}$ is given as in (5.5.6).

For this purpose, we will consider each expression of $(p_x)^k_{i,j}$, given in (5.5.7)(a similar analysis also holds for $(p_q)^k_{i,j}$). For the first case, we assume $(p_x)^k_{i,j} = \frac{p^k_{i,j} - p^k_{i-1,j}}{h}$. We then have

$$p^+_{i+1/2,j} = \frac{1}{2}p^k_{i+1,j} + \frac{1}{2}p^k_{i,j},$$

which is non-negative, since $p^k_{i,j} \geq 0$ for all $i,j = 1,\dots,N_x$. We also have, $p^-_{i+1/2,j} = p^k_{i,j} + \frac{h}{2}\left[\frac{p^k_{i,j} - p^k_{i-1,j}}{h}\right]$. If $\frac{p^k_{i,j} - p^k_{i-1,j}}{h} > 0$, we then have $p^-_{i+1/2,j} > 0$. On the other hand, if $\frac{p^k_{i,j}-p^k_{i-1,j}}{h} < 0$, then by the definition of the minmod limiter, we have $\frac{p^k_{i,j}-p^k_{i-1,j}}{h} \geq \frac{p^k_{i+1,j}-p^k_{i,j}}{h}$. This implies

$$p^-_{i+1/2,j} \geq p^k_{i,j} + \frac{h}{2}\left[\frac{p^k_{i+1,j}-p^k_{i,j}}{h}\right] = \frac{p^k_{i+1,j}+p^k_{i,j}}{2} \geq 0.$$

The other cases for the value of $(p_x)^k_{i,j} \neq 0$ follow analogously. If $(p_x)^k_{i,j} = 0$, then $p^\pm_{i+1/2,j} = p_{i+1,j} \geq 0$ and $p^\pm_{i,j+1/2} = p_{i,j+1} \geq 0$. This completes the proof. □

We next prove the discrete L^1 stability of the EKT scheme.

Lemma 5.5.3 (Stability)**.** The solution $p^k_{i,j}$ obtained with the EKT-scheme in (5.5.8) is discrete L^1 stable in the sense that

$$\left\|p^k_{\cdot,\cdot}\right\|_{1,h} = \left\|p^0_{\cdot,\cdot}\right\|_{1,h}, \qquad k = 1, \ldots, N_t,$$

under the CFL condition (5.5.11).

Proof. The conservativeness property in Lemma 5.5.1 implies

$$\sum_{i,j=0}^{N_x} p^k_{i,j} = \sum_{i,j=0}^{N_x} p^0_{i,j}, \qquad k = 1, \ldots, N_t.$$

The positivity property from Lemma 5.5.2 implies

$$\sum_{i,j=0}^{N_x} |p^k_{i,j}| = \sum_{i,j=0}^{N_x} |p^0_{i,j}|, \qquad k = 1, \ldots, N_t,$$

which proves the desired result. □

We next aim at proving the L^1 convergence of the EKT scheme. For this purpose, we state the following stability result, whose proof can be found in [9].

Lemma 5.5.4. Let $p^k_{i,j}$ be the numerical solution to the Liouville equations (5.2.2) and (5.3.2), with a Lipschitz continuous right-hand side $g(x, q, t)$, obtained with the EKT scheme. Then under the CFL condition (5.5.11), this solution satisfies the following stability estimate

$$\left\|p^{k+1}_{\cdot,\cdot}\right\|_{1,h} \leq \left\|p^0_{\cdot,\cdot}\right\|_{1,h} + \Delta t \sum_{m=0}^{k} \left\|g^m_{\cdot,\cdot}\right\|_{1,h},$$

where $g_{i,j}^m = g(x^i, q^j, t^m)$.

We now consider the local consistency error of our EKT at the point (x^i, q^j, t^k) defined as

$$T_{i,j}^k = \frac{p(x^i, q^j, t^{k+1}) - p(x^i, q^j, t^k)}{\Delta t} + \frac{1}{2h}(L_i^k + L_j^k)(p(x^i, q^j, t^k)) - g_{i,j}^k,$$

where

$$\begin{aligned} L_i^k(p) =& \big(|b_{i+1/2,j}^1| - b_{i+1/2,j}^1\big)p_{i+1/2,j}^{k+} - \big(|b_{i+1/2,j}^1| + b_{i+1/2,j}^1\big)p_{i+1/2,j}^{k-} \\ &+ \big(|b_{i-1/2,j}^1| + b_{i-1/2,j}^1\big)p_{i-1/2,j}^{k-} - \big(|b_{i-1/2,j}^1| - b_{i-1/2,j}^1\big)p_{i-1/2,j}^{k+}, \\ L_j^k(p) =& \big(|b_{i,j+1/2}^2| - b_{i,j+1/2}^2\big)p_{i,j+1/2}^{k+} - \big(|b_{i,j+1/2}^2| + b_{i,j+1/2}^2\big)p_{i,j+1/2}^{k-} \\ &+ \big(|b_{i,j-1/2}^2| + b_{i,j-1/2}^2\big)p_{i,j-1/2}^{k-} - \big(|b_{i,j-1/2}^2| - b_{i,j-1/2}^2\big)p_{i,j-1/2}^{k+} \end{aligned}$$

The accuracy result for the KT scheme, given in [9], the MUSCL reconstruction error given in Equation (60) in [71, Section 4.4] for the case when $\kappa = 0$, give us the following result

Lemma 5.5.5. Let $p \in C^3$ be the exact solution of the Liouville equations (5.2.2) and (5.3.2) Under the CFL condition (5.5.11), the consistency error $T_{i,j}^k$ satisfies the following error estimate

$$|T_{i,j}^k| \,=\, \mathcal{O}(h^2) + \mathcal{O}(\Delta t)$$

except possibly at the points of extrema of p where the consistency error can be first-order in h.

We now define the error at the point (x^i, q^j, t^k) as

$$e_{i,j}^k = p_{i,j}^k - p(x^i, q^j, t^k).$$

We then note that e satisfies (5.5.8) with the source term given by $-T_{i,j}^k$. Lemma 5.5.4 gives us

$$\left\|e_{\cdot,\cdot}^{k+1}\right\|_{1,h} \leq \left\|e_{\cdot,\cdot}^0\right\|_{1,h} + \Delta t \sum_{m=0}^{k} \left\|T_{\cdot,\cdot}^m\right\|_{1,h}.$$

With the aforementioned preparation, we now have the following result on the L^1 convergence of the solution obtained using the EKT scheme.

Theorem 5.5.1. Let $p \in C^3$ be the exact solution of the Liouville equations (5.2.2) and (5.3.2), with finite many extrema, and let $\left\|p^0_{\cdot,\cdot} - p_0(\cdot,\cdot)\right\|_{1,h} = \mathcal{O}(h)$. Under the CFL condition (5.5.11), the solution $p^k_{i,j}$ obtained with the EKT scheme, given by (5.5.8), is first-order accurate in the discrete L^1-norm as follows

$$\left\|p^k_{\cdot,\cdot} - \rho(\cdot,\cdot,t^k)\right\|_{1,h} \leq D(T,\Omega,\lambda)\, h.$$

For the adjoint equations (ADJ:LIOUV) and (ADJU:LIOUV), we first convert the equations into a divergence form, which results in additional zeroth order terms in w. We then use the Euler time discretization and the KT spatial derivative discretization to solve the adjoint equations numerically. For the optimization problems, we again use the NCG algorithm.

5.6 Numerical results

In this section, we present the results of numerical simulations with the Liouville parameter estimation and optimal control frameworks. For the parameter estimation problem, given in (5.3.1), we choose our domain $\Omega = (0,6)^2$ and discretize it using $N_x = 51$ points. The final time t is chosen to be 1.0 and the maximum number of time steps N_t is chosen to be 1000. We generate the patient data, using different true parameter values of θ, by first considering target PDFs $p^d_i(x),\ i = 1,\cdots,N$ with $N = 100$, where p^d_i are described by a normal distribution about the measured mean value $\mathbb{E}[p^d_i]$ and variance 0.05. We then use a 3D interpolation to obtain the data function $p^d(x,q,t)$ at all discrete times $t_k,\ k = 1,\cdots,N_t$. The regularization parameters are chosen to be $\alpha = 1,\ \beta = 0.1$.

5.6.1 Parameter estimation results

Test Case 1: In the first test case, the true parameters and the initial guess for the NCG algorithm are given in Table 5.2. We then solve the Liouville parameter estimation problem, given in (5.3.1). For comparison purposes, we use the reduced ODE system (5.2.1) and use the parameter estimation framework presented in Chapter 3. The results of this comparison are shown in Figure 5.1.

Parameters	μ_m	d	s	A
True	3.3	1.7	0.9	3.9
Guess	2.5	0.5	0.1	3

Table 5.2: Test case 1: Patient-specific parameter values

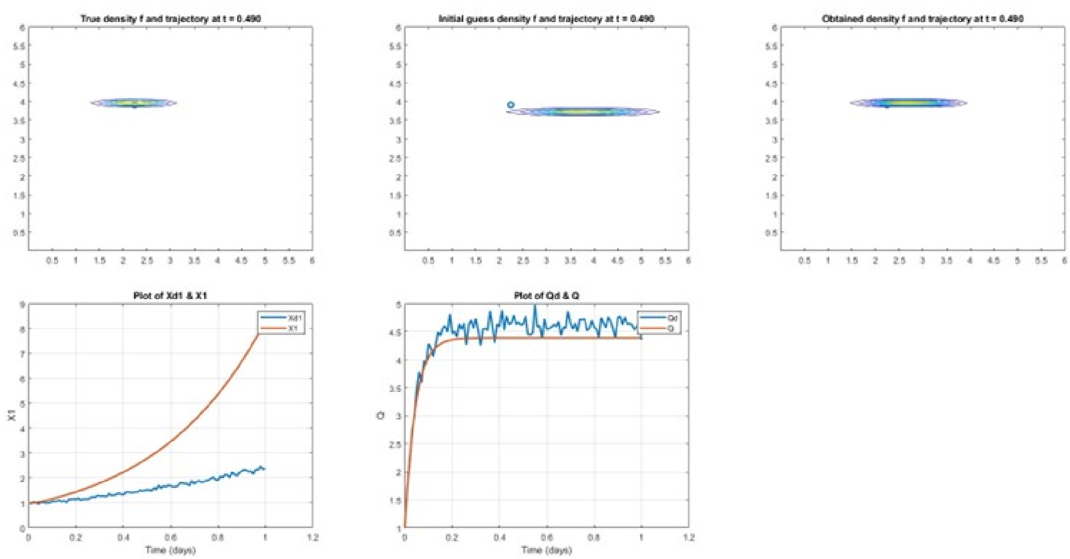

Figure 5.1: Test Case 1: Comparison between the ODE and Liouville parameter estimation case

In the first row of Figure 5.1, the first figure represents the PDF obtained by solving the Liouville equation (5.2.2) with the true parameters at $t = 0.49$. The small dot represents the corresponding trajectory point of the ODE (5.2.1) and is at the same location across all the figures in the first row. We note that the center of the PDF approximately matches the trajectory point, which is because the expected value of the Liouville PDF should give the solution of the ODE (5.2.1). The second figure in the first row represents the PDF obtained by using the initial guess for the parameters. We note that the center of this PDF does not match the trajectory point, which means we are not close to the true parameters. By solving the parameter estimation problem, we obtain the PDF in the third figure of the first row whose center now is very close to the trajectory point. On the other hand, the ODE parameter estimation framework results are shown in the second row and we clearly see that the trajectory for the X variable does not resemble the true trajectory. This implies the accuracy of our Liouville parameter estimation framework over the ODE parameter estimation framework.

Test Case 2: In our second test case, we now have a set of different true parameters and, correspondingly, different initial guesses, given in Table 5.3.

Parameters	μ_m	d	s	A
True	3.5	1.9	1.1	3.9
Initial guess	4	1.0	0.5	3.0

Table 5.3: Test case 2: Patient-specific parameter values

We again perform a comparison between the Liouville parameter estimation framework and the ODE parameter estimation framework. The results are shown in Figure 5.2.

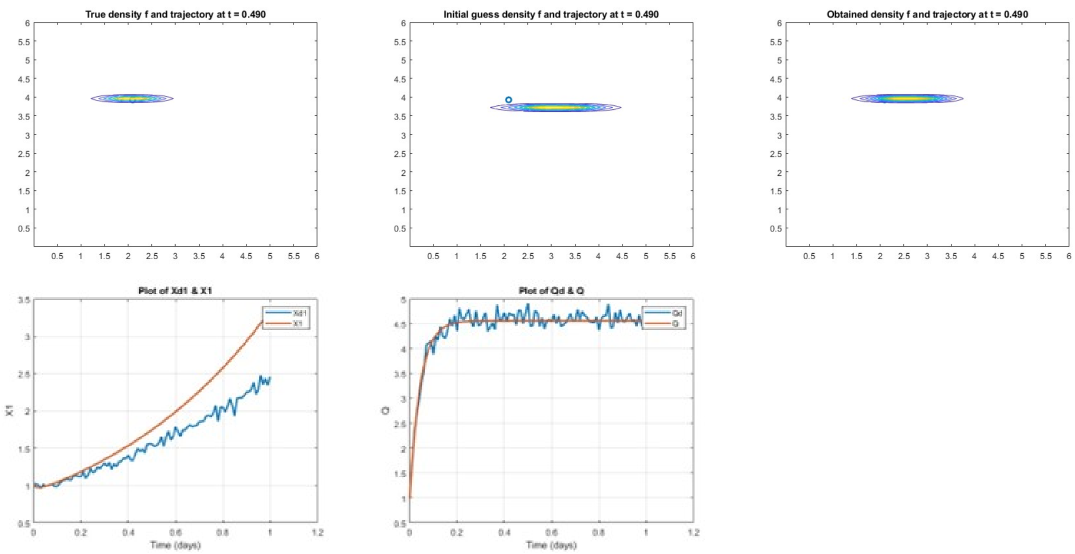

Figure 5.2: Test Case 2: Comparison between the ODE and Liouville parameter estimation case.

Using a similar analysis as in Test Case 1, we again note that the Liouville parameter estimation framework provides more accurate results as compared to the ODE parameter estimation framework. We also compute the respective relative L^2 errors for the 2 test cases. The relative L^2 error between 2 functions $X(t)$ and $X^d(t)$ is defined as

$$Err(X, X^d) = \frac{\|X - X^d\|_{L_2([0,T])}}{\|X^d\|_{L_2([0,T])}},$$

whereas the relative $L^2 error$ between 2 functions $p(x, q, t)$ and $p^d(x, q, t)$ is defined as

$$Err_p(p, p^d) = \frac{\|p - p^d\|_{L_2(\Omega\times[0,T])}}{\|p^d\|_{L_2(\Omega\times[0,T])}}$$

,

Test Case	$Err(X^1, X_1^d)$	$Err(Q, Q^d)$	$Err_p(p, p^d)$
1	0.4761	0.0803	0.1314
2	0.3312	0.0347	0.1219

Table 5.4: L^2 error table

From Table 5.4, we observe that the error between the ODE solution (X^1, Q^1) and the data is far more higher than the corresponding difference between the Liouville PDF p and the data function p^d. This further shows that the Liouville modeling and parameter estimation framework is more accurate than the ODE framework.

5.6.2 Optimal control results

We now present the results of our optimal control framework. For this purpose, we consider the patient-specific parameters obtained from Test Case 1 in Section 5.6.1. We then considered a PDF along a desired trajectory and the goal of the optimal control problem is to drive the uncontrolled PDF to the desired PDF. We consider two such cases whose plots are shown in Figures 5.3 and 5.4.

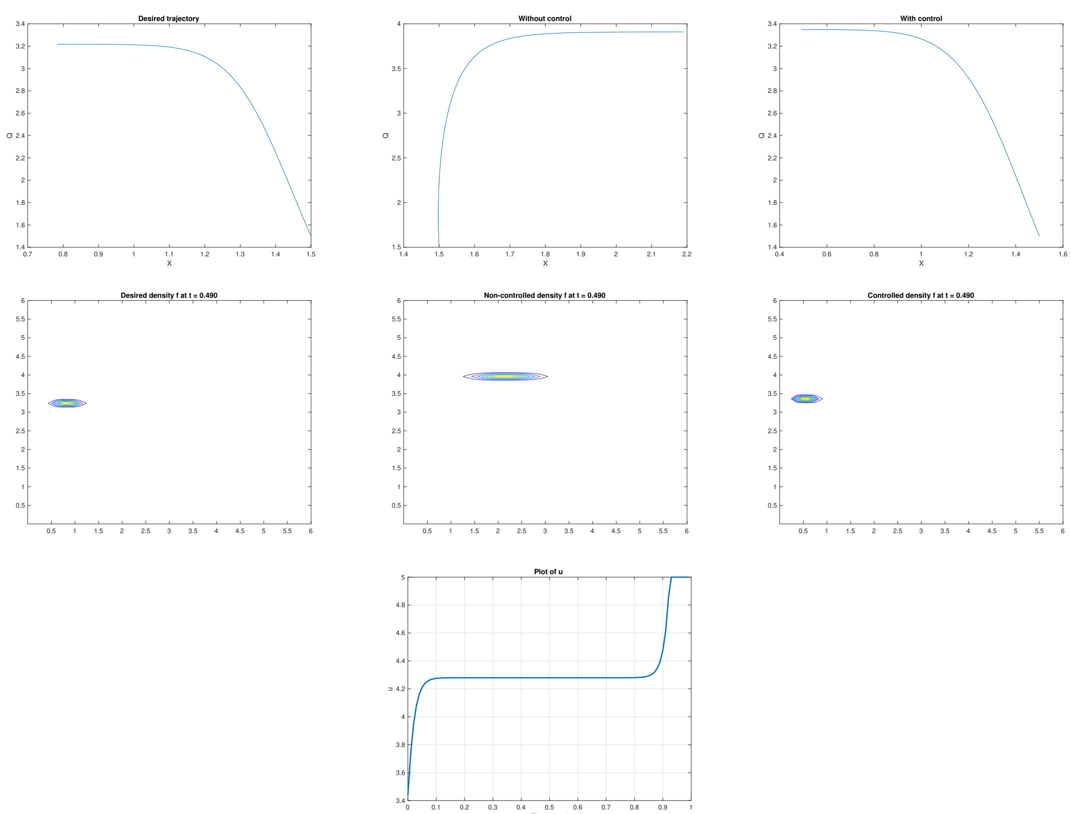

Figure 5.3: Test Case 1: Optimal control results

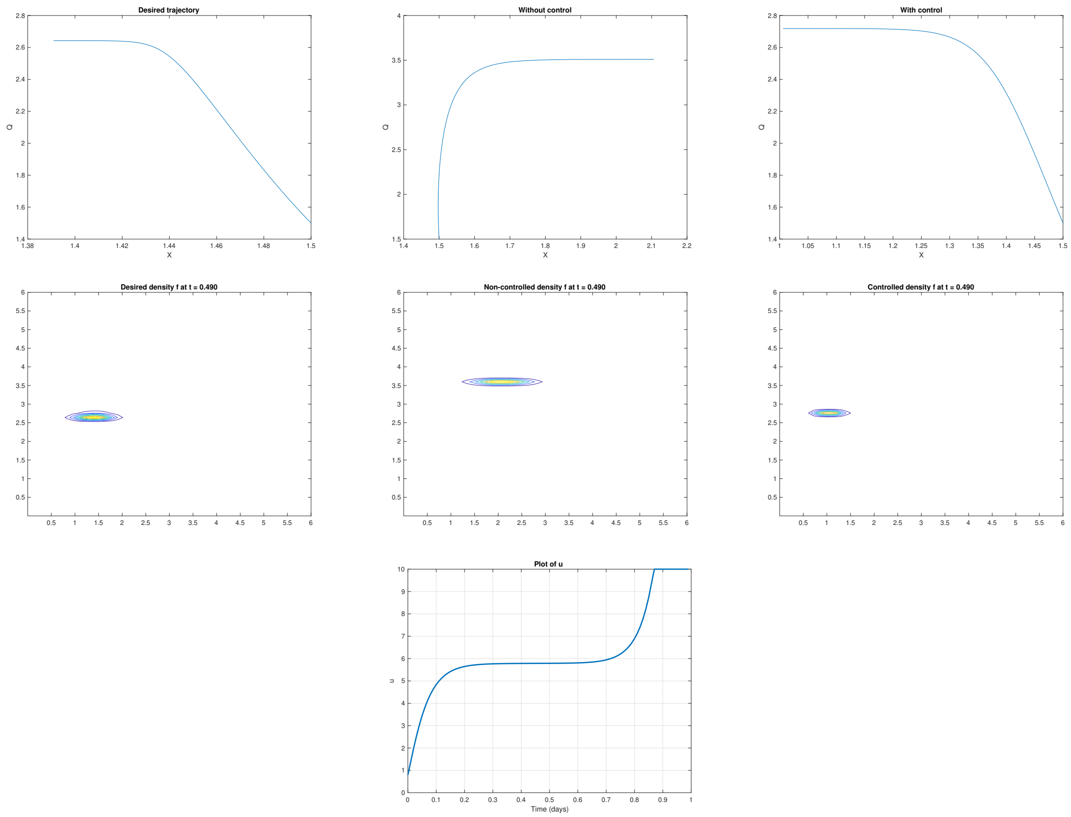

Figure 5.4: Test Case 2: Optimal control results

In each set of plots, the first row is composed of three figures. The first figure represents the desired trajectory, the second figure represents the trajectory without control, and the third figure represents the trajectory with control strategies. Progressing to the following row, again composed of three figures, the first figure represents the desired Probability Density Function (PDF) at the specific time point of $t = 0.49$. The second figure in this row represents the PDF without control, and the last figure represents the controlled PDF. Concluding the sequence, the last row contains the plot of the controls.

We observe that in both cases, the control drives the PDF to the desired state in an accurate way. The major difference between the two test cases is the asymptotic level of the desired value of Q, which is lower in the second case. For this reason, we also observe that the control value is higher in the second case compared to the first case.

CHAPTER 6

Conclusion

In the first part of this dissertation, We used an ODE system to represent the dynamics of prostate cancer. We solved a parameter estimation problem to obtain the unknown parameters of the ODE system from noisy data. We chose some case studies to test our work. We used the same true parameters but different initial guesses. The results of the estimated parameters showed that our estimated parameters are very close to the true parameters.

Next, we formulated a robust framework and solved an optimal control problem for obtaining optimal androgen suppression treatments for treating prostate cancer patients. In the plots, we saw that the number of androgen-dependent and independent cancer cells are decreasing. We also note that androgen level decreases until it reaches the normal level. Also, the resultant solution of the optimal control problem demonstrated that the treatment profile changes over time, unlike the standard constant profile, which leads to a more efficiient treatment regime. Results of numerical experiments suggest the feasibility and robustness of the framework for getting the optimal therapies. However, from the parameter estimation results, we noted that the results are very accurate. To address this issue, we used a stochastic model for cancer dynamics based on the Liouville equation.

Next, we have presented a Liouville framework for parameter estimation and optimal control in prostate cancer. The primary rationale behind this framework is the uncertainty in carrying out similar trials in a given environment, which leads to random evolution mechanisms. We compared the Liouville parameter estimation framework and the ODE parameter estimation framework and demonstrated that the Liouville parameter estimation framework provides a more accurate and robust parameter estimation technique. Finally, we also implemented the Liouville optimal control framework, and the results validated the robustness and accuracy of our proposed methods.

APPENDIX A

Derivation of ODE optimality system

A.1 The first adjoint equation:

$$
\begin{aligned}
\frac{dL}{dX_1} =& \lim_{\varepsilon\to 0} \frac{L\left(X_1+\varepsilon\bar{X}_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0 \\
=& \lim_{\varepsilon\to 0} \frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T \left(\left(X_1+\varepsilon\bar{X}_1\right)(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \right.\\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 + \int_0^T \left[-\left(X_1+\varepsilon\bar{X}_1\right)\frac{d\tilde{X}_1}{dt}\right.\\
&- \left(\mu_m\left(1-\frac{q_1}{Q}\right)\left(X_1+\varepsilon\bar{X}_1\right) - d_1\left(X_1+\varepsilon\bar{X}_1\right) - m_1(Q)\left(X_1+\varepsilon\bar{X}_1\right)\right.\\
&+ m_2(Q)X_2)) \tilde{X}_1 dt + \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt}\right.\\
&- \left.\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)\left(X_1+\varepsilon\bar{X}_1\right)\right)\tilde{X}_2\right] dt\\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right] dt\\
&+ \left[\left(X_1+\varepsilon\bar{X}_1\right)(T)\left(\tilde{X}_1\right)(T) - \left(X_1+\varepsilon\bar{X}_1\right)(0)\left(\tilde{X}_1\right)(0)\right]\\
&+ \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] + \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]\\
&- \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right.\\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2\\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt\\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt\\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right] dt\\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] + \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left(\left(X_1+\varepsilon\bar{X}_1\right)(t)-X_1{}^*(t)\right)^2dt+\int_0^T\left[-\left(X_1+\varepsilon\bar{X}_1\right)\frac{d\tilde{X}_1}{dt}\right.\right.\\
&-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\left(X_1+\varepsilon\bar{X}_1\right)-d_1\left(X_1+\varepsilon\bar{X}_1\right)-m_1\left(Q\right)\left(X_1+\varepsilon\bar{X}_1\right)+m_2\left(Q\right)X_2\right)\tilde{X}_1dt\\
&+\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)\left(X_1+\varepsilon\bar{X}_1\right)\right)\tilde{X}_2\right]dt\\
&+\left[\left(X_1+\varepsilon\bar{X}_1\right)(T)\left(\tilde{X}_1\right)(T)-\left(X_1+\varepsilon\bar{X}_1\right)(0)\left(\tilde{X}_1\right)(0)\right]\\
&-\left(\frac{\alpha_1}{2}\int_0^T\left(X_1(t)-X_1{}^*(t)\right)^2dt\right.\\
&+\int_0^T\left[-X_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\tilde{X}_1\right]dt\\
&+\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\tilde{X}_2\right]dt\\
&+\left[X_1(T)\tilde{X}_1(T)-X_1(0)\tilde{X}_1(0)\right]))
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left(\left(X_1+\varepsilon\bar{X}_1\right)(t)-X_1{}^*(t)\right)^2dt+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1\right.\right.\right.\\
&-d_1\varepsilon\bar{X}_1-m_1\left(Q\right)\varepsilon\bar{X}_1\tilde{X}_1dt+\int_0^T m_1\left(Q\right)\varepsilon\bar{X}_1\tilde{X}_2dt+\left[\varepsilon\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]\\
&-\frac{\alpha_1}{2}\int_0^T\left(X_1(t)-X_1{}^*(t)\right)^2dt)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left(\left(X_1+\varepsilon\bar{X}_1\right)(t)-X_1{}^*(t)\right)^2dt-\frac{\alpha_1}{2}\int_0^T\left(X_1(t)-X_1{}^*(t)\right)^2dt\right.\\
&+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1-d_1\varepsilon\bar{X}_1-m_1\left(Q\right)\varepsilon\bar{X}_1\right)\tilde{X}_1\right]dt\\
&\left.+\int_0^T m_1\left(Q\right)\varepsilon\bar{X}_1\tilde{X}_2dt+\left[\varepsilon\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]\right)
\end{aligned}
$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\left(\int_0^T\left(\left(X_1+\varepsilon\bar{X}_1\right)(t)-X_1{}^*(t)\right)^2dt-\int_0^T\left(X_1(t)-X_1{}^*(t)\right)^2dt\right)\right.$$
$$+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1-d_1\varepsilon\bar{X}_1-m_1(Q)\,\varepsilon\bar{X}_1\right)\tilde{X}_1\right]dt$$
$$\left.+\int_0^T m_1(Q)\,\varepsilon\bar{X}_1\tilde{X}_2dt+\left[\varepsilon\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]\right)$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left[\left(X_1+\varepsilon\bar{X}_1\right)^2-2X_1{}^*\left(X_1+\varepsilon\bar{X}_1\right)+\left(X_1{}^*(t)\right)^2-\left(X_1(t)\right)^2-2\left(X_1(t)X_1{}^*(t)\right.\right.\right.$$
$$+\left(X_1{}^*(t)\right)^2dt+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1-d_1\varepsilon\bar{X}_1-m_1(Q)\,\varepsilon\bar{X}_1\right)\tilde{X}_1\right.$$
$$+m_1(Q)\,\varepsilon\bar{X}_1\tilde{X}_2dt+\left[\varepsilon\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\tilde{X}_1(0)\right])$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left[\left(X_1(t)\right)^2+2\varepsilon X_1(t)\bar{X}_1(t)+\left(\varepsilon\bar{X}_1\right)^2-2X_1(t)X_1^*(t)-2\varepsilon X_1^*(t)\bar{X}_1(t)+\left(X_1^*(t)\right)^2\right.\right.$$
$$-\left(X_1(t)\right)^2-2X_1(t)X_1^*(t)+\left(X_1^*(t)\right)^2dt$$
$$+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1-d_1\varepsilon\bar{X}_1-m_1(Q)\,\varepsilon\bar{X}_1\right)\tilde{X}_1+m_1(Q)\,\varepsilon\bar{X}_1\tilde{X}_2\right]dt$$
$$+\left[\varepsilon\bar{X}_1(\ T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T\left[2\varepsilon X_1(t)\bar{X}_1(t)+\left(\varepsilon\bar{X}_1\right)^2-2\varepsilon X_1{}^*(t)\bar{X}_1(t)\right]dt+\int_0^T\left[-\varepsilon\bar{X}_1\frac{d\tilde{X}_1}{dt}\right.\right.$$
$$-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\bar{X}_1-d_1\varepsilon\bar{X}_1-m_1(Q)\,\varepsilon\bar{X}_1\right)\tilde{X}_1\ +m_1(Q)\,\varepsilon\bar{X}_1\tilde{X}_2\Big]\,dt$$
$$+\left[\varepsilon\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$=\lim_{\varepsilon\to 0}\frac{\alpha_1}{2}\int_0^T [2\ \frac{1}{\varepsilon}\varepsilon X_1(t)\bar{X}_1(t)+\frac{1}{\varepsilon}\left(\varepsilon\bar{X}_1\right)^2-2\varepsilon\frac{1}{\varepsilon}X_1{}^*(t)\bar{X}_1(t)\Big]\,dt$$
$$+\int_0^T\left[-\varepsilon\frac{1}{\varepsilon}\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_1-d_1\varepsilon\frac{1}{\varepsilon}\bar{X}_1-m_1\left(Q\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_1\right)\tilde{X}_1\right.$$
$$\left.+m_1\left(Q\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_1\tilde{X}_2\right]dt+\left[\varepsilon\frac{1}{\varepsilon}\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\varepsilon\frac{1}{\varepsilon}\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$=\lim_{\varepsilon\to 0}\frac{\alpha_1}{2}\int_0^T [2X_1(t)\bar{X}_1(t)+\frac{1}{\varepsilon}\varepsilon^2\bar{X}_1^2-2X_1{}^*(t)\bar{X}_1(t)\Big]\,dt$$
$$+\int_0^T\left[-\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\bar{X}_1-d_1\bar{X}_1-m_1\left(Q\right)\bar{X}_1\right)\tilde{X}_1\right.$$
$$\left.+m_1\left(Q\right)\bar{X}_1\tilde{X}_2\right]dt+\left[\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$=\alpha_1\int_0^T\left(X_1(t)\ -X_1{}^*(t)\right)\bar{X}_1(t)dt+\int_0^T\left[-\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\bar{X}_1-d_1\bar{X}_1-m_1\left(Q\right)\bar{X}_1\right)\tilde{X}_1\right.$$
$$\left.+m_1\left(Q\right)\bar{X}_1\tilde{X}_2\right]dt+\left[\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\bar{X}_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$=\int_0^T\left[\left(X_1(t)-X_1{}^*(t)\right)\alpha_1\bar{X}_1(t)-\bar{X}_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)\bar{X}_1-d_1\bar{X}_1-m_1\left(Q\right)\bar{X}_1\right)\tilde{X}_1\right.$$
$$\left.+m_1\left(Q\right)\bar{X}_1\tilde{X}_2\right]dt+\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\bar{X}_1(0)\left(\tilde{X}_1\right)(0)=0$$

$$=\int_0^T-\bar{X}_1\frac{d\tilde{X}_1}{dt}+\left[\left(X_1(t)-X_1{}^*(t)\right)\alpha_1-\left(\mu_m\left(1-\frac{q_1}{Q}\right)-d_1-m_1\left(Q\right)\right)\tilde{X}_1\right.$$
$$\left.+m_1\left(Q\right)\tilde{X}_2\right]\bar{X}_1(t)dt+\bar{X}_1(T)\left(\tilde{X}_1\right)(T)-\bar{X}_1(0)\left(\tilde{X}_1\right)(0)=0$$

Since $\left(\tilde{X}_1\right)(0)=0$ Remove the test function $\bar{X}_1(t)$

$$=\int_0^T-\frac{d\tilde{X}_1}{dt}+\left[\left(X_1(t)-X_1{}^*(t)\right)\alpha_1-\left(\mu_m\left(1-\frac{q_1}{Q}\right)-d_1-m_1\left(Q\right)\right)\tilde{X}_1+m_1\left(Q\right)\tilde{X}_2\right]dt$$
$$+\left(\tilde{X}_1\right)(T)=0$$

So, the first adjoint equation

$$\frac{d\tilde{X_1}}{dt} = (X_1(t) - {X_1}^*(t))\,\alpha_1 - \left(\mu_m\left(1 - \frac{q_1}{Q}\right) - d_1 - m_1\,(Q)\right)\tilde{X}_1 + m_1\,(Q)\,\tilde{X}_2$$

$$Condition: \left(\tilde{X}_1\right)(T) = 0$$

A.2 The second adjoint equation:

$$\frac{dL}{dX_2} = \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2+\varepsilon\bar{X}_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0$$

$$= \lim_{\varepsilon\to 0} \frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-X_1{}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(\left(X_2+\varepsilon\bar{X}_2\right)(t) - X_2{}^*(t)\right)^2 dt\right.$$

$$+ \frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 + \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt}\right.$$

$$\left. - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)(t)\right)\tilde{X}_1\right] dt$$

$$+ \int_0^T \left[-\left(X_2+\varepsilon\bar{X}_2\right)\frac{d\tilde{X}_2}{dt}\right.$$

$$- \left(\mu_m\left(1-\frac{q_2}{Q}\right)\left(X_2+\varepsilon\bar{X}_2\right) - d_2\left(X_2+\varepsilon\bar{X}_2\right) - m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)\right.$$

$$+ m_1(Q)X_1\tilde{X}_2 dt + \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right] dt$$

$$+ \left[X_1(T)\left(\tilde{X}_1\right)(T) - X_1(0)\left(\tilde{X}_1\right)(0)\right]$$

$$+ \left[\left(X_2+\varepsilon\bar{X}_2\right)(T)\left(\tilde{X}_2\right)(T) - \left(X_2+\varepsilon\bar{X}_2\right)(0)\left(\tilde{X}_2\right)(0)\right]$$

$$+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right] - \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-X_1{}^*(t)\right)^2 dt\right.$$

$$+ \frac{\alpha_2}{2}\int_0^T \left(X_2(t)-X_2{}^*(t)\right)^2 dt + \frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2$$

$$+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt$$

$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt$$

$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A-v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right] dt$$

$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$

$$\left.\left. + \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]\right)\right)$$

$$
\begin{aligned}
=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}&\left(\frac{\alpha_2}{2}\int_0^T\left(\left(X_2+\varepsilon\bar{X}_2\right)(t)-X_2{}^*(t)\right)^2dt+\int_0^T m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)(t)\tilde{X}_1dt\right.\\
&+\int_0^T\left[-\left(X_2+\varepsilon\bar{X}_2\right)\frac{d\tilde{X}_2}{dt}\right.\\
&\left.-\left(\mu_m\left(1-\frac{q_2}{Q}\right)\left(X_2+\varepsilon\bar{X}_2\right)-d_2\left(X_2+\varepsilon\bar{X}_2\right)-m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)\ +m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&+\left[\left(X_2+\varepsilon\bar{X}_2\right)(T)\left(\tilde{X}_2\right)(T)-\left(X_2+\varepsilon\bar{X}_2\right)(0)\left(\tilde{X}_2\right)(0)\right]\\
&-\left(\frac{\alpha_2}{2}\int_0^T\left(X_2(t)-X_2{}^*(t)\right)^2dt+\int_0^T m_2(Q)X_2\right)\tilde{X}_1dt\\
&+\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2(Q)X_2+m_1(Q)X_1\tilde{X}_2\right]dt\\
&\left.+\left[X_2(T)\tilde{X}_2(T)-X_2(0)\tilde{X}_2(0)\right]\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}&\left(\frac{\alpha_2}{2}\int_0^T\left(\left(X_2+\varepsilon\bar{X}_2\right)(t)-X_2{}^*(t)\right)^2dt+\int_0^T\left(m_2(Q)X_2+m_2(Q)\varepsilon\bar{X}_2\right)\right)\left(\tilde{X}_1\right)dt\\
&+\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\varepsilon\bar{X}_2\frac{d\tilde{X}_2}{dt}-\mu_m\left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2-\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2\tilde{X}_2+d_2X_2\tilde{X}_2\right.\\
&\left.+d_2\varepsilon\bar{X}_2\tilde{X}_2-m_2(Q)X_2\tilde{X}_2-m_2(Q)\varepsilon\bar{X}_2\tilde{X}_2+m_1(Q)X_1\tilde{X}_2\right]dt\\
&+\left[\left(X_2(T)\left(\tilde{X}_2\right)(T)+\varepsilon\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-X_2(0)\left(\tilde{X}_2\right)(0)-\varepsilon\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]\right.\\
&+\left(\frac{\alpha_2}{2}\int_0^T\left(X_2(t)-X_2{}^*(t)\right)^2dt+\int_0^T m_2(Q)X_2\tilde{X}_1dt\right.\\
&+\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2(Q)X_2+m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&\left.+\left[X_2(T)\tilde{X}_2(T)-X_2(0)\tilde{X}_2(0)\right]\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}&\left(\frac{\alpha_2}{2}\int_0^T\left(\left(X_2+\varepsilon\bar{X}_2\right)(t)-X_2{}^*(t)\right)^2dt+\int_0^T m_2(Q)\varepsilon\bar{X}_2\tilde{X}_1dt\right.\\
&+\int_0^T\left[-\varepsilon\bar{X}_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2-d_2\varepsilon\bar{X}_2-m_2(Q)\varepsilon\bar{X}_2\right)\tilde{X}_2\right]dt\\
&\left.+\left[\varepsilon\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-\varepsilon\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]-\frac{\alpha_2}{2}\int_0^T\left(X_2(t)-X_2{}^*(t)\right)^2dt\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_2}{2}\int_0^T \left(\left(X_2+\varepsilon\bar{X}_2\right)(t)-X_2{}^*(t)\right)^2 dt-\frac{\alpha_2}{2}\int_0^T \left(X_2(t)-X_2{}^*(t)\right)^2 dt\right.\\
&+\int_0^T m_2\left(Q\right)\varepsilon\bar{X}_2\tilde{X}_1 dt\\
&+\int_0^T\left[-\varepsilon\bar{X}_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2-d_2\varepsilon\bar{X}_2-m_2\left(Q\right)\varepsilon\bar{X}_2\right)\tilde{X}_2\right]dt\\
&\left.+\left[\varepsilon\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-\varepsilon\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_2}{2}\int_0^T\left[\left(X_2(t)\right)^2+2\varepsilon X_2(t)\bar{X}_2(t)\right.\right.\\
&+\left(\varepsilon\bar{X}_2\right)^2-2X_2(t)X_2{}^*(t)-2\varepsilon X_2{}^*(t)\bar{X}_2(t)+\left(X_2{}^*(t)\right)^2\\
&\left.-\left(X_2(t)\right)^2-2X_2(t)X_2{}^*(t)+\left(X_2{}^*(t)\right)^2\right]dt+\int_0^T m_2\left(Q\right)\varepsilon\bar{X}_2\tilde{X}_1 dt\\
&+\int_0^T\left[-\varepsilon\bar{X}_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2-d_2\varepsilon\bar{X}_2-m_2\left(Q\right)\varepsilon\bar{X}_2\right)\tilde{X}_2\right]dt\\
&+\left[\varepsilon\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-\varepsilon\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{\alpha_2}{2}\int_0^T [2\varepsilon\,\frac{1}{\varepsilon}X_2(t)\bar{X}_2(t)+\frac{1}{\varepsilon}\left(\varepsilon\bar{X}_2\right)^2-2\varepsilon\frac{1}{\varepsilon}X_2^*(t)\bar{X}_2(t)\Big]dt\\
&+\int_0^T\left[-\varepsilon\frac{1}{\varepsilon}\bar{X}_2\frac{d\tilde{X}_2}{dt}-\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_2-d_2\varepsilon\frac{1}{\varepsilon}\bar{X}_2-m_2\left(Q\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_2\right.\\
&\left.+m_2\left(Q\right)\varepsilon\frac{1}{\varepsilon}\bar{X}_2\tilde{X}_1\right]dt+\left[\varepsilon\frac{1}{\varepsilon}\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-\varepsilon\frac{1}{\varepsilon}\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{\alpha_2}{2}\int_0^T\left[2X_2(t)\bar{X}_2(t)+\frac{1}{\varepsilon}\varepsilon^2\left(\bar{X}_2\right)^2-2X_2^*(t)\bar{X}_2(t)\right]dt\\
&+\int_0^T\left[-\bar{X}_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)\bar{X}_2-d_2\bar{X}_2-m_2\left(Q\right)\bar{X}_2\right)\tilde{X}_2+m_2\left(Q\right)\bar{X}_2\tilde{X}_1\right]dt\\
&+\left[\bar{X}_2(T)\left(\tilde{X}_2\right)(T)-\bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{\alpha_2}{2}\int_0^T \left[2X_2(t)\bar{X}_2(t) - 2X_2^*(t)\bar{X}_2(t)\right] dt \\
&+\int_0^T \left[-\bar{X}_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\bar{X}_2 - d_2\bar{X}_2 - m_2\left(Q\right)\bar{X}_2\right)\tilde{X}_2 + m_2\left(Q\right)\bar{X}_2\tilde{X}_1\right] dt \\
&+\left[\ \bar{X}_2(T)\left(\tilde{X}_2\right)(T) - \bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\alpha_2\int_0^T \left[X_2(t)\ \bar{X}_2(t) - X_2{}^*(t)\bar{X}_2(t)\right] dt \\
&+\int_0^T \left[-\bar{X}_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\bar{X}_2 - d_2\bar{X}_2 - m_2\left(Q\right)\bar{X}_2\right)\tilde{X}_2 + m_2\left(Q\right)\bar{X}_2\tilde{X}_1\right] dt \\
&+\left[\bar{X}_2(T)\left(\tilde{X}_2\right)(T) - \bar{X}_2(0)\left(\tilde{X}_2\right)(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\int_0^T \left(X_2(t) - X_2{}^*(t)\right)\alpha_2\bar{X}_2(t) - \bar{X}_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\bar{X}_2 - d_2\bar{X}_2 - m_2\left(Q\right)\bar{X}_2\right)\tilde{X}_2 \\
&+m_2\left(Q\right)\bar{X}_2\tilde{X}_1 dt + \bar{X}_2(T)\left(\tilde{X}_2\right)(T) - \bar{X}_2(0)\left(\tilde{X}_2\right)(0) \\
&+\bar{X}_2(T)\left(\tilde{X}_2\right)(T) - \bar{X}_2(0)\left(\tilde{X}_2\right)(0)
\end{aligned}
$$

$$
\begin{aligned}
=&\int_0^T -\bar{X}_2\frac{d\tilde{X}_2}{dt} + \left(X_2(t) - X_2{}^*(t)\right)\alpha_2\bar{X}_2(t) - \left(\mu_m\left(1-\frac{q_2}{Q}\right) - d_2 - m_2\left(Q\right)\right)\tilde{X}_2\bar{X}_2 \\
&+m_2\left(Q\right)\bar{X}_2\tilde{X}_1 dt + \bar{X}_2(T)\left(\tilde{X}_2\right)(T) - \bar{X}_2(0)\left(\tilde{X}_2\right)(0) = 0
\end{aligned}
$$

Since $\left(\tilde{X}_2\right)(0) = 0$. Remove the test function $\bar{X}_2(t)$

$$
\begin{aligned}
=&\int_0^T \left(-\frac{d\tilde{X}_2}{dt} + \left(X_2(t) - X_2{}^*(t)\right)\alpha_2 - \left(\mu_m\left(1-\frac{q_2}{Q}\right) - d_2 - m_2\left(Q\right)\right)\tilde{X}_2 + m_2\left(Q\right)\tilde{X}_1\right) dt \\
&+\left(\tilde{X}_2\right)(T) = 0
\end{aligned}
$$

$$
\begin{aligned}
&-\frac{d\tilde{X}_2}{dt} + \left(X_2(t) - X_2{}^*(t)\right)\alpha_2 - \left(\mu_m\left(1-\frac{q_2}{Q}\right) - d_2 - m_2\left(Q\right)\right)\tilde{X}_2 + m_2\left(Q\right)\tilde{X}_1 dt \\
&+\left(\tilde{X}_2\right)(T) = 0
\end{aligned}
$$

So, the second adjoint equation:

$$\frac{d\tilde{X}_2}{dt} = (X_2(t) - {X_2}^*(t))\,\alpha_2 - \left(\mu_m \left(1 - \frac{q_2}{Q}\right)\tilde{X}_2 - d_2\tilde{X}_2 - m_2\,(Q)\,\tilde{X}_2\right) + m_2\,(Q)\,\tilde{X}_1 dt,$$

$$\left(\tilde{X}_2\right)(T) = 0$$

A.3 The third adjoint equation:

$$\frac{dL}{dQ} = \lim_{\varepsilon \to 0} \frac{L\left(X_1, X_2, Q + \varepsilon \bar{Q}, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0$$

$$= \lim_{\varepsilon \to 0} \frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T (X_1(t) - {X_1}^*(t))^2\, dt + \frac{\alpha_2}{2}\int_0^T (X_2(t) - {X_2}^*(t))^2\, dt\right.$$

$$+ \frac{\alpha_3}{2}\int_0^T \left((Q + \varepsilon\bar{Q})(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2$$

$$+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{(Q + \varepsilon\bar{Q})(t)}\right) X_1 - d_1X_1 - m_1\left((Q + \varepsilon\bar{Q})(t)\right) X_1\right.\right.$$

$$+ m_2\left((Q + \varepsilon\bar{Q})(t)\right) X_2 \left(\tilde{X}_1\right) dt$$

$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1 - \frac{q_2}{(Q + \varepsilon\bar{Q})(t)}\right) X_2 - d_2X_2 - m_2\left((Q + \varepsilon\bar{Q})(t)\right) X_2\right.\right.$$

$$+ m_1\left((Q + \varepsilon\bar{Q})(t)\right) X_1 \left(\tilde{X}_2\right) dt$$

$$+ \int_0^T \left[-(Q + \varepsilon\bar{Q})\frac{d\tilde{Q}}{dt}\right.$$

$$- \left(v_m\frac{q_m - (Q + \varepsilon\bar{Q})}{q_m - q}\frac{A}{A + v_h} - \mu_m(((Q + \varepsilon\bar{Q}) - q) - b(Q + \varepsilon\bar{Q}))\tilde{Q}\right] dt$$

$$+ \left[X_1(T)\left(\tilde{X}_1\right)(T) - X_1(0)\left(\tilde{X}_1\right)(0)\right] + \left[X_2(T)\left(\tilde{X}_2\right)(T) - X_2(0)\left(\tilde{X}_2\right)(0)\right]$$

$$+ [(Q + \varepsilon\bar{Q})(T)(\tilde{Q})(T) - (Q + \varepsilon\bar{Q})(0)(\tilde{Q})(0)] - \left(\frac{\alpha_1}{2}\int_0^T (X_1(t) - {X_1}^*(t))^2\, dt\right.$$

$$+ \frac{\alpha_2}{2}\int_0^T (X_2(t) - {X_2}^*(t))^2\, dt + \frac{\alpha_3}{2}\int_0^T (Q(t) - Q^*(t))^2\, dt + \frac{\beta}{2}\|\theta\|^2$$

$$+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{Q}\right) X_1 - d_1X_1 - m_1(Q) X_1 + m_2(Q) X_2\right)\tilde{X}_1\right] dt$$

$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1 - \frac{q_2}{Q}\right) X_2 - d_2X_2 - m_2(Q) X_2 + m_1(Q) X_1\right)\tilde{X}_2\right] dt$$

$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\tilde{Q}\right] dt$$

$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$

$$+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]))$$

$$
\begin{aligned}
=&\lim_{\epsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q^*dt+\frac{\alpha_1}{2}\left((Q+\varepsilon\bar{Q})(T)-Q\right)^2-\frac{\alpha_1}{2}\left(Q(T)-Q\right)^2\right.\\
&+\int_0^T\left[\frac{q_1}{(Q+\varepsilon\bar{Q})}\mu_m X_1\tilde{X}_1+\frac{q_2}{(Q+\varepsilon\bar{Q})}\mu_m X_2\tilde{X}_2+\frac{c_1k_1X_1\tilde{X}_1}{Q+\varepsilon\bar{Q}+k_1}-\frac{c_1k_1X_1\tilde{X}_2}{Q+\varepsilon\bar{Q}+k_1}\right.\\
&-\frac{Q+\varepsilon\bar{Q}}{Q+\varepsilon\bar{Q}+k_2}c_2X_2\bar{X}_1+\frac{Q+\varepsilon\bar{Q}}{Q+\varepsilon\bar{Q}+k_2}c_2X_2\bar{X}_2-\frac{q_1}{Q}\mu_m X_1\bar{X}_1-\frac{q_2}{Q}\mu_m X_2\tilde{X}_2-\frac{c_1k_1X_1\tilde{X}_1}{Q+k_1}\\
&\left.+\frac{c_1k_1X_1\bar{X}_2}{Q+k_1}+\frac{c_2QX_2\bar{X}_1}{Q+k_2}-\frac{c_2QX_2\bar{X}_2}{Q+k_2}\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\bar{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\right.\\
&\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+[(Q+\varepsilon\bar{Q})(T)\tilde{Q}(T)-(Q+\varepsilon\bar{Q})(0)\tilde{Q}(0)]\\
&\left.-[Q(T)\tilde{Q}(T)-Q(0)\tilde{Q}(0)]\right)\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q^*dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q^*\right)\right.\\
&+\int_0^T\left[\frac{\mu_m}{(Q+\varepsilon Q)}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\frac{c_1k_1X_1}{Q+\varepsilon Q+k_1}\left(\bar{X}_1-\bar{X}_2\right)\right.\\
&+\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon Q+k_2}\left(\tilde{X}_2-\tilde{X}_1\right)\\
&\left.-\frac{\mu_m}{Q}\left(q_1X_1\bar{X}_1+q_2X_2\bar{X}_2\right)+\frac{c_1k_1X_1}{Q+k_1}\left(\tilde{X}_2-\bar{X}_1\right)+\frac{c_2QX_2}{Q+k_2}\left(\bar{X}_1-\bar{X}_2\right)\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\tilde{Q}\right.\\
&\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q^*dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q^*\right)\right.\\
&+\int_0^T\left[\frac{\mu_m}{(Q+\varepsilon\tilde{Q})}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)-\frac{\mu m}{Q}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\frac{c1k_1X_1}{Q+\varepsilon\bar{Q}+k_1}\left(\tilde{X}_1-\tilde{X}_2\right)\right.\\
&\left.-\frac{c_1k_1X_1}{Q+k_1}\left(\tilde{X}_1-\tilde{X}_2\right)+\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon\bar{Q}+k_2}\left(\bar{X}_2-\tilde{X}_1\right)-\frac{c_2QX_2}{Q+k_2}\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\tilde{Q}\right.\\
&\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)
\end{aligned}
$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\ddot{Q}Q^* \quad dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q^*\right)\right.$$

$$+\int_0^T\left[\left(\frac{\mu_m}{(Q+\varepsilon\bar{Q})}-\frac{\mu_m}{Q}\right)\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\left(\frac{1}{Q+\varepsilon\bar{Q}+k1}-\frac{1}{Q+k_1}\right)\right.$$

$$\left.c_1k_1X_1\left(\tilde{X}_1-\tilde{X}_2\right)+\left(\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon\bar{Q}+k_2}-\frac{c_2QX_2}{Q+k_2}\right)\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt$$

$$+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-v_m\frac{-\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\tilde{Q}\right.$$

$$\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q^*dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q^*\right)\right.$$

$$+\int_0^T\left[\left(\frac{\mu_mQ-Q\mu_m-\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q}\right)\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)\right.$$

$$+\left(\frac{Q+k_1-Q-\varepsilon\bar{Q}-k_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)}\right)c_1k_1X_1\left(\tilde{X}_1-\tilde{X}_2\right)$$

$$+\left(\frac{c_2QX_2Q+c_2QX_2k_2+c_2\varepsilon\bar{Q}X_2Q+c_2\varepsilon\bar{Q}X_2k_2-c_2QX_2Q-c_2\varepsilon\bar{Q}QX_2-c_2QX_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)}\right)\left(\tilde{X}_2\right.$$

$$\left.\left.-\tilde{X}_1\right)\right]dt+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(v_m\frac{\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\tilde{Q}\right]dt$$

$$+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0))$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_3}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q^* \quad dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q^*\right)\right.$$

$$+\int_0^T\left[\left(\frac{-\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q}\right)\left(q_1X_1\bar{X}_1+q_2X_2\bar{X}_2\right)+\left(\frac{-\varepsilon\bar{Q}c_1k_1X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)}\right)\left(\bar{X}_1-\bar{X}_2\right)\right.$$

$$\left.+\left(\frac{c_2\varepsilon\bar{Q}X_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)}\right)\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt$$

$$+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(v_m\frac{\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}\right)\tilde{Q}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)$$

$$-\varepsilon\bar{Q}(0)\tilde{Q}(0))$$

$$= \lim_{\varepsilon\to 0} \frac{1}{\varepsilon} \left(\frac{\alpha_3}{2} \int_0^r 2Q\varepsilon\bar{Q} + (\varepsilon\bar{Q})^2 - 2\varepsilon\bar{Q}Q^* - \left(\frac{\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q} \right) \left(q_1 X_1 \bar{X}_1 + q2 X_2 \bar{X}_2 \right) \right.$$

$$- \left(\frac{\varepsilon\bar{Q}c_1 k_1 X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)} \right) \left(\tilde{X}_1 - \bar{X}_2 \right) + \left(\frac{c_2 \varepsilon\bar{Q} X_2 k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)} \right) \left(\tilde{X}_2 - \bar{X}_1 \right)$$

$$\left. - \varepsilon\bar{Q}\frac{d\tilde{Q}}{dt} + \left(v_m \frac{\varepsilon\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m \varepsilon\bar{Q} + b\varepsilon\bar{Q} \right) \tilde{Q} \right) dt$$

$$+ \frac{\alpha_1}{2} \left(2\varepsilon Q(T)\bar{Q}(T) + (\varepsilon\bar{Q}(T))^2 - 2\varepsilon\bar{Q}(T)Q^* \right) + \varepsilon\bar{Q}(T)\tilde{Q}(T) - \varepsilon\bar{Q}(0)\tilde{Q}(0)$$

$$= \lim_{\varepsilon\to 0} \left(\frac{\alpha_3}{2} \int_0^\tau 2Q\bar{Q} + (\varepsilon\bar{Q})^2 - 2\bar{Q}Q^* - \left(\frac{\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) \right.$$

$$- \left(\frac{\bar{Q}c_1 k_1 X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)} \right) \left(\bar{X}_1 - \tilde{X}_2 \right) + \left(\frac{c_2 \bar{Q} X_2 k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)} \right) \left(\bar{X}_2 - \bar{X}_1 \right) - \bar{Q}\frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m \bar{Q} + b\bar{Q} \right) \tilde{Q} \right) dt$$

$$+ \frac{\alpha_1}{2} \left(2Q(T)\bar{Q}(T) + \varepsilon(\bar{Q}(T))^2 - 2\bar{Q}(T)Q^* \right) + \bar{Q}(T)\tilde{Q}(T) - \bar{Q}(0)\tilde{Q}(0)$$

$$= \left(\frac{\alpha_3}{2} \int_0^T 2Q\bar{Q} + (\varepsilon\bar{Q})^2 - 2\bar{Q}Q^* - \left(\frac{\bar{Q}\mu_m}{(Q)Q} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) \right.$$

$$- \left(\frac{\bar{Q}c_1 k_1 X_1}{(Q+k_1)(Q+k_1)} \right) \left(\tilde{X}_1 - \tilde{X}_2 \right) + \left(\frac{c_2 \bar{Q} X_2 k_2}{(Q+k_2)(Q+k_2)} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) - \bar{Q}\frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m \bar{Q} + b\bar{Q} \right) \tilde{Q} \right) dt + \frac{\alpha_1}{2} \left(2Q(T)\bar{Q}(T) - 2\bar{Q}(T)Q^* \right)$$

$$+ \bar{Q}(T)\tilde{Q}(T) - \bar{Q}(0)\tilde{Q}(0) = 0$$

Since $\tilde{Q}(0)$

Remove the test function $\bar{Q}(t)$

$$\left(\int_0^T \alpha_3 \left(Q - Q^* \right) - \left(\frac{\mu_m}{Q^2} \right) \left(q_1 X_1 \bar{X}_1 + q_2 X_2 \tilde{X}_2 \right) - \left(\frac{c_1 k_1 X_1}{\left(Q+k_1\right)^2} \right) \left(\bar{X}_1 - \tilde{X}_2 \right) \right.$$

$$+ \left(\frac{c_2 X_2 k_2}{\left(Q+k_2\right)^2} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) - \frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{1}{q_m - q} \frac{A}{A+v_h} + \mu_m + b \right) \tilde{Q} \right) dt + \frac{\alpha_1}{2} \left(2Q(T) - 2Q^* \right) + \tilde{Q}(T)$$

$$\frac{d\tilde{Q}}{dt} = \alpha_3\left(Q(t) - Q^*\right) - \left(\frac{\mu_m}{Q^2}\right)\left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2\right) - \left(\frac{c_1 k_1 X_1}{\left(Q + k_1\right)^2}\right)\left(\tilde{X}_1 - \tilde{X}_2\right)$$

$$+ \left(\frac{c_2 X_2 k_2}{\left(Q + k_2\right)^2}\right)\left(\tilde{X}_2 - \tilde{X}_1\right) + v_m \frac{\tilde{Q}}{q_m - q}\frac{A}{A + v_h} + \mu_m \tilde{Q} + b\tilde{Q},$$

$$\tilde{Q}(T) = \alpha_1\left(Q(T) - Q^*\right)$$

The third adjoint equation:

$$\frac{d\tilde{Q}}{dt} = \alpha_3\left(Q(t) - Q^*\right) - \left(\frac{\mu_m}{Q^2}\right)\left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2\right) - \left(\frac{c_1 k_1 X_1}{\left(Q + k_1\right)^2}\right)\left(\tilde{X}_1 - \tilde{X}_2\right)$$

$$+ \left(\frac{c_2 X_2 k_2}{\left(Q + k_2\right)^2}\right)\left(\tilde{X}_2 - \tilde{X}_1\right) + v_m \frac{\tilde{Q}}{q_m - q}\frac{A}{A + v_h} + \mu_m \tilde{Q} + b\tilde{Q},$$

$$\tilde{Q}(T) = \alpha_3\left(Q(T) - Q^*\right)$$

A.4 First forward equations:

$$\frac{dL}{d\tilde{X}_1} = \lim_{\varepsilon \to 0} \frac{L\left(X_1, X_2, Q, \tilde{X}_1 + \varepsilon \bar{\tilde{X}}_1, \tilde{X}_2, \tilde{Q}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0$$

$$= \lim_{\varepsilon \to 0} \frac{1}{\varepsilon} \left(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - X_1{}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - X_2{}^*(t)\right)^2 dt \right.$$

$$+ \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \|\theta\|^2$$

$$+ \int_0^T \left[-X_1 \frac{d\left(\tilde{X}_1 + \varepsilon \bar{\tilde{X}}_1\right)}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2\right) \right.$$

$$\left. \left(\tilde{X}_1 + \varepsilon \bar{\tilde{X}}_1\right) dt \right.$$

$$+ \int_0^T \left[-X_2 \frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1\right) \tilde{X}_2 \right] dt$$

$$+ \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ\right) \tilde{Q} \right] dt$$

$$+ \left[X_1(T)\left(\tilde{X}_1 + \varepsilon \tilde{\tilde{X}}_1\right)(T) - X_1(0)\left(\tilde{X}_1 + \varepsilon \tilde{X}_1\right)(0)\right]$$

$$+ \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] + \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]$$

$$- \left(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - X_1{}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - X_2{}^*(t)\right)^2 dt \right.$$

$$+ \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \|\theta\|^2$$

$$+ \int_0^T \left[-X_1 \frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2\right) \tilde{X}_1 \right] dt$$

$$+ \int_0^T \left[-X_2 \frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1\right) \tilde{X}_2 \right] dt$$

$$+ \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ\right) \tilde{Q} \right] dt$$

$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$

$$\left. \left. + \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right] \right) \right)$$

$$
\begin{aligned}
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_1\frac{d\left(\tilde{X}_1+\varepsilon\bar{\tilde{X}}_1\right)}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\right.\right.\\
&\quad \left(\tilde{X}_1+\varepsilon\bar{\tilde{X}}_1\right)]dt + X_1(T)\left(\tilde{X}_1+\varepsilon\bar{\tilde{X}}_1\right)(T) - X_1(0)\left(\tilde{X}_1+\varepsilon\bar{\tilde{X}}_1\right)\Big)(0)\\
&\quad -\left(\int_0^T\left[-X_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\tilde{X}_1\right]dt\right.\\
&\quad \left.+\left[X_1(T)\tilde{X}_1(T)-X_1(0)\tilde{X}_1(0)\right]\right)\\
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_1\frac{d\tilde{X}_1}{dt}-X_1\frac{d\varepsilon\bar{\tilde{X}}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\left(\tilde{X}_1\right)\right.\right.\\
&\quad -\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\varepsilon\bar{\tilde{X}}_1\quad]dt\\
&\quad +\left[X_1(T)\tilde{X}_1(T)+X_1(T)\varepsilon\bar{\tilde{X}}_1(T)-X_1(0)\tilde{X}_1(0)-X_1(0)\varepsilon\bar{\tilde{X}}_1(0)\right]\\
&\quad -\left(\int_0^T\left[-X_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\tilde{X}_1\right]dt\right.\\
&\quad \left.+\left[X_1(T)\tilde{X}_1(T)-X_1(0)\tilde{X}_1(0)\right]\right)\\
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_1\frac{d\varepsilon\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\left(\varepsilon\bar{\tilde{X}}_1\right)\right]dt\right.\\
&\qquad \left.+\left[X_1(T)\varepsilon\bar{\tilde{X}}_1(T)-X_1(0)\varepsilon\bar{\tilde{X}}_1(0)\right]\right)\\
&= \lim_{\varepsilon\to 0}\left(\int_0^T\left[-X_1\frac{1}{\varepsilon}\frac{d\varepsilon\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{X}}_1\right]dt\right.\\
&\qquad \left.+\frac{1}{\varepsilon}X_1(T)\varepsilon\bar{\tilde{X}}_1(T)-\frac{1}{\varepsilon}X_1(0)\varepsilon\bar{\tilde{X}}_1(0)\right)\\
&\ = \int_0^T\left[-X_1\frac{d\tilde{X}_1}{dt}-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\bar{\tilde{X}}_1\right]dt\\
&\qquad\quad + X_1(T)\bar{\tilde{X}}_1(T)-X_1(0)\bar{\tilde{X}}_1(0)\\
&\qquad\qquad = \int_0^T -X_1\frac{d\tilde{X}_1}{dt}+X_1(T)\bar{\tilde{X}}_1(T)-X_1(0)\bar{\tilde{X}}_1(0)-\\
&\qquad\qquad\quad \int_0^T\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1-d_1X_1-m_1\left(Q\right)X_1+m_2\left(Q\right)X_2\right)\bar{\tilde{X}}_1dt
\end{aligned}
$$

$$= \int_0^T \left(\frac{dX_1}{dt} - \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \bar{\tilde{X}}_1 \; dt$$

Remove the test function $\bar{\tilde{X}}_1$

$$= \int_0^T \left(\frac{dX_1}{dt} - \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \; dt = 0$$

$$\frac{dX_1}{dt} - \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 = 0$$

First forward equation:

$$\frac{dX_1}{dt} = \mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2$$

A.5 second forward equation:

$$
\begin{aligned}
\frac{dL}{d\tilde{X}_2} =& \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2 + \varepsilon\bar{\tilde{X}}_2, \tilde{Q}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0 \\
=& \lim_{\varepsilon\to 0} \frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right. \\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\left(\tilde{X}_1\right)\right] dt \\
&+ \int_0^T \left[-X_2\frac{d\left(\tilde{X}_2 + \varepsilon\bar{\tilde{X}}_2\right)}{dt} - \left(\mu_m\left(1 - \frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2\right.\right. \\
&\left.\left. + m_1(Q)X_1\right)\left(\tilde{X}_2 + \varepsilon\bar{\tilde{X}}_2\right)\right] dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\tilde{Q}\right] dt \\
&+ \left[X_1(T)\left(\tilde{X}_1\right)(T) - X_1(0)\left(\tilde{X}_1\right)(0)\right] \\
&+ \left[X_2(T)\left(\tilde{X}_2 + \varepsilon\bar{\tilde{X}}_2\right)(T) - X_2(0)\left(\tilde{X}_2 + \varepsilon\bar{\tilde{X}}_2\right)(0)\right] + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)] \\
&- \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right. \\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt \\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1 - \frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\tilde{Q}\right] dt \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&\left.\left. + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_2\frac{d\left(\tilde{X}_2+\varepsilon\bar{\tilde{X}}_2\right)}{dt}\right.\right.\\
&-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\left(\tilde{X}_2\ +\varepsilon\bar{\tilde{X}}_2\right)\Big]\,dt\\
&+\left[X_2(T)\left(\tilde{X}_2+\varepsilon\bar{\tilde{X}}_2\right)(T)-X_2(0)\left(\tilde{X}_2+\varepsilon\bar{\tilde{X}}_2\right)(0)\right]\\
&-\left(\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\tilde{X}_2\right]dt\right.\\
&\left.\left.+\left[X_2(T)\tilde{X}_2(T)-X_2(0)\tilde{X}_2(0)\right]\right)\right)\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-X_2\frac{d\varepsilon\bar{\tilde{X}}_2}{dt}\right.\right.\\
&-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\tilde{X}_2\\
&-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\varepsilon\bar{\tilde{X}}_2]dt\\
&+\left[X_2(T)\tilde{X}_2(T)+X_2(T)\varepsilon\bar{\tilde{X}}_2(T)-X_2(0)\tilde{X}_2(0)-X_2(0)\varepsilon\bar{\tilde{X}}_2(0)\right]\\
&\quad-\left(\int_0^T\left[-X_2\frac{d\tilde{X}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\tilde{X}_2\right]dt\right.\\
&\quad\left.\left.+\left[X_2(T)\tilde{X}_2(T)-X_2(0)\tilde{X}_2(0)\right]\right)\right)\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-X_2\frac{d\varepsilon\bar{\tilde{X}}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\left(\varepsilon\bar{\tilde{X}}_2\right)\right]dt\right.\\
&\quad+\left[X_2(T)\varepsilon\bar{\tilde{X}}_2(T)-X_2(0)\varepsilon\bar{\tilde{X}}_2(0)\right]\\
=&\lim_{\varepsilon\to 0}\int_0^T\left[-X_2\frac{1}{\varepsilon}\frac{d\varepsilon\bar{\tilde{X}}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{X}}_2\right]dt\\
&+\left[X_2(T)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{X}}_2(T)-X_2(0)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{X}}_2(0)\right]\\
&=\int_0^T\left[-X_2\frac{d\bar{\tilde{X}}_2}{dt}-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2-d_2X_2-m_2\left(Q\right)X_2+m_1\left(Q\right)X_1\right)\bar{\tilde{X}}_2\right]dt\\
&\quad+X_2(T)\bar{\tilde{X}}_2(T)-X_2(0)\bar{\tilde{X}}_2(0)=0
\end{aligned}
$$

$$= \int_0^T -X_2 \frac{d\bar{\tilde{X}}_2}{dt}\ dt + X_2(T)\bar{\tilde{X}}_2(T) - X_2(0)\bar{\tilde{X}}_2(0)$$

$$- \int_0^T \left[\left(\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2\left(Q\right) X_2 + m_1\left(Q\right) X_1 \right) \bar{\tilde{X}}_2 \right] = 0$$

$$= \int_0^T \left(\frac{dX_2}{dt} \bar{\tilde{X}}_2 - \mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2\left(Q\right) X_2 + m_1\left(Q\right) X_1 \right) \bar{\tilde{X}}_2 dt = 0$$

Remove the test function $\bar{\tilde{X}}_2$:

$$= \int_0^T \left(\frac{dX_2}{dt} - \mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2\left(Q\right) X_2 + m_1\left(Q\right) X_1 \right) dt = 0$$

Second forward equation:

$$\frac{dX_2}{dt} = \mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2\left(Q\right) X_2 + m_1\left(Q\right) X_1$$

A.6 Third forward equation:

$$
\begin{aligned}
\frac{dL}{d\tilde{Q}} &= \lim_{\varepsilon\to 0}\frac{L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}+\varepsilon\bar{\tilde{Q}}, \theta\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0 \\
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right. \\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{Q}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt \\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt \\
&+ \int_0^T \left[-Q\frac{d(\tilde{Q}+\varepsilon\bar{\tilde{Q}})}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A - v_h} - \mu_m(Q-q) - bQ\right)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})\right]dt \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+ \left[Q(T)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})(T) - Q(0)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})(0)\right] - \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt\right. \\
&+ \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - X_2^*(t)\right)^2 dt + \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|\theta\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt \\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]))
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-Q\frac{d(\tilde{Q}+\varepsilon\bar{\tilde{Q}})}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})\right]dt\right.\\
&+[Q(T)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})(T)-Q(0)(\tilde{Q}+\varepsilon\bar{\tilde{Q}})(0)]\\
&-\left(\int_0^T\left[-Q\frac{d\tilde{Q}}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\tilde{Q}\right]dt\right.\\
&\left.\left.+[Q(T)\tilde{Q}(T)-Q(0)\tilde{Q}(0)]\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-Q\frac{d\tilde{Q}}{dt}-Q\frac{d\varepsilon\bar{\tilde{Q}}}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\tilde{Q}\right.\right.\\
&\quad\left.-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\varepsilon\bar{\tilde{Q}}\right]dt\\
&\quad+[Q(T)\tilde{Q}(T)+Q(T)\varepsilon\bar{\tilde{Q}}(T)-Q(0)\tilde{Q}(0)-Q(0)\varepsilon\bar{\tilde{Q}})(0)]\\
&\quad-\left(\int_0^T\left[-Q\frac{d\tilde{Q}}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\tilde{Q}\right]dt\right.\\
&\left.\left.+[Q(T)\tilde{Q}(T)-Q(0)\tilde{Q}(0)]\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T\left[-Q\frac{d\varepsilon\bar{\tilde{Q}}}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\varepsilon\bar{\tilde{Q}}\right]dt\right.\\
&+[Q(T)\varepsilon\bar{\tilde{Q}}(T)-Q(0)\varepsilon\bar{\tilde{Q}})(0)]
\end{aligned}
$$

$$
\begin{aligned}
=&\lim_{\varepsilon\to 0}\int_0^T[-Q\ \frac{1}{\varepsilon}\frac{d\varepsilon\bar{\tilde{Q}}}{dt}-\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{Q}}\Bigg]dt\\
&+\left[Q(T)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{Q}}(T)-Q(0)\frac{1}{\varepsilon}\varepsilon\bar{\tilde{Q}}(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
=&\int_0^T\left[-Q\frac{d\bar{\tilde{Q}}}{dt}\ -\left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-\mu_m(Q-q)-bQ\right)\bar{\tilde{Q}}\right]dt\\
&+Q(T)\bar{\tilde{Q}}(T)-Q(0)\bar{\tilde{Q}}(0)
\end{aligned}
$$

$$= \int_0^T -Q\frac{d\bar{\tilde{Q}}}{dt}dt + Q(T)\bar{\tilde{Q}}(T) - Q(0)\bar{\tilde{Q}}(0) - \int_0^T \left(v_m \frac{q_m - Q}{q_m - q}\frac{A}{A - v_h} - \mu_m(Q - q) - bQ\right)\bar{\tilde{Q}}dt$$

$$= \int_0^T \frac{dQ}{dt}\bar{\tilde{Q}} - \left(v_m \frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\bar{\tilde{Q}}dt$$

Remove the test function $\bar{\tilde{Q}}$

$$= \int_0^T \frac{dQ}{dt} - \left(v_m \frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)dt$$

Third forward equation:

$$\frac{dQ}{dt} = v_m \frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ$$

A.7 Optimality condition:

$$\theta = \{\mu_m, q_1, q_2, d_{\mathrm{F}}, d_2, A\}$$

$$
\begin{aligned}
\frac{dL}{d\theta} &= \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta + \varepsilon\bar{\theta}\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, \theta\right)}{\varepsilon} = 0 \\
\frac{dL}{d\mu} &= \frac{1}{\varepsilon} \lim_{\varepsilon\to 0} \Bigg(\Bigg(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
&\quad + \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \left\| (\mu_m + \varepsilon\bar{\mu}_m, q_1, q_2, d_1, d_2, A) \right\|^2 + \int_0^T \Bigg[-X_1 \frac{d\tilde{X}_1}{dt} \\
&\quad - \left((\mu_m + \varepsilon\bar{\mu}_m) \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \tilde{X}_1 \Bigg] dt \\
&\quad + \int_0^T \Bigg[-X_2 \frac{d\tilde{X}_2}{dt} \\
&\quad - \left((\mu_m + \varepsilon\bar{\mu}_m) \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1 \right) \tilde{X}_2 \Bigg] dt \\
&\quad + \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A - v_h} - (\mu_m + \varepsilon\bar{\mu}_m)(Q - q) - bQ \right) \tilde{Q} \right] dt \\
&\quad + \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0) \right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0) \right] \\
&\quad + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]) \\
&\quad - \Bigg(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
&\quad + \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 \\
&\quad + \int_0^T \left[-X_1 \frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \tilde{X}_1 \right] dt \\
&\quad + \int_0^T \left[-X_2 \frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q}\right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1 \right) \tilde{X}_2 \right] dt \\
&\quad + \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ \right) \tilde{Q} \right] dt \\
&\quad + \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0) \right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0) \right] \\
&\quad + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)])
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} (\left(\frac{\beta}{2} \left\| (\mu_m + \varepsilon\bar{\mu}_m, q_1, q_2, d_1, d_2, A) \right\|^2 + \int_0^T \left[- \left((\mu_m + \varepsilon\bar{\mu}_m) \left(1 - \frac{q_1}{Q} \right) X_1 \right) \tilde{X}_1 \right] dt \right. \\
&+ \int_0^T \left[- \left((\mu_m + \varepsilon\bar{\mu}_m) \left(1 - \frac{q_2}{Q} \right) X_2 \right) \tilde{X}_2 \right] dt \\
&\left. + \int_0^T \left[- \left(- (\mu_m + \varepsilon\bar{\mu}_m) (Q - q) \right) \tilde{Q} \right] dt \right) \\
&- \left(\frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 + \int_0^T \left[- \left(\mu_m \left(1 - \frac{q_1}{Q} \right) X_1 \right) \tilde{X}_1 \right] dt \right. \\
&\left. \left. + \int_0^T \left[- \left(\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 \right) \tilde{X}_2 \right] dt + \int_0^T \left[- \left(-\mu_m (Q - q) \right) \tilde{Q} \right] dt \right) \right)
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\left(\frac{\beta}{2} \left\| (\mu_m + \varepsilon\bar{\mu}_m, q_1, q_2, d_1, d_2, A) \right\|^2 \right. \right. \\
&+ \int_0^T \left[-\mu_m \left(1 - \frac{q_1}{Q} \right) X_1 \tilde{X}_1 - \varepsilon\bar{\mu}_m \left(1 - \frac{q_1}{Q} \right) X_1 \tilde{X}_1 \right] dt \\
&+ \int_0^T \left[-\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 \tilde{X}_2 - \varepsilon\bar{\mu}_m \left(1 - \frac{q_2}{Q} \right) X_2 \tilde{X}_2 \right] dt \\
&\left. + \int_0^T \left[\mu_m (Q - q) \tilde{Q} + \varepsilon\bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right) \\
&- \left(\frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 + \int_0^T \left[-\mu_m \left(1 - \frac{q_1}{Q} \right) X_1 \tilde{X}_1 \right] dt \right. \\
&\left. \left. + \int_0^T \left[-\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 \tilde{X}_2 \right] dt + \int_0^T \left[\mu_m (Q - q) \tilde{Q} \right] dt \right) \right)
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left\| (\mu_m + \varepsilon\bar{\mu}_m, q_1, q_2, d_1, d_2, A) \right\|^2 \right. \\
&+ \int_0^T \left[-\varepsilon\bar{\mu}_m \left(1 - \frac{q_1}{Q} \right) X_1 \tilde{X}_1 - \varepsilon\bar{\mu}_m \left(1 - \frac{q_2}{Q} \right) X_2 \tilde{X}_2 + \varepsilon\bar{\mu}_m (Q - q) \tilde{Q} \right] dt \\
&\left. - \frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 \right)
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left\| (\mu_m + \varepsilon\bar{\mu}_m, q_1, q_2, d_1, d_2, A) \right\|^2 - \frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 \right. \\
&\left. + \int_0^T \left[-\varepsilon\bar{\mu}_m \left(1 - \frac{q_1}{Q} \right) X_1 \tilde{X}_1 - \varepsilon\bar{\mu}_m \left(1 - \frac{q_2}{Q} \right) X_2 \tilde{X}_2 + \varepsilon\bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right)
\end{aligned}
$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left(\left(\sqrt{(\mu_m + \varepsilon \bar{\mu}_m)^2 + (q_1)^2 + (q_2)^2 + (d_1)^2 + (d_2)^2 + (A)^2} \right)^2 \right.\right.$$
$$- \left(\sqrt{(\mu_m)^2 + (q_1)^2 + (q_2)^2 + (d_1)^2 + (d_2)^2 + (A)^2} \right)^2$$
$$\left. + \int_0^T \left[-\varepsilon \bar{\mu}_m \left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \varepsilon \bar{\mu}_m \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + \varepsilon \bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \frac{\beta}{2} \left((\mu_m)^2 + 2\varepsilon \mu_m \bar{\mu}_m + (\varepsilon \bar{\mu}_m)^2 + (q_1)^2 + (q_2)^2 + (d_1)^2 + (d_2)^2 + (A)^2 \right.$$
$$\left. - \left((\mu_m)^2 + (q_1)^2 + (q_2)^2 + (d_1)^2 + (d_2)^2 + (A)^2 \right) \right)$$
$$\left. + \int_0^T \left[-\varepsilon \bar{\mu}_m \left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \varepsilon \bar{\mu}_m \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + \varepsilon \bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left((\mu_m)^2 + 2\varepsilon \mu_m \bar{\mu}_m + (\varepsilon \bar{\mu}_m)^2 + (q_1)^2 + (q_2)^2 + (d_1)^2 + (d_2)^2 + (A)^2 \right.\right.$$
$$\left. - (\mu_m)^2 - (q_1)^2 - (q_2)^2 - (d_1)^2 - (d_2)^2 - (A)^2 \right)$$
$$\left. + \int_0^T \left[-\varepsilon \bar{\mu}_m \left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \varepsilon \bar{\mu}_m \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + \varepsilon \bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left(2\varepsilon \mu_m \bar{\mu}_m + \varepsilon^2 (\bar{\mu}_m)^2 \right) \right.$$
$$\left. + \int_0^T \left[-\varepsilon \bar{\mu}_m \left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \varepsilon \bar{\mu}_m \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + \varepsilon \bar{\mu}_m (Q - q) \tilde{Q} \right] dt \right)$$

$$= (\beta \mu_m \bar{\mu}_m) + \bar{\mu}_m \int_0^T \left[-\left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + (Q - q) \tilde{Q} \right] dt$$

$$= \left(\beta \mu_m + \int_0^T \left[-\left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + (Q - q) \tilde{Q} \right] dt \right) \bar{\mu}_m$$

Remove the test function $\bar{\mu}_m$

$$\beta \mu_m = -\int_0^T \left[-\left(1 - \frac{q_1}{Q}\right) X_1 \tilde{X}_1 - \left(1 - \frac{q_2}{Q}\right) X_2 \tilde{X}_2 + (Q - q) \tilde{Q} \right] dt$$

$$
\begin{aligned}
\frac{dL}{dq_1} =& \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \Bigg(\Bigg(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
& + \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \left\| (\mu_m, q_1 + \varepsilon \bar{q}_1, q_2, d_1, d_2, A) \right\|^2 \\
& + \int_0^T \Bigg[-X_1 \frac{d\tilde{X}_1}{dt} \\
& - \left(\mu_m \left(1 - \frac{q_1 + \varepsilon \bar{q}_1}{Q} \right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \tilde{X}_1 \Bigg] dt \\
& + \int_0^T \left[-X_2 \frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1 \right) \tilde{X}_2 \right] dt \\
& + \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ \right) \tilde{Q} \right] dt \\
& + \left[X_1(T) \tilde{X}_1(T) - X_1(0) \tilde{X}_1(0) \right] + \left[X_2(T) \tilde{X}_2(T) - X_2(0) \tilde{X}_2(0) \right] \\
& + [Q(T) \tilde{Q}(T) - Q(0) \tilde{Q}(0)]) \\
& - \Bigg(\frac{\alpha_1}{2} \int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2} \int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
& + \frac{\alpha_3}{2} \int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2} \left\| (\mu_m, q_1, q_2, d_1, d_2, A) \right\|^2 \\
& + \int_0^T \left[-X_1 \frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q} \right) X_1 - d_1 X_1 - m_1(Q) X_1 + m_2(Q) X_2 \right) \tilde{X}_1 \right] dt \\
& + \int_0^T \left[-X_2 \frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q} \right) X_2 - d_2 X_2 - m_2(Q) X_2 + m_1(Q) X_1 \right) \tilde{X}_2 \right] dt \\
& + \int_0^T \left[-Q \frac{d\tilde{Q}}{dt} - \left(v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m (Q - q) - bQ \right) \tilde{Q} \right] dt \\
& + \left[X_1(T) \tilde{X}_1(T) - X_1(0) \tilde{X}_1(0) \right] + \left[X_2(T) \tilde{X}_2(T) - X_2(0) \tilde{X}_2(0) \right] \\
& + [Q(T) \tilde{Q}(T) - Q(0) \tilde{Q}(0)]))
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\left(\frac{\beta}{2}\left\|(\mu_m, q_1+\varepsilon\bar{q}_1, q_2, d_1, d_2, A)\right\|^2+\int_0^T -\mu_m\left(1-\frac{q_1+\varepsilon\bar{q}_1}{Q}\right)X_1\tilde{X}_1 dt\right)\right.\\
&\left.-\left(\frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2+\int_0^T\left[-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1\right)\tilde{X}_1\right]dt\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\left(\frac{\beta}{2}\left\|(\mu_m, q_1+\varepsilon\bar{q}_1, q_2, d_1, d_2, A)\right\|^2+\int_0^T -\mu_m\left(1-\frac{q_1}{Q}\right)X_1\tilde{X}_1-\mu_m\frac{\varepsilon\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)\right.\\
&\left.-\left(\frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2+\int_0^T -\mu_m\left(1-\frac{q_1}{Q}\right)X_1\tilde{X}_1 dt\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(q_1+\varepsilon\bar{q}_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right.\right.\\
&\left.-\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right)\\
&\left.+\int_0^T -\mu_m\frac{\varepsilon\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+2\varepsilon q_1\bar{q}_1+(\varepsilon\bar{q}_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2\right.\right.\\
&\left.\left.-\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2\right)\right)+\int_0^T -\mu_m\frac{\varepsilon\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+2\varepsilon q_1\bar{q}_1+(\varepsilon\bar{q}_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2-(\mu_m)^2\right.\right.\\
&\left.\left.-(q_1)^2-(q_2)^2-(d_1)^2-(d_2)^2-(A)^2\right)+\int_0^T -\mu_m\frac{\varepsilon\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon q_1\bar{q}_1+(\varepsilon\bar{q}_1)^2\right)+\int_0^T -\mu_m\frac{\varepsilon\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)\\
=&\lim_{\varepsilon\to 0}\left(\beta\left(q_1\bar{q}_1+\frac{\beta\varepsilon}{2}(\bar{q}_1)^2\right)+\int_0^T -\mu_m\frac{\bar{q}_1}{Q}X_1\tilde{X}_1 dt\right)\\
=&\beta q_1\bar{q}_1+\int_0^T -\mu_m\frac{\bar{q}_1}{Q_1}X_1\tilde{X}_1 dt=0
\end{aligned}
$$

Remove the test function $\bar{q}_1$

$$\beta q_1 + \int_0^T -\mu_m \frac{X_1 \tilde{X}_1}{Q_1} dt = 0$$

$$\begin{aligned}
\frac{dL}{dq_2} =& \frac{\beta}{2\varepsilon}\left(\lim_{\varepsilon\to 0} \|(\mu_m, q_1, q_2 + \varepsilon\bar{q}_2, d_1, d_2, A)\|^2 - \|(\mu_m, q_1, q_2, d_1, d_2, A)\|^2\right) = 0 \\
=& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right.\right. \\
& + \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|(\mu_m, q_1, q_2 + \varepsilon\bar{q}_2, d_1, d_2, A)\|^2 \\
& + \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt \\
& + \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt}\right. \\
& - \left.\left(\mu_m\left(1 - \frac{q_2 + \varepsilon\bar{q}_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt \\
& + \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\tilde{Q}\right] dt \\
& + \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
& + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]) \\
& - \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt\right. \\
& + \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\|(\mu_m, q_1, q_2, d_1, d_2, A)\|^2 \\
& + \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1 - \frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt \\
& + \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1 - \frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt \\
& + \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q - q) - bQ\right)\tilde{Q}\right] dt \\
& + \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
& + [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]) = 0
\end{aligned}$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\left(\frac{\beta}{2}\left\|(\mu_m, q_1, q_2+\varepsilon\bar{q}_2, d_1, d_2, A)\right\|^2 - \frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\right.$$

$$\left. + \int_0^T -\mu_m\left(1-\frac{q_2+\varepsilon\bar{q}_2}{Q}\right)X_2\tilde{X}_2 dt\right) - \int_0^T\left[-\mu_m\left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2\right]dt\Big)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2+\varepsilon\bar{q}_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right.$$

$$\left. - \left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right)$$

$$+\int_0^T\left(-\mu_m\left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2 - \mu_m\frac{\varepsilon\bar{q}_2}{Q}X_2\tilde{X}_2\right)dt - \int_0^T\left[-\mu_m\left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2\right]dt\Big)$$

$$\frac{dL}{dq_2} = \frac{1}{\varepsilon\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+2\varepsilon q_2\bar{q}_2+(\varepsilon\bar{q}_2)^2+(d_1)^2+(d_2)^2+(A)^2\right.\right.$$

$$\left.\left. - \left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2\right)\right) + \int_0^T\left(-\mu_m\frac{\varepsilon\bar{q}_2}{Q}X_2\tilde{X}_2\right)dt\right)$$

$$\frac{dL}{dq_2} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+2\varepsilon q_2\bar{q}_2+(\varepsilon\bar{q}_2)^2+(d_1)^2+(d_2)^2+(A)^2-(\mu_m)^2\right.\right.$$

$$\left.\left. -(q_1)^2-(q_2)^2-(d_1)^2-(d_2)^2-(A)^2\right) + \int_0^T\left(-\mu_m\frac{\varepsilon\bar{q}_2}{Q}X_2\tilde{X}_2\right)dt\right)$$

$$=\frac{1}{\varepsilon\varepsilon\to 0}\lim_{\varepsilon\to}\left(\frac{\beta}{2}\left(2\varepsilon q_2\bar{q}_2+(\varepsilon\bar{q}_2)^2\right)+\int_0^T\left(-\mu_m\frac{\varepsilon\bar{q}_2}{Q}X_2\tilde{X}_2\right)dt\right)$$

$$=\lim_{\varepsilon\to 0}\left(\left(\beta q_2\bar{q}_2+\frac{\beta\varepsilon}{2}(\bar{q}_2)^2\right)+\int_0^T\left(-\mu_m\frac{\bar{q}_2}{Q}X_2\tilde{X}_2\right)dt\right)$$

$$=\beta q_2\bar{q}_2 + \int_0^T -\mu_m\frac{\bar{q}_2}{Q_2}X_2\tilde{X}_2 dt$$

$$\beta q_2 + \int_0^T -\mu_m\frac{1}{Q_2}X_2\tilde{X}_2 dt = 0$$

$$\frac{dL}{dd_1} = \frac{\beta}{2\varepsilon}\left(\lim_{\varepsilon\to 0}\left\|\left(\mu_m, q_1, q_2, d_1+\varepsilon\bar{d}_1, d_2, A\right)\right\|^2 - \left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\right) = 0$$

$$\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\Bigg(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-{X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t)-{X_2}^*(t)\right)^2 dt \\
&+\frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|\left(\mu_m, q_1, q_2, d_1+\varepsilon\bar{d}_1, d_2, A\right)\right\|^2 + \int_0^T \Bigg[-X_1\frac{d\tilde{X}_1}{dt} \\
&-\left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - \left(d_1+\varepsilon\bar{d}_1\right)X_1 - m_1\left(Q\right)X_1 + m_2\left(Q\right)X_2\right)\tilde{X}_1\Bigg]dt \\
&+\int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2\left(Q\right)X_2 + m_1\left(Q\right)X_1\right)\tilde{X}_2\right]dt \\
&+\int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt \\
&+\left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]) \\
&-\Bigg(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-{X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t)-{X_2}^*(t)\right)^2 dt \\
&+\frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2 \\
&+\int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1\left(Q\right)X_1 + m_2\left(Q\right)X_2\right)\tilde{X}_1\right]dt \\
&+\int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2\left(Q\right)X_2 + m_1\left(Q\right)X_1\right)\tilde{X}_2\right]dt \\
&+\int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt \\
&+\left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]))
\end{aligned}$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left\|\left(\mu_m, q_1, q_2, d_1+\varepsilon\bar{d}_1, d_2, A\right)\right\|^2-\frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\right.$$
$$\left.+\int_0^T\left(d_1+\varepsilon\bar{d}_1\right)X_1\tilde{X}_1dt-\int_0^T d_1X_1\tilde{X}_1dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+\left(d_1+\varepsilon\bar{d}_1\right)^2+(d_2)^2+(A)^2}^{\,2}\right)^2\right.\right.$$
$$\left.\left.-\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right)+\int_0^T\varepsilon\bar{d}_1X_1\tilde{X}_1dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+2\varepsilon d_1\bar{d}_1+\left(\varepsilon\bar{d}_1\right)^2+(d_2)^2+(A)^2-(\mu_m)^2\right.\right.$$
$$\left.\left.-(q_1)^2-(q_2)^2-(d_1)^2-(d_2)^2-(A)^2\right)+\int_0^T\varepsilon\bar{d}_1X_1\tilde{X}_1dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon d_1\bar{d}_1+\left(\varepsilon\bar{d}_1\right)^2\right)+\int_0^T\varepsilon\bar{d}_1X_1\tilde{X}_1dt\right)$$

$$=\beta d_1\bar{d}_1+\int_0^T\bar{d}_1X_1\tilde{X}_1dt$$

$$\left(\beta d_1+\int_0^T X_1\tilde{X}_1dt\right)\bar{d}_1=0$$

Remove the test function $\bar{d}_1$

$$\beta d_1+\int_0^T X_1\tilde{X}_1dt=0$$

$$
\begin{aligned}
\frac{dL}{dd_2} =& \frac{\beta}{2\varepsilon}\left(\lim_{\varepsilon\to 0}\left\|\left(\mu_m, q_1, q_2, d_1, d_2+\varepsilon\bar{d}_2, A\right)\right\|^2 - \left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\right) = 0\\
=& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-{X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t)-{X_2}^*(t)\right)^2 dt\right.\right.\\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt\\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt}\right.\\
&\left.-\left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - \left(d_2+\varepsilon\bar{d}_2\right)X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt\\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]\\
&+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)])\\
&- \left(\frac{\alpha_1}{2}\int_0^T \left(X_1(t)-{X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t)-{X_2}^*(t)\right)^2 dt\right.\\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t)-Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt\\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt\\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]\\
&+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)])
\end{aligned}
$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left(\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+\left(d_2+\varepsilon\bar{d}_2\right)^2+(A)^2}^{\,2}\right)^2\right.\right.\right.$$

$$\left.\left.\left.-\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\right)^T\varepsilon\bar{d}_2X_2\tilde{X}_2dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+2\varepsilon d_2\bar{d}_2+\left(\varepsilon\bar{d}_2\right)^2+(A)^2-(\mu_m)^2\right.\right.$$

$$\left.\left.-(q_1)^2-(q_2)^2-(d_1)^2-(d_2)^2-(A)^2\right)+\int_0^T\varepsilon\bar{d}_2X_2\tilde{X}_2dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon d_2\bar{d}_2+\left(\varepsilon\bar{d}_2\right)^2\right)+\int_0^T\varepsilon\bar{d}_2X_2\tilde{X}_2dt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon d_2\bar{d}_2+\left(\varepsilon\bar{d}_2\right)^2\right)+\int_0^T\varepsilon\bar{d}_2X_2\tilde{X}_2dt\right)$$

$$=\lim_{\varepsilon\to 0}\left(\beta d_2\bar{d}_2+\frac{\beta\varepsilon}{2}\left(\bar{d}_2\right)^2\right)+\int_0^T\bar{d}_2X_2\tilde{X}_2dt$$

$$=\beta d_2\bar{d}_2+\int_0^T\bar{d}_2X_2\tilde{X}_2dt=0$$

$$\left(\beta d_2+\int_0^T X_2\tilde{X}_2dt\right)\bar{d}_2=0$$

Remove the test function $\bar{d}_2$

$$\beta d_2+\int_0^T X_2\tilde{X}_2dt=0$$

$$
\begin{aligned}
\frac{dL}{dA} =& \frac{\beta}{2\varepsilon}\left(\lim_{\varepsilon\to 0}\left\|\left(\mu_m, q_1, q_2, d_1, d_2, A+\varepsilon\bar{A}\right)\right\|^2 - \left\|\left(\mu_m, q_1, q_2, d_1, d_2, A\right)\right\|^2\right) = 0 \\
\frac{dL}{dA} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\Bigg(\frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|\left(\mu_m, q_1, q_2, d_1, d_2, A+\varepsilon\bar{A}\right)\right\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt \\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{(A+\varepsilon\bar{A})}{(A+\varepsilon\bar{A}) - v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]) \\
&- \int \frac{\alpha_1}{2}\int_0^T \left(X_1(t) - {X_1}^*(t)\right)^2 dt + \frac{\alpha_2}{2}\int_0^T \left(X_2(t) - {X_2}^*(t)\right)^2 dt \\
&+ \frac{\alpha_3}{2}\int_0^T \left(Q(t) - Q^*(t)\right)^2 dt + \frac{\beta}{2}\left\|\left(\mu_m, q_1, q_2, d_1, d_2, A\right)\right\|^2 \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt \\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A + v_h} - \mu_m(Q-q) - bQ\right)\tilde{Q}\right]dt \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right] \\
&+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]
\end{aligned}
$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\bigg(\frac{\beta}{2}\left\|\left(\mu_m, q_1, q_2, d_1, d_2, A+\varepsilon\bar{A}\right)\right\|^2+\int_0^T\left[-v_m\frac{q_m-Q}{q_m-q}\frac{(A+\varepsilon\bar{A})}{(A+\varepsilon\bar{A})-v_h}\tilde{Q}\right]dt\bigg)$$

$$-\left(\frac{\beta}{2}\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2+\int_0^T\left[-v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\tilde{Q}\right]dt\right)=0$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\frac{\beta}{2}\left(\left\|\left(\mu_m, q_1, q_2, d_1, d_2, A+\varepsilon\bar{A}\right)\right\|^2-\left\|(\mu_m, q_1, q_2, d_1, d_2, A)\right\|^2\right)$$

$$+\int_0^T\left[-v_m\frac{q_m-Q}{q_m-q}\frac{(A+\varepsilon\bar{A})}{(A+\varepsilon\bar{A})-v_h}\tilde{Q}\right]dt-\int_0^T\left[-v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\tilde{Q}\right]dt\Bigg)=0$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\Bigg(\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A+\varepsilon\bar{A})^2)^2}\right)^2$$

$$-\left(\sqrt{(\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2}\right)^2\Bigg)$$

$$+\int_0^T\left[-v_m\frac{q_m-Q}{q_m-q}\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}-v_h}\tilde{Q}+v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\tilde{Q}\right]dt\Bigg)=0$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2++(d_2)^2+(A)^2+2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2\right.$$

$$\left.-\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2\right)\right)$$

$$+\int_0^T-v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}-v_h}-\frac{A}{A+v_h}\right]dt\Bigg)=0$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\Bigg(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2+2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2\right.$$

$$\left.-\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2\right)\right)$$

$$+\int_0^T-v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}-v_h}-\frac{A}{A+v_h}\right]dt\Bigg)=0$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2+(q_1)^2+(q_2)^2+(d_1)^2+(d_2)^2+(A)^2+2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2-(\mu_m)^2\right.\right.\\
&\left.-(q_1)^2-(q_2)^2-(d_1)^2-(d_2)^2-(A)^2\right)\\
&\left.+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{(A+\varepsilon\bar{A})(A+v_h)-A\left(A+\varepsilon\bar{A}-v_h\right)}{\left(A+\varepsilon\bar{A}-v_h\right)(A+v_h)}\right]dt\right)\\
&\quad+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{A^2-Av_h+\varepsilon A\bar{A}-\varepsilon\bar{A}v_h-A^2-\varepsilon A\bar{A}+Av_h}{\left(A+\varepsilon\bar{A}-v_h\right)(A+v_h)}\right]dt\Bigg)=0
\end{aligned}
$$

$$
\begin{aligned}
=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2\right)\right.\\
&\left.+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{A^2-Av_h+\varepsilon A\bar{A}-\varepsilon\bar{A}v_h-A^2-\varepsilon A\bar{A}+Av_h}{\left(A+\varepsilon\bar{A}-v_h\right)(A+v_h)}\right]dt\right)
\end{aligned}
$$

$$
=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2\right)+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{-\varepsilon\bar{A}v_h}{\left(A+\varepsilon\bar{A}-v_h\right)(A+v_h)}\right]dt\right)
$$

$$
=\lim_{\varepsilon\to 0}\left(\beta A\bar{A}+\frac{\beta\varepsilon}{2}(\bar{A})^2+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{-\bar{A}v_h}{\left(A+\varepsilon\bar{A}+v_h\right)(A+v_h)}\right]dt\right)
$$

$$
\begin{aligned}
=&\beta A\bar{A}+\int_0^T -v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\left[\frac{-\bar{A}v_h}{(A+v_h)(A+v_h)}\right]dt\\
=&\beta A\bar{A}+\int_0^T v_m\frac{q_m-Q}{q_m-q}\frac{\bar{A}v_h}{(A+v_h)^2}\tilde{Q}dt
\end{aligned}
$$

$$
\left(\beta A+\int_0^T v_m\frac{q_m-Q}{q_m-q}\frac{v_h}{(A+v_h)^2}\tilde{Q}dt\right)\bar{A}=0
$$

Remove test function $\bar{A}$

$$
\beta A+\int_0^T v_m\frac{q_m-Q}{q_m-q}\frac{v_h}{(A+v_h)^2}\tilde{Q}dt=0
$$

Optimality condition:

$$(\beta\mu_m) + \int_0^T \left[-\left(1-\frac{q_1}{Q}\right)X_1\tilde{X}_1 - \left(1-\frac{q_2}{Q}\right)X_2\tilde{X}_2 + (Q-q)\tilde{Q}\right]dt = 0$$

$$\beta q_1 + \int_0^T -\mu_m\frac{1}{Q}X_1\tilde{X}_1 dt = 0$$

$$\beta q_2 + \int_0^T -\mu_m\frac{1}{Q}X_2\tilde{X}_2 dt = 0$$

$$\beta d_1 + \int_0^T X_1\tilde{X}_1 dt = 0$$

$$\beta d_2 + \int_0^T X_2\tilde{X}_2 dt = 0,$$

$$\beta A + \int_0^T v_m\frac{q_m - Q}{q_m - q}\frac{v_h}{(A+v_h)^2}\tilde{Q}dt = 0$$

APPENDIX B

Derivation of ODE optimality system with drugs

In this appendix, we present the derivation of the optimality system for treatment.

B.1 The first adjoint equation:

$$
\begin{aligned}
\frac{dL}{dX_1} =& \lim_{\varepsilon\to 0} \frac{L\left(X_1+\varepsilon\tilde{X}_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right)}{\varepsilon} = 0\\
=& \lim_{\varepsilon\to 0} \frac{1}{\varepsilon}\left(\frac{a_0}{2}\int_0^T (Q(t)-Q_m(t))^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt\right) + \frac{\alpha_1}{2}\left(Q(T)-Q_m\right)^2\\
&+ \int_0^T \left[-\left(X_1+\varepsilon\bar{X}_1\right)\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)\left(X_1+\varepsilon\bar{X}_1\right) - d_1\left(X_1+\varepsilon\bar{X}_1\right)\right.\right.\\
&- m_1(Q)\left(X_1+\varepsilon\bar{X}_1\right) + m_2(Q)X_2\tilde{X}_1 dt\\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)\left(X_1+\varepsilon\bar{X}_1\right)\right)\tilde{X}_2\right] dt\\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-Q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)Q\right] dt\\
&+ \left[\left(X_1+\varepsilon\bar{X}_1\right)(T)\bar{X}_1(T) - \left(X_1+\varepsilon\bar{X}_1\right)(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]\\
&+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]\\
&- \left(\frac{\alpha_0}{2}\int_0^T \left(Q(t)-Q_m(t)\right)^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_1}{2}\left(Q(T)-Q_m\right)^2\right.\\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt\\
&+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)(X_1)\tilde{X}_2\right] dt\\
&+ \int_0^T \left[-Q\frac{dQ}{dt} - \left(v_m\frac{q_m-Q}{q_m-Q}\frac{A}{A+v_n} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right] dt\\
&+ \left[(X_1)(T)\tilde{X}_1(T) - (X_1)(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]\\
&+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)])) = 0
\end{aligned}
$$

$$= \lim_{\varepsilon\to\infty} \frac{1}{\varepsilon} \left(\int_0^T \left[-\varepsilon \tilde{X}_1 \frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) \varepsilon \tilde{X}_1 - d_1 \varepsilon \tilde{X}_1 - m_1(Q) \varepsilon \tilde{X}_1 \right) \tilde{X}_1 \right] dt \right)$$
$$+ \lim_{\varepsilon\to\infty} \frac{1}{\varepsilon} \left(\int_0^T \left| -m_1(Q) \varepsilon \tilde{X}_1 \tilde{X}_2 \right| dt + \left| \varepsilon \bar{X}_1(T) \tilde{X}_1(T) - \varepsilon \bar{X}_1(0) \tilde{X}_1(0) \right| \right)$$

$$= \lim_{\varepsilon\to 0} \frac{1}{\varepsilon} \left(\int_0^T \left[-\varepsilon \tilde{X}_1 \frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) \varepsilon \tilde{X}_1 - d_1 \varepsilon \tilde{X}_1 - m_1(Q) \varepsilon \tilde{X}_1 \right) \tilde{X}_1 \right] \right)$$
$$- \lim_{\varepsilon\to 0} \frac{1}{\varepsilon} \left(\left[\varepsilon \bar{X}_1(T) \tilde{X}_1(T) - \varepsilon \tilde{X}_1(0) \tilde{X}_1(0) \right] \right)$$

$$= \int_0^T \left[-\bar{X}_1 \frac{dX_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) \bar{X}_1 - d_1 \bar{X}_1 - m_1(Q) \bar{X}_1 \right) \bar{X}_1 - m_1(Q) \bar{X}_1 \bar{X}_2 \right] dt$$
$$+ \left[\bar{X}_1(T) \tilde{X}_1(T) - \bar{X}_1(0) \tilde{X}_1(0) \right]$$

Remove the test function $\bar{X}_1(t)$

$$= \int_0^T \left[-\frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) - d_1 - m_1(Q) \right) \tilde{X}_1 - m_1(Q) \tilde{X}_2 \right] dt + \left[\tilde{X}_1(T) - \tilde{X}_1(0) \right] = 0$$

Since $X_1(0) = 0$

$$= \int_0^T \left[-\frac{d\tilde{X}_1}{dt} - \left(\mu_m \left(1 - \frac{q_1}{Q}\right) - d_1 - m_1(Q) \right) \tilde{X}_1 - m_1(Q) \tilde{X}_2 \right] dt + \tilde{X}_1(T) = 0$$

The first adjoint equation:

$$\frac{d\tilde{X}_1}{dt} = -\left(\mu_m \left(1 - \frac{q_1}{Q}\right) - d_1 - m_1(Q) \right) \tilde{X}_1 - m_1(Q) \tilde{X}_2, \qquad X_1(T) = 0$$

B.2 The second adjoint equation:

$$
\begin{aligned}
\frac{dL}{dX_2} &= \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2+\varepsilon\bar{X}_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right)}{\varepsilon} = 0 \\
&= \lim_{\varepsilon\to 0} \frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T \left(Q(t)-Q_m(t)\right)^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_1}{2}\left(Q(T)-Q_m\right)^2\right. \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(u_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)\right)\tilde{X}_1\right] dt \\
&+ \int_0^T \left[-\left(X_2+\varepsilon\bar{X}_2\right)\frac{d\tilde{X}_2}{dt}\right. \\
&- \left.\left(\mu_m\left(1-\frac{q_2}{Q}\right)\left(X_2+\varepsilon\bar{X}_2\right) - d_2\left(X_2+\varepsilon\bar{X}_2\right) - m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right) + m_1(Q)X_1\right)\tilde{X}_2\right] dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right] \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[\left(X_2+\varepsilon\tilde{X}_2\right)(T)X_2(T) - \left(X_2+\varepsilon\tilde{X}_2\right)(0)\tilde{X}_2(0)\right] \\
&+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right] \\
&- \left(\frac{\alpha_0}{2}\int_0^T \left(Q(t)-Q_m(t)\right)^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_1}{2}\left(Q(T)-Q_m\right)^2\right. \\
&+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(u_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)\left(X_2\right)\right)\tilde{X}_1\right] dt \\
&+ \int_0^T \left[-\left(X_2\right)\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\left(X_2\right) - d_2\left(X_2\right) - m_2(Q)\left(X_2\right) + m_1(Q)X_1\right)\tilde{X}_2\right] dt \\
&+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right] \\
&+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[\left(X_2\right)(T)X_2(T) - \left(X_2\right)(0)\tilde{X}_2(0)\right] \\
&+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right]
\end{aligned}
$$

$$
\begin{aligned}
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right)\right)\tilde{X}_1\right]dt\right.\\
&\quad + \int_0^T \left[-\left(X_2+\varepsilon\bar{X}_2\right)\frac{d\tilde{X}_2}{dt}\right.\\
&\quad \left. - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\left(X_2+\varepsilon\bar{X}_2\right) - d2\left(X_2+\varepsilon\bar{X}_2\right) - m_2(Q)\left(X_2+\varepsilon\bar{X}_2\right) + m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&\quad + \left[\left(X_2+\varepsilon\bar{X}_2\right)(T)\tilde{X}_2(T) - \left(X_2+\varepsilon\bar{X}_2\right)(0)\tilde{X}_2(0)\right]\\
&\quad - \left(\int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt\right.\\
&\quad + \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt\\
&\quad \left.\left. + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]\right)\right) = 0\\
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T -m_2(Q)\varepsilon\bar{X}_2\tilde{X}_1 dt\right.\\
&\quad + \int_0^T \left[-X_2\frac{d\bar{X}_2}{dt} - \varepsilon\bar{X}_2\frac{d\bar{X}_2}{dt}\right.\\
&\quad - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 + \mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2 - d2X_2 - d_2\varepsilon\bar{X}_2 - m_2(Q)X_2 - m_2(Q)\varepsilon\bar{X}_2\right.\\
&\quad \left.\left.+m_1(Q)X_1\right)\tilde{X}_2\right]dt + \left[\left(\varepsilon\bar{X}_2\right)(T)\tilde{X}_2(T) - \left(\varepsilon\bar{X}_2\right)(0)\tilde{X}_2(0)\right]\\
&\quad \left. - \left(\int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt\right)\right) = 0\\
&\quad = \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T -m_2(Q)\varepsilon\bar{X}_2\tilde{X}_1 dt\right.\\
&\qquad + \int_0^T \left[-\varepsilon\bar{X}_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2 - d_2\varepsilon\bar{X}_2 - m_2(Q)\varepsilon\bar{X}_2\right)\tilde{X}_2\right]dt\\
&\qquad + \left[\left(\varepsilon\bar{X}_2\right)(T)\tilde{X}_2(T) - \left(\varepsilon\bar{X}_2\right)(0)\tilde{X}_2(0)\right] = 0\\
&= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\int_0^T \left[-\varepsilon\bar{X}_2\,\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)\varepsilon\bar{X}_2 - d_2\varepsilon\bar{X}_2 - m_2(Q)\varepsilon\bar{X}_2\right)X_2 - m_2(Q)\varepsilon\bar{X}_2\bar{X}_1 dt\right.\right.\\
&\qquad\qquad \left. + \left[\left(\varepsilon\bar{X}_2\right)(T)\bar{X}_2(T) - \left(\varepsilon\ddot{X}_2\right)(0)\bar{X}_2(0)\right]\right) = 0
\end{aligned}
$$

$$= \int_0^T \left[-\bar{X}_2 \frac{d\bar{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q} \right) \bar{X}_2 - d_2 \bar{X}_2 - m_2(Q) \bar{X}_2 \right) \tilde{X}_2 - m_2(Q) \bar{X}_2 \bar{X}_1 dt \right.$$

$$\left. + \left[\left(\bar{X}_2 \right) (T) \bar{X}_2(T) - \left(\bar{X}_2 \right) (0) \bar{X}_2(0) \right] \right) = 0$$

Since $\left(\bar{X}_2 \right) (0) = 0$

Remove the test function $\bar{X}_2(t)$

$$= -\frac{d\tilde{X}_2}{dt} - \left(\mu_m \left(1 - \frac{q_2}{Q} \right) - d_2 - m_2(Q) \right) \tilde{X}_2 - m_2(Q) \bar{X}_1 + \tilde{X}_2(T) = 0$$

$$\frac{d\tilde{X}_2}{dt} = -\left(\mu_m \left(1 - \frac{q_2}{Q} \right) - d_2 - m_2(Q) \right) \bar{X}_2 - m_2(Q) \tilde{X}_1, \quad \bar{X}_2(T) = 0$$

The second adjoint equation:

$$\frac{d\tilde{X}_2}{dt} = -\mu_m \left(1 - \frac{q_2}{Q} \right) \tilde{X}_2 + d_2 \tilde{X}_2 + m_2(Q) \tilde{X}_2 - m_2(Q) \tilde{X}_1, \quad \tilde{X}_2(T) = 0$$

B.3 The third adjoint equation:

$$\frac{dL}{dQ} = \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2, Q+\varepsilon\bar{Q}, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right) - L\left(X_1, X_2, Q, \tilde{X}_1, \tilde{X}_2, \tilde{Q}, u\right)}{\varepsilon} = 0$$

$$= \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T \left((Q+\varepsilon\bar{Q})(t) - Q_m(t)\right)^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_1}{2}\left((Q+\varepsilon\bar{Q})(T) - Q_m\right)^2\right.$$
$$+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right] dt$$
$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt$$
$$+ \int_0^T \left[-(Q+\varepsilon\bar{Q})\frac{d\tilde{Q}}{dt}\right.$$
$$\left. - \left(v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_n} - \mu_m((Q+\varepsilon\bar{Q}) - q) - b(Q+\varepsilon\bar{Q}) - \gamma(Q+\varepsilon\bar{Q})u\right)\tilde{Q}\right] dt$$
$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[(X_2)(T)\tilde{X}_2(T) - (X_2)(0)\tilde{X}_2(0)\right]$$
$$+ \left[(Q+\varepsilon\bar{Q})(T)\tilde{Q}(T) - (Q+\varepsilon\bar{Q})(0)\tilde{Q}(0)\right]$$
$$- \left(\frac{\alpha_0}{2}\int_0^T (Q(t)-Q(t))^2 dt + \frac{\beta_0}{2}\int_0^T (u(t))^2 dt + \frac{\alpha_1}{2}(Q(T)-Q)^2\right.$$
$$+ \int_0^T \left[-X_1\frac{d\tilde{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\bar{X}_1\right] dt$$
$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right] dt$$
$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right] dt$$
$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$
$$+ \left[X_1(T)\tilde{X}_1(T) - X1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$
$$+ \left[Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)\right])) = 0$$

$$
\begin{aligned}
=&\lim_{\epsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q_m dt+\frac{\alpha_1}{2}\left((Q+\varepsilon\bar{Q})(T)-Q\right)^2-\frac{\alpha_1}{2}\left(Q(T)-Q\right)^2\right.\\
&+\int_0^T\left[\frac{q_1}{(Q+\varepsilon\bar{Q})}\mu_m X_1\tilde{X}_1+\frac{q_2}{(Q+\varepsilon\bar{Q})}\mu_m X_2\tilde{X}_2+\frac{c_1k_1X_1\tilde{X}_1}{Q+\varepsilon\bar{Q}+k_1}-\frac{c_1k_1X_1\tilde{X}_2}{Q+\varepsilon\bar{Q}+k_1}\right.\\
&-\frac{Q+\varepsilon\bar{Q}}{Q+\varepsilon\bar{Q}+k_2}c_2X_2\bar{X}_1+\frac{Q+\varepsilon\bar{Q}}{Q+\varepsilon\bar{Q}+k_2}c_2X_2\bar{X}_2-\frac{q_1}{Q}\mu_m X_1\bar{X}_1-\frac{q_2}{Q}\mu_m X_2\tilde{X}_2-\frac{c_1k_1X_1\tilde{X}_1}{Q+k_1}\\
&\left.+\frac{c_1k_1X_1\bar{X}_2}{Q+k_1}+\frac{c_2QX_2\bar{X}_1}{Q+k_2}-\frac{c_2QX_2\bar{X}_2}{Q+k_2}\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\bar{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma(\varepsilon\bar{Q})u\right)\bar{Q}\right.\\
&\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+[(Q+\varepsilon\bar{Q})(T)\tilde{Q}(T)-(Q+\varepsilon\bar{Q})(0)\tilde{Q}(0)]\\
&\left.-[Q(T)\tilde{Q}(T)-Q(0)\tilde{Q}(0)]\right)=0\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q_m dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q_m\right)\right.\\
&+\int_0^T\left[\frac{\mu_m}{(Q+\varepsilon Q)}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\frac{c_1k_1X_1}{Q+\varepsilon Q+k_1}\left(\bar{X}_1-\bar{X}_2\right)\right.\\
&+\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon Q+k_2}\left(\tilde{X}_2-\tilde{X}_1\right)\\
&\left.-\frac{\mu_m}{Q}\left(q_1X_1\bar{X}_1+q_2X_2\bar{X}_2\right)+\frac{c_1k_1X_1}{Q+k_1}\left(\tilde{X}_2-\bar{X}_1\right)+\frac{c_2QX_2}{Q+k_2}\left(\bar{X}_1-\bar{X}_2\right)\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma\varepsilon\bar{Q}u\right)\tilde{Q}\right.\\
&\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)=0\\
=&\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q_m dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q_m\right)\right.\\
&+\int_0^T\left[\frac{\mu_m}{(Q+\varepsilon\tilde{Q})}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)-\frac{\mu m}{Q}\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\frac{c1k_1X_1}{Q+\varepsilon\bar{Q}+k_1}\left(\tilde{X}_1-\tilde{X}_2\right)\right.\\
&\left.-\frac{c_1k_1X_1}{Q+k_1}\left(\tilde{X}_1-\tilde{X}_2\right)+\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon\bar{Q}+k_2}\left(\bar{X}_2-\tilde{X}_1\right)-\frac{c_2QX_2}{Q+k_2}\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt\\
&+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-(Q+\varepsilon\bar{Q})}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma\varepsilon\bar{Q}u\right)\tilde{Q}\right.\\
&\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)=0
\end{aligned}
$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\ddot{Q}Q_m \quad dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q_m\right)\right.$$

$$+\int_0^T\left[\left(\frac{\mu_m}{(Q+\varepsilon\bar{Q})}-\frac{\mu_m}{Q}\right)\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)+\left(\frac{1}{Q+\varepsilon\bar{Q}+k1}-\frac{1}{Q+k_1}\right)\right.$$

$$\left.c_1k_1X_1\left(\tilde{X}_1-\tilde{X}_2\right)+\left(\frac{c_2QX_2+c_2\varepsilon\bar{Q}X_2}{Q+\varepsilon\bar{Q}+k_2}-\frac{c_2QX_2}{Q+k_2}\right)\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt$$

$$+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(-v_m\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}-v_m\frac{-\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma\varepsilon\bar{Q}u\right)\tilde{Q}\right.$$

$$\left.\left.+v_m\tilde{Q}\frac{q_m-Q}{q_m-q}\frac{A}{A+v_h}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0)\right)=0$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q_m dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q_m\right)\right.$$

$$+\int_0^T\left[\left(\frac{\mu_mQ-Q\mu_m-\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q}\right)\left(q_1X_1\tilde{X}_1+q_2X_2\tilde{X}_2\right)\right.$$

$$+\left(\frac{Q+k_1-Q-\varepsilon\bar{Q}-k_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)}\right)c_1k_1X_1\left(\tilde{X}_1-\tilde{X}_2\right)$$

$$+\left(\frac{c_2QX_2Q+c_2QX_2k_2+c_2\varepsilon\bar{Q}X_2Q+c_2\varepsilon\bar{Q}X_2k_2-c_2QX_2Q-c_2\varepsilon\bar{Q}QX_2-c_2QX_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)}\right)\left(\tilde{X}_2\right.$$

$$\left.\left.-\tilde{X}_1\right)\right]dt+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(v_m\frac{\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma\varepsilon\bar{Q}u\right)\tilde{Q}\right]dt$$

$$+\varepsilon\bar{Q}(T)\tilde{Q}(T)-\varepsilon\bar{Q}(0)\tilde{Q}(0))=0$$

$$=\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left(\frac{\alpha_0}{2}\int_0^T 2Q\varepsilon\bar{Q}+(\varepsilon\bar{Q})^2-2\varepsilon\bar{Q}Q_m \quad dt+\frac{\alpha_1}{2}\left(2\varepsilon Q(T)\bar{Q}(T)+(\varepsilon\bar{Q}(T))^2-2\varepsilon\bar{Q}(T)Q_m\right)\right.$$

$$+\int_0^T\left[\left(\frac{-\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q}\right)\left(q_1X_1\bar{X}_1+q_2X_2\bar{X}_2\right)+\left(\frac{-\varepsilon\bar{Q}c_1k_1X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)}\right)\left(\bar{X}_1-\bar{X}_2\right)\right.$$

$$\left.+\left(\frac{c_2\varepsilon\bar{Q}X_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)}\right)\left(\tilde{X}_2-\tilde{X}_1\right)\right]dt$$

$$+\int_0^T\left[-\varepsilon\bar{Q}\frac{d\tilde{Q}}{dt}+\left(v_m\frac{\varepsilon\bar{Q}}{q_m-q}\frac{A}{A+v_h}+\mu_m\varepsilon\bar{Q}+b\varepsilon\bar{Q}+\gamma\varepsilon\bar{Q}u\right)\tilde{Q}\right]dt+\varepsilon\bar{Q}(T)\tilde{Q}(T)$$

$$-\varepsilon\bar{Q}(0)\tilde{Q}(0))=0$$

$$= \lim_{\varepsilon \to 0} \frac{1}{\varepsilon} \left(\frac{\alpha_0}{2} \int_0^r 2Q\varepsilon\bar{Q} + (\varepsilon\bar{Q})^2 - 2\varepsilon\bar{Q}Q_m - \left(\frac{\varepsilon\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q} \right) \left(q_1 X_1 \bar{X}_1 + q2 X_2 \bar{X}_2 \right) \right.$$

$$- \left(\frac{\varepsilon\bar{Q}c_1k_1X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)} \right) \left(\tilde{X}_1 - \bar{X}_2 \right) + \left(\frac{c_2\varepsilon\bar{Q}X_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)} \right) \left(\tilde{X}_2 - \bar{X}_1 \right)$$

$$\left. - \varepsilon\bar{Q}\frac{d\tilde{Q}}{dt} + \left(v_m \frac{\varepsilon\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m\varepsilon\bar{Q} + b\varepsilon\bar{Q} + \gamma\varepsilon\bar{Q}u \right) \tilde{Q} \right) dt$$

$$+ \frac{\alpha_1}{2} \left(2\varepsilon Q(T)\bar{Q}(T) + (\varepsilon\bar{Q}(T))^2 - 2\varepsilon\bar{Q}(T)Q_m \right) + \varepsilon\bar{Q}(T)\tilde{Q}(T) - \varepsilon\bar{Q}(0)\tilde{Q}(0) = 0$$

$$= \lim_{\varepsilon \to 0} \left(\frac{\alpha_0}{2} \int_0^\tau 2Q\bar{Q} + (\varepsilon\bar{Q})^2 - 2\bar{Q}Q_m - \left(\frac{\bar{Q}\mu_m}{(Q+\varepsilon\bar{Q})Q} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) \right.$$

$$- \left(\frac{\bar{Q}c_1k_1X_1}{\left(Q+\varepsilon\bar{Q}+k_1\right)(Q+k_1)} \right) \left(\bar{X}_1 - \tilde{X}_2 \right) + \left(\frac{c_2\bar{Q}X_2k_2}{\left(Q+\varepsilon\bar{Q}+k_2\right)(Q+k_2)} \right) \left(\bar{X}_2 - \bar{X}_1 \right) - \bar{Q}\frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m\bar{Q} + b\bar{Q} + \gamma\bar{Q}u \right) \tilde{Q} \right) dt$$

$$+ \frac{\alpha_1}{2} \left(2Q(T)\bar{Q}(T) + \varepsilon(\bar{Q}(T))^2 - 2\bar{Q}(T)Q_m \right) + \bar{Q}(T)\tilde{Q}(T) - \bar{Q}(0)\tilde{Q}(0) = 0$$

$$= \left(\frac{\alpha_0}{2} \int_0^T 2Q\bar{Q} + (\varepsilon\bar{Q})^2 - 2\bar{Q}Q_m - \left(\frac{\bar{Q}\mu_m}{(Q)Q} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) \right.$$

$$- \left(\frac{\bar{Q}c_1k_1X_1}{(Q+k_1)(Q+k_1)} \right) \left(\tilde{X}_1 - \tilde{X}_2 \right) + \left(\frac{c_2\bar{Q}X_2k_2}{(Q+k_2)(Q+k_2)} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) - \bar{Q}\frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{\bar{Q}}{q_m - q} \frac{A}{A+v_h} + \mu_m\bar{Q} + b\bar{Q} + \gamma\bar{Q}u \right) \tilde{Q} \right) dt + \frac{\alpha_1}{2} \left(2Q(T)\bar{Q}(T) - 2\bar{Q}(T)Q_m \right)$$

$$+ \bar{Q}(T)\tilde{Q}(T) - \bar{Q}(0)\tilde{Q}(0) = 0$$

Since $\tilde{Q}(0) = 0$

Remove the test function $\bar{Q}(t)$

$$\left(\int_0^T \alpha_0 (Q - Q_m) - \left(\frac{\mu_m}{Q^2} \right) \left(q_1 X_1 \bar{X}_1 + q_2 X_2 \tilde{X}_2 \right) - \left(\frac{c_1k_1X_1}{(Q+k_1)^2} \right) \left(\bar{X}_1 - \tilde{X}_2 \right) \right.$$

$$+ \left(\frac{c_2X_2k_2}{(Q+k_2)^2} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) - \frac{d\tilde{Q}}{dt}$$

$$\left. + \left(v_m \frac{1}{q_m - q} \frac{A}{A+v_h} + \mu_m + b + \gamma u \right) \tilde{Q} \right) dt + \frac{\alpha_1}{2} \left(2Q(T) - 2Q_m \right) + \tilde{Q}(T) = 0$$

$$\frac{d\tilde{Q}}{dt} = \alpha_0 \left(Q(t) - Q_m \right) - \left(\frac{\mu_m}{Q^2} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) - \left(\frac{c_1 k_1 X_1}{\left(Q + k_1\right)^2} \right) \left(\tilde{X}_1 - \tilde{X}_2 \right)$$

$$+ \left(\frac{c_2 X_2 k_2}{\left(Q + k_2\right)^2} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) + v_m \frac{\tilde{Q}}{q_m - q} \frac{A}{A + v_h} + \mu_m \tilde{Q} + b\tilde{Q} + \gamma u \tilde{Q},$$

$$\tilde{Q}(T) = \alpha_1 \left(Q(T) - Q_m \right)$$

The third adjoint equation:

$$\frac{d\tilde{Q}}{dt} = \alpha_0 \left(Q(t) - Q_m \right) - \left(\frac{\mu_m}{Q^2} \right) \left(q_1 X_1 \tilde{X}_1 + q_2 X_2 \tilde{X}_2 \right) - \left(\frac{c_1 k_1 X_1}{\left(Q + k_1\right)^2} \right) \left(\tilde{X}_1 - \tilde{X}_2 \right)$$

$$+ \left(\frac{c_2 X_2 k_2}{\left(Q + k_2\right)^2} \right) \left(\tilde{X}_2 - \tilde{X}_1 \right) + v_m \frac{\tilde{Q}}{q_m - q} \frac{A}{A + v_h} + \mu_m \tilde{Q} + b\tilde{Q} + \gamma u \tilde{Q},$$

$$\tilde{Q}(T) = \alpha_1 \left(Q(T) - Q_m \right)$$

B.4 Optimality condition:

$$\frac{dL}{du} = \lim_{\varepsilon\to 0} \frac{L\left(X_1, X_2, Q, \bar{X}_1, \bar{X}_2, \bar{Q}, u+\varepsilon\bar{u}\right) - L\left(X_1, X_2, Q, \bar{X}_1, \bar{X}_2, \bar{Q}, u\right)}{\varepsilon} = 0$$

$$= \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\Bigg(\frac{\alpha_1}{2}\int_0^T (X_1(t) - X_1(t))^2\,dt + \frac{\alpha_2}{2}\int_0^T (X_2(t) - X_2(t))^2\,dt$$

$$+ \frac{\alpha_3}{2}\int_0^T (Q(t) - Q_m(t))^2\,dt + \frac{\beta}{2}\int_0^T (u+\varepsilon\bar{u})^2 dt$$

$$+ \int_0^T \left[-X_1\frac{d\bar{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\tilde{X}_1\right]dt$$

$$+ \int_0^T \left[-X_2\frac{d\tilde{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt$$

$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Q(u+\varepsilon\bar{u})\right)\tilde{Q}\right]dt$$

$$+ \left[X_1(T)\bar{X}_1(T) - X1(0)\bar{X}_1(0)\right] + \left[X_2(T)\bar{X}_2(T) - X_2(0)\bar{X}_2(0)\right] + [Q(T)\bar{Q}(T) - Q(0)\bar{Q}(0)]$$

$$- \left(\frac{\alpha_1}{2}\int_0^T (X_1(t) - X_1(t))^2\,dt + \frac{\alpha_2}{2}\int_0^T (X_2(t) - X_2(t))^2\,dt + \frac{\alpha_3}{2}\int_0^T (Q(t) - Q_m(t))^2\,dt\right.$$

$$+ \frac{\beta}{2}\int_0^T (u)^2 dt + \int_0^T \left[-X_1\frac{d\bar{X}_1}{dt} - \left(\mu_m\left(1-\frac{q_1}{Q}\right)X_1 - d_1X_1 - m_1(Q)X_1 + m_2(Q)X_2\right)\bar{X}_1\right]dt$$

$$+ \int_0^T \left[-X_2\frac{d\bar{X}_2}{dt} - \left(\mu_m\left(1-\frac{q_2}{Q}\right)X_2 - d_2X_2 - m_2(Q)X_2 + m_1(Q)X_1\right)\tilde{X}_2\right]dt$$

$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right]dt$$

$$+ \left[X_1(T)\tilde{X}_1(T) - X_1(0)\tilde{X}_1(0)\right] + \left[X_2(T)\tilde{X}_2(T) - X_2(0)\tilde{X}_2(0)\right]$$

$$+ [Q(T)\tilde{Q}(T) - Q(0)\tilde{Q}(0)]))$$

$$= \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\Bigg(\frac{\beta}{2}\int_0^T (u+\varepsilon\bar{u})^2 dt$$

$$+ \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Q(u+\varepsilon\bar{u})\right)\tilde{Q}\right]dt\Bigg)$$

$$- \left(\frac{\beta}{2}\int_0^r (u)^2 dt + \int_0^T \left[-Q\frac{d\tilde{Q}}{dt} - \left(v_m\frac{q_m - Q}{q_m - q}\frac{A}{A+v_h} - \mu_m(Q-q) - bQ - \gamma Qu\right)\tilde{Q}\right]dt\right)\Bigg)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \int_0^T (u + \varepsilon \bar{u})^2 dt - \frac{\beta}{2} \int_0^T (u)^2 dt + \int_0^T [-\gamma Q u \tilde{Q} - \gamma Q \varepsilon \bar{u} \tilde{Q}] dt - \int_0^T -\gamma Q u \tilde{Q} dt \right)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} (\left(\frac{\beta}{2} \int_0^T (u)^2 + 2\varepsilon u \bar{u} + (\varepsilon \bar{u})^2 dt - \frac{\beta}{2} \int_0^T (u)^2 dt - \int_0^T \gamma Q \varepsilon \bar{u} \tilde{Q} dt \right)$$

$$= \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \int_0^T 2\varepsilon u \bar{u} + (\varepsilon \bar{u})^2 dt - \int_0^T \gamma Q \varepsilon \bar{u} \tilde{Q} dt \right)$$

$$= \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \int_0^T 2u \bar{u} + (\varepsilon \bar{u})^2 dt - \int_0^T \gamma Q \bar{u} \tilde{Q} dt \right) = 0$$
$$= \frac{\beta}{2} \int_0^T 2u \bar{u} - \int_0^T \gamma Q \bar{u} \tilde{Q} dt$$

$$= \beta \int_0^T u \bar{u} - \int_0^T \gamma Q \bar{u} \tilde{Q} dt$$

$$= \int_0^T (\beta u - \gamma Q \tilde{Q}) \bar{u} dt$$

Remove $\bar{u}(t)$, then optimality condition:

$$\int_0^T \beta u - \gamma Q \tilde{Q} dt = 0$$

APPENDIX C

Derivation of Liouville optimality system

C.1 Forward equations:

$$
\begin{aligned}
&\frac{dL}{dw} = \lim_{\varepsilon\to 0}\frac{L(p,w+\varepsilon\widetilde{w},\theta)-L(p,w,\theta)}{\varepsilon} = 0\\
&\frac{dL(p,w,\theta)}{dw} = \frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt + \frac{\beta}{2}\|\theta\|^2\right.\\
&+\int_0^T\int_\Omega\left(\frac{dp}{dt}(w+\varepsilon\widetilde{w})(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot(w+\varepsilon\widetilde{w})(x,q,t)\right)dxdqdt\\
&-\left(\frac{\alpha}{2}\int_0^T\int_\Omega\big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt+\frac{\beta}{2}\|\theta\|^2\right.\\
&\left.\left.+\int_0^T\int_\Omega\left(\frac{dp}{dt}w(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot w(x,q,t)\right)dxdqdt\right)\right)=0\\
&=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\int_0^T\int_\Omega\left(\frac{dp}{dt}(w+\varepsilon\widetilde{w})(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot(w+\varepsilon\widetilde{w})(x,q,t)\right)dxdqdt\right.\\
&\left.-\left(\int_0^T\int_\Omega\left(\frac{dp}{dt}w(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot w(x,q,t)\right)dxdqdt\right)\right)=0\\
&=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\int_0^T\int_\Omega\left(\frac{dp}{dt}\varepsilon\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot\varepsilon\widetilde{w}(x,q,t)\right)dxdqdt\right)=0\\
&=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot\widetilde{w}(x,q,t)\right)dxdqdt=0\\
&=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot\widetilde{w}(x,q,t)+\int_0^T\int_\Omega[b(x,q)p(x,q,t)\cdot\vec{n}]w\right)dxdqdt=0\\
&=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-\nabla\cdot(b(x,q)p(x,q,t))\widetilde{w}(x,q,t)\right)dxdqdt=0
\end{aligned}
$$

$$
=\int_0^T\int_\Omega\left(\frac{dp}{dt}+\nabla\cdot(b(x,q)p(x,q,t))\right)\widetilde{w}(x,q,t)dxdqdt=0
$$

Remove $\widetilde{w}(x,q,t)$, then we have

$$
\frac{dp}{dt}+\nabla\cdot(b(x,q)p(x,q,t))=0
$$

$$
p(x,q,0)=p_0(x,q)=0
$$

C.2 Adjoint equation:

$$
\begin{aligned}
&\frac{dL(p,w,\theta)}{dp} = \lim_{\varepsilon\to 0}\frac{L(p+\varepsilon\tilde{p},w,\theta)-L(p,w,\theta)}{\varepsilon} = 0\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \big((p+\varepsilon\tilde{p})(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt + \frac{\beta}{2}\|\theta\|^2\\
&+\int_0^T\int_\Omega \frac{d(p+\varepsilon\tilde{p})}{dt}w(x,q,t)dxdqdt - \int_0^T\int_\Omega (b(x,q)(p+\varepsilon\tilde{p})(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\\
&-\Bigg(\frac{\alpha}{2}\int_0^T\int_\Omega \big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt + \frac{\beta}{2}\|\theta\|^2\\
&+\int_0^T\int_\Omega \frac{dp}{dt}w(x,q,t)dxdqdt - \int_0^T\int_\Omega (b(x,q)p(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)\Bigg)\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \big((p+\varepsilon\tilde{p})(x,q,t)-p^d(x,q,t)\big)^2 - \big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt\\
&+\int_0^T\int_\Omega^T \left(\frac{d(p+\varepsilon\tilde{p}-p)}{dt}\right)w(x,q,t)dxdqdt\\
&-\int_0^T\int_\Omega (b(x,q)(p+\varepsilon\tilde{p}-p)(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \big((p+\varepsilon\widetilde{p})(x,q,t)-p^d(x,q,t)\big)^2 - \big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt\\
&+\varepsilon\int_0^T\int_\Omega \frac{d\widetilde{p}}{dt}w(x,q,t)dxdqdt - \varepsilon\int_0^T\int_\Omega (b(x,q)\widetilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \big((p+\varepsilon\widetilde{p})(x,q,t)-p^d(x,q,t)\big)^2 - \big(p(x,q,t)-p^d(x,q,t)\big)^2\,dxdqdt\\
&+\varepsilon\int_0^T\int_\Omega \frac{d\widetilde{p}}{dt}w(x,q,t)dxdqdt - \varepsilon\int_0^T\int_\Omega (b(x,q)\widetilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega (p+\varepsilon\tilde{p})^2 - 2pp^d - 2\varepsilon\tilde{p}p^d + \big(p^d\big)^2 - (p)^2 + 2pp^d - \big(p^d\big)^2\,dxdqdt\\
&+\varepsilon\int_0^T\int_\Omega \frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt - \varepsilon\int_0^T\int_\Omega (b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)\\
&= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega \Big((p)^2 + 2p\varepsilon\tilde{p} + (\varepsilon\tilde{p})^2 - 2pp^d - 2\varepsilon\tilde{p}p^d + \big(p^d\big)^2 - (p)^2 + 2pp^d - \big(p^d\big)^2\Big)\,dxdqdt\\
&+\varepsilon\int_0^T\int_\Omega \frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt - \varepsilon\int_0^T\int_\Omega (b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\Bigg)
\end{aligned}
$$

$$=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega^T\left((p)^2+2p\varepsilon\tilde{p}+(\varepsilon\tilde{p})^2-2pp^d-2\varepsilon\tilde{p}p^d+\left(p^d\right)^2-(p)^2+2pp^d-\left(p^d\right)^2\right)dxdqdt\right.$$
$$\left.+\varepsilon\int_0^T\int_\Omega\frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt-\varepsilon\int_0^T\int_\Omega(b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\right)$$

$$=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega\left(2p\varepsilon\tilde{p}+(\varepsilon)^2(\tilde{p})^2-2\varepsilon\tilde{p}p^d\right)dxdqdt\right.$$
$$\left.+\varepsilon\int_0^T\int_\Omega\frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt-\varepsilon\int_0^T\int_\Omega(b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt\right)$$

$$=\frac{\alpha}{2}\int_0^T\int_\Omega 2\left(p-p^d\right)\tilde{p}dxdqdt$$
$$+\int_0^T\int_\Omega^T\frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega^T(b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt$$

$$=\alpha\int_0^T\int_\Omega\left(p-p^d\right)\tilde{p}dxdqdt-\int_\Omega\int_0^T\frac{dw}{dt}\tilde{p}(x,q,t)dxdqdt+\int_\Omega^T\tilde{p}(T)w(T)dxdq$$
$$-\int_\Omega\tilde{p}(0)w(0)dxdq-\int_0^T\int_\Omega(b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt$$

Choose $w(T)=0$

$$\alpha\int_0^T\int_\Omega^T\left(p-p^d\right)\tilde{p}dxdqdt-\int_\Omega\int_0^T\frac{dw}{dt}\tilde{p}(x,q,t)dxdqdt$$
$$-\int_0^T\int_\Omega(b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt$$

Take

$$\alpha\left(p-p^d\right)-\frac{dw}{dt}-b(x,q).\nabla w(x,q,t)=0$$

Then, the adjoint equation:

$$\alpha\left(p-p^d\right)-\frac{dw}{dt}-b(x,q)\cdot\nabla w(x,q,t)=0$$

$$w(x,q,T)=0$$

$$w(x,q)=0\quad\text{on }\partial\Omega$$

The adjoint equation:

$$\alpha\left(p-p^{d}\right)=\frac{dw}{dt}+b(x,q)\cdot\nabla w(x,q,t)$$

$$w(x,q,T)=0$$

$$w(x,q)=0 \quad \text{on } \partial\Omega$$

C.3 Optimality condition

The unknown parameters $\theta=\{\mu_{\boldsymbol{m}},s,d,A\}$

Lagrange multipliers equal

$$\begin{aligned}L(p,w,\theta)=&\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d(x,q,t)\right)^2dxdqdt+\frac{\beta}{2}\|\theta\|^2\\&+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega(b(x,q)p(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\end{aligned}$$

$$\begin{aligned}L(p,w,\theta)=&\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d(x,q,t)\right)^2dxdqdt+\frac{\beta}{2}\|\theta\|^2+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt\\&-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x,v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)\right.\right.\\&-bq)p(x,q,t))\cdot\nabla wdxdqdt\end{aligned}$$

We want to find the optimality condition.

$$\frac{dL}{d\theta}=\lim_{\varepsilon\to 0}\frac{L(p,w,\theta+\varepsilon\bar{\theta})-L(p,w,\theta)}{\varepsilon}=0$$

$$\begin{aligned}\frac{dL}{d\mu_m}=&\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d(x,q,t)\right)^2dxdqdt+\frac{\beta}{2}\left\|(\mu_m+\varepsilon\bar{\mu}m,s,d,A)\right\|^2\right.\\&+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega\left(\left((\mu_m+\varepsilon\bar{\mu}m)\left(1-\frac{s}{q}\right)x-dx\right.\right.\\&\left.\left.-c\frac{k^n}{q^n+k^n}x,v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-(\mu_m+\varepsilon\bar{\mu}_m)(q-s)-bq)p(x,q,t)\right)\cdot\nabla wdxdqdt\right)\\&-\left(\frac{\alpha}{2}\int_0^T\int_\Omega^T\left(p(x,q,t)-p^d(x,q,t)\right)^2dxdqdt+\frac{\beta}{2}\left\|(\mu_m,s,d,A)\right\|^2+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt\right.\\&-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x,v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq\right)p(x,q,t)\right)\\&\nabla wdxdqdt)=0\end{aligned}$$

$$\frac{dL}{d\mu_m} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left\|(\mu_m+\varepsilon\bar{\mu}_m, s, d, A)\right\|^2 - \frac{\beta}{2}\left\|(\mu_m, s, d, A)\right\|^2\right.$$

$$-\int_0^T\int_\Omega\left(\left((\mu_m+\varepsilon\bar{\mu}m)\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - (\mu_m+\varepsilon\bar{\mu}_m)(q-s)\right.\right.$$

$$-bq)p(x,q,t))\cdot\nabla w dxdqdt$$

$$+\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq\right)p(x,q,t)\right)$$

$$\nabla w dxdqdt) = 0$$

$$\frac{dL}{d\mu_m} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\frac{\beta}{2}\left\|(\mu_m+\varepsilon\bar{\mu}_m, s, d, A)\right\|^2 - \frac{\beta}{2}\left\|(\mu_m, s, d, A)\right\|^2$$

$$-\int_0^T\int_\Omega\left(\left(\varepsilon\bar{\mu}_m\left(1-\frac{s}{q}\right)x, -\varepsilon\bar{\mu}_m(q-s)\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\Big) = 0$$

$$\frac{dL}{d\mu_m} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m+\varepsilon\bar{\mu}_m)^2+(s)^2+(d)^2+(A)^2}\right)^2 - \left(\sqrt{(\mu_m)^2+(s)^2+(d)^2+(A)^2}\right)^2\right)$$

$$-\int_0^T\int_\Omega\left(\left(\varepsilon\bar{\mu}_m\left(1-\frac{s}{q}\right)x, -\varepsilon\bar{\mu}_m(q-s)\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\Big) = 0$$

$$\frac{dL}{d\mu_m} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left((\mu_m)^2 + 2\varepsilon\mu_m\bar{\mu}_m + (\varepsilon\bar{\mu}_m)^2 + (s)^2 + (d)^2 + (A)^2 - (\mu_m)^2 - (s)^2 - (d)^2 - (A)^2\right)\right.$$

$$-\int_0^T\int_\Omega\left(\left(\varepsilon\bar{\mu}_m\left(1-\frac{s}{q}\right)x, -\varepsilon\bar{\mu}_m(q-s)\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\Big) = 0$$

$$\frac{dL}{d\mu_m} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon\mu_m\bar{\mu}_m + \varepsilon^2(\bar{\mu}_m)^2\right) - \int_0^T\int_\Omega^T\left(\left(\varepsilon\bar{\mu}_m\left(1-\frac{s}{q}\right)x, -\varepsilon\bar{\mu}_m(q-s)\right)p(x,q,t)\right)\right.$$

$$\nabla w dxdqdt) = 0$$

$$\frac{dL}{d\mu_m} = \beta\mu_m\bar{\mu}m - \int_0^T\int_\Omega\left(\left(\bar{\mu}_m\left(1-\frac{s}{q}\right)x, -\bar{\mu}_m(q-s)\right)p(x,q,t)\right)\cdot\nabla w dxdqdt = 0$$

Remove $\bar{\mu}_m$, then we have

$$\frac{dL}{d\mu_m} = \beta\mu_m - \int_0^T\int_\Omega\left(\left(\left(1-\frac{s}{q}\right)x, -(q-s)\right)p(x,q,t)\right)\cdot\nabla w dxdqdt = 0$$

Now, the following unknown parameter.

$$\begin{aligned}
\frac{dL}{ds} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d(x,q,t)\right)^2 dxdqdt + \frac{\beta}{2}\left\|(\mu_m, s+\varepsilon\bar{s}, d, A)\right\|^2 \\
&+\int_0^T\int_\Omega^T \frac{dp}{dt}w(x,q,t)dxdqdt \\
&-\int_0^T\int_\Omega^T \left(\left(\mu_m\left(1-\frac{(s+\varepsilon\bar{s})}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s)\right.\right. \\
&- bq)p(x,q,t))\cdot\nabla w dxdqdt) \\
&-\left(\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d(x,q,t)\right)^2 dxdqdt + \frac{\beta}{2}\left\|(\mu_m,s,d,A)\right\|^2 + \int_0^T\int_\Omega \frac{dp}{dt}w(x,q,t)dxdqdt\right. \\
&-\int_0^T\int_\Omega^T\left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq\right)p(x,q,t)\right) \\
&\nabla w dxdqdt) = 0 \\
\frac{dL}{ds} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\left\|(\mu_m, s+\varepsilon\bar{s}, d, A)\right\|^2 - \frac{\beta}{2}\left\|(\mu_m,s,d,A)\right\|^2 \\
&-\int_0^T\int_\Omega \left(\left(\mu_m\left(1-\frac{(s+\varepsilon\bar{s})}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s)\right.\right. \\
&- bq)p(x,q,t))\cdot\nabla w dxdqdt \\
&+\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq\right)p(x,q,t)\right) \\
&\nabla w dxdqdt) \\
\frac{dL}{ds} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(s+\varepsilon\bar{s})^2+(d)^2+(A)^2}\right)^2 - \left(\sqrt{(\mu_m)^2+(s)^2+(d)^2+(A)^2}\right)^2\right) \\
&-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{(s+\varepsilon\bar{s})}{q}\right)x, 0\right)p(x,q,t)\right)\cdot\nabla w dxdqdt \\
&+\int_0^T\int_\Omega^T\left(\left(\mu_m\left(1-\frac{s}{q}\right)x, 0\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\Bigg) = 0 \\
\frac{dL}{ds} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\left((\mu_m)^2+(s)^2+2\varepsilon s\bar{s}+(\varepsilon\bar{s})^2+(d)^2+(A)^2-(\mu_m)^2-(s)^2-(d)^2-(A)^2\right) \\
&-\int_0^T\int_\Omega^T\left(\left(\mu_m\frac{\varepsilon\bar{s}}{q}x, 0\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\Bigg) = 0 \\
\frac{dL}{ds} =& \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon s\bar{s}+(\varepsilon\bar{s})^2\right) - \int_0^T\int_\Omega^T\left(\left(\mu_m\frac{\varepsilon\bar{s}}{q}x, 0\right)p(x,q,t)\right)\cdot\nabla w dxdqdt\right) = 0 \\
\frac{dL}{ds} =& \beta s\bar{s} - \int_0^T\int_\Omega\left(\left(\mu_m\frac{\bar{s}}{q}x, 0\right)p(x,q,t)\right)\cdot\nabla w dxdqdt = 0
\end{aligned}$$

Remove $\bar{s}$, then we have

$$\frac{dL}{ds} = \beta s - \int_0^T \int_\Omega \left(\left(\mu_m \frac{1}{q} x, 0 \right) p(x,q,t) \right) \cdot \nabla w dx dq dt = 0$$

Now, the next unknown parameter.

$$\frac{dL}{dd} = \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d(x,q,t) \right)^2 dx dq dt + \frac{\beta}{2} \left\| \left(\mu_m, s, d + \varepsilon \bar{d}, A \right) \right\|^2 \right.$$

$$+ \int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t) dx dq dt$$

$$- \int_0^T \int_\Omega \left(\left(\mu_m \left(1 - \frac{s}{q} \right) x - (d + \varepsilon \bar{d}) x - c \frac{k^n}{q^n + k^n} x, v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m (q - s) \right. \right.$$

$$- bq) p(x,q,t)) \cdot \nabla w dx dq dt)$$

$$- \left(\frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d(x,q,t) \right)^2 dx dq dt + \frac{\beta}{2} \| (\mu_m, s, d, A) \|^2 + \int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t) dx dq dt \right.$$

$$- \int_0^T \int_\Omega \left(\left(\mu_m \left(1 - \frac{s}{q} \right) x - dx - c \frac{k^n}{q^n + k^n} x, v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m (q - s) - bq \right) p(x,q,t) \right)$$

$$\cdot \nabla w dx dq dt) = 0$$

$$\frac{dL}{dd} = \frac{1}{\varepsilon} \lim_{\varepsilon \to 0} \left(\frac{\beta}{2} \left(\left\| \left(\mu_m, s, d + \varepsilon \bar{d}, A \right) \right\|^2 - \| (\mu_m, s, d, A) \|^2 \right) \right.$$

$$- \int_0^T \int_\Omega \left(\left(\mu_m \left(1 - \frac{s}{q} \right) x - (d + \varepsilon \bar{d}) x - c \frac{k^n}{q^n + k^n} x, v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m (q - s) \right. \right.$$

$$- bq) p(x,q,t)) \cdot \nabla w dx dq dt$$

$$- \left(- \int_0^T \int_\Omega \left(\left(\mu_m \left(1 - \frac{s}{q} \right) x - dx - c \frac{k^n}{q^n + k^n} x, v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m (q - s) \right. \right. \right.$$

$$- bq) p(x,q,t)) \cdot \nabla w dx dq dt)) = 0$$

$$\frac{dL}{dd} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\ \left\|\left(\mu_m, s, d+\varepsilon\bar{d}, A\right)\right\|^2 - \|(\mu_m, s, d, A)\|^2\Bigg)$$

$$- \int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x - (d+\varepsilon\bar{d})x - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s)\right.\right.$$

$$\left.- bq)p(x,q,t)\right)\cdot\nabla w dxdqdt$$

$$- \left(-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s)\right.\right.\right.$$

$$\left.- bq)p(x,q,t)\right)\cdot\nabla w dxdqdt)) = 0$$

$$\frac{dL}{dd} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(s)^2+(d+\varepsilon\bar{d})^2+(A)^2}\right)^2 - \left(\sqrt{(\mu_m)^2+(s)^2+(d)^2+(A)^2}\right)^2\right)\right.$$

$$\left.+\int_0^T\int_\Omega((\varepsilon\bar{d}x,0)p(x,q,t))\cdot\nabla w dxdqdt\right) = 0$$

$$\frac{dL}{dd} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\Bigg(\frac{\beta}{2}\left((\mu_m)^2+(s)^2+(d)^2+2\varepsilon d\bar{d}+(\varepsilon\bar{d})^2+(A)^2-(\mu_m)^2-(s)^2-(d)^2-(A)^2\right)$$

$$\left.+\int_0^T\int_\Omega((\varepsilon\bar{d}x,0,0)p(x,q,t))\cdot\nabla w dxdqdt\right) = 0$$

$$\frac{dL}{dd} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon d\bar{d}+(\varepsilon\bar{d})^2\right) + \int_0^T\int_\Omega((\varepsilon\bar{d}x,0)p(x,q,t))\cdot\nabla w dxdqdt\right) = 0$$

$$\frac{dL}{dd} = \beta d\bar{d} + \int_0^T\int_\Omega((\bar{d}x,0)p(x,q,t))\cdot\nabla w dxdqdt = 0$$

Remove $\bar{d}$, then we have

$$\frac{dL}{dd} = \beta d + \int_0^T\int_\Omega((x,0)p(x,q,t))\cdot\nabla w dxdqdt = 0$$

Now, the next unknown parameter.

$$
\begin{aligned}
\frac{dL}{dA} =& \frac{1}{\varepsilon}\lim_{\epsilon\to 0}\left(\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d(x,q,t)\right)^2 dxdqdt + \frac{\beta}{2}\left\|\left(\mu_m,s,d,A+\varepsilon\bar{A}\right)\right\|^2\right. \\
&+\int_0^T\int_\Omega^T \frac{dp}{dt}w(x,q,t)dxdqdt \\
&-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}+v_h}-\mu_m(q-s)\right.\right. \\
&-bq)p(x,q,t))\cdot\nabla wdxdqdt) \\
&-\left(\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d(x,q,t)\right)^2dxdqdt+\frac{\beta}{2}\|(\mu_m,s,d,A)\|^2+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt\right. \\
&-\int_0^T\int_\Omega\left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq\right)p(x,q,t)\right) \\
&\cdot\nabla wdxdqdt
\end{aligned}
$$

$$
\begin{aligned}
&=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left\|\left(\mu_m,s,d,A+\varepsilon\bar{A}\right)\right\|^2-\frac{\beta}{2}\|(\mu_m,s,d,A)\|^2\right. \\
&-\int_0^T\int_\Omega\left(\left(v_m\frac{q_m-q}{q_m-s}\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}+v_h}-\mu_m(q-s)-bq\right)p(x,q,t)\right)\cdot\nabla wdxdqdt\Bigg) \\
&-\left(-\int_0^T\int_\Omega\left(\left(v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq\right)p(x,q,t)\right)\cdot\nabla wdxdqdt\right)
\end{aligned}
$$

$$
\begin{aligned}
&=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left\|\left(\mu_m,s,d,A+\varepsilon\bar{A}\right)\right\|^2-\|(\mu_m,s,d,A)\|^2\right)\right. \\
&-\int_0^T\int_\Omega\left(\left(0,v_m\frac{q_m-q}{q_m-s}\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}+v_h}\right)p(x,q,t)\right)\cdot\nabla wdxdqdt \\
&+\int_0^T\int_\Omega^T\left(\left(0,v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}\right)p(x,q,t)\right)\cdot\nabla wdxdqdt\Bigg)
\end{aligned}
$$

$$
\begin{aligned}
&=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left(\sqrt{(\mu_m)^2+(s)^2+(d)^2+(A+\varepsilon\bar{A})^2}\right)^2-\left(\sqrt{(\mu_m)^2+(s)^2+(d)^2+(A)^2}\right)^2\right)\right. \\
&-\int_0^T\int_\Omega\left(\left(0,v_m\frac{q_m-q}{q_m-s}\left[\frac{A+\varepsilon\bar{A}}{A+\varepsilon\bar{A}+v_h}-\frac{A}{A+v_h}\right]\right)p(x,q,t)\right)\cdot\nabla wdxdqdt\Bigg)
\end{aligned}
$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(\left((\mu_m)^2+(s)^2+(d)^2+(A)^2+2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2-(\mu_m)^2-(s)^2-(d)^2-(A)^2\right)\right)-\right.$$
$$\left.\int_0^T\int_\Omega\left(\left(0,v_m\frac{q_m-q}{q_m-s}\left[\frac{(A+\varepsilon\bar{A})(A+v_h)-A\left(A+\varepsilon\bar{A}+v_h\right)}{\left(A+\varepsilon\bar{A}+v_h\right)(A+v_h)}\right]\right)p(x,q,t)\right)\nabla w dxdqdt\right)$$

$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\left(2\varepsilon A\bar{A}+(\varepsilon\bar{A})^2\right)\right.$$
$$-\int_0^T\int_\Omega^T\left(\left(0,v_m\frac{q_m-q}{q_m-s}\left[\frac{A^2+Av_h+\varepsilon A\bar{A}+\varepsilon\bar{A}v_h-A^2-\varepsilon A\bar{A}-Av_h}{\left(A+\varepsilon\bar{A}+v_h\right)(A+v_h)}\right]\right)p(x,q,t)\right)$$
$$\left.\cdot\nabla w dxdqdt\right)$$
$$=\beta A\bar{A}-\int_0^T\int_\Omega\left(\left(0,v_m\frac{q_m-q}{q_m-s}\left[\frac{\bar{A}v_h}{\left(A+\bar{A}+v_h\right)(A+v_h)}\right]\right)p(x,q,t)\right)\cdot\nabla w dxdqdt=0$$

Remove $\bar{A}$, then we have

$$\frac{dL}{dA}=\beta A-\int_0^T\int_\Omega\left(0,v_m\frac{q_m-q}{q_m-s}\frac{v_h}{(A+v_h)^2}\right)p(x,q,t).\nabla w dxdqdt=0$$

C.4 Optimal control problem with drugs

$$\frac{dX}{dt}=\mu_m\left(1-\frac{s}{Q}\right)X-dX-c\frac{k^n}{Q^n+k^n}X$$
$$\frac{dQ}{dt}=v_m\frac{q_m-Q}{q_m-s}\frac{A}{A+v_h}-\mu_m(Q-s)-bQ-\gamma qu(t)$$

the Liouville equation

$$\frac{dp}{dt}+\nabla\cdot(b(x,q)p(x,q,t))=0$$

$$p(x,q,0)=p_0(x,q)$$

Where

$$b(x,q)=(b_1(x,q),b_3(x,q))$$

with the PDF initial condition at $t=0$ given by $p(x,q,0)=p_0(x,q)$. $(x,q)\in\mathbb{R}^+\cup\{0\}\times\mathbb{R}^+\cup\{0\}$, $\nabla\equiv(\frac{\partial}{\partial x},\frac{\partial}{\partial q})$, $p_0(x,q)$ is the PDF of the initial condition

$(X(0), Q(0))$

$$
\begin{aligned}
b_1(x,q) &= \mu_m \left(1 - \frac{s}{q}\right) x\_d_1 x - k_1 \frac{k_1^n}{q^n + k_1^n} x \\
b_3(x,q) &= v_m \frac{q_m - q}{q_m - s} \frac{A}{A + v_h} - \mu_m (q - s) - bq - \gamma q u(t),
\end{aligned}
\tag{C.4.1}
$$

b_1, b_3 are essentially the right hand sides of the ODE (C.4) replacing X with $x$and Q with q.

$$
\min_u J(p,u) = \frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d(x, q_m, t)\right)^2 dx dq dt + \frac{\beta}{2} \int_0^T (u(t))^2 dt
$$

Subject to the equations:

$$
\frac{dp}{dt} + \nabla \cdot (b(x,q) p(x,q,t)) = 0
$$

$$
p(x,q,0) = p_0(x,q)
$$

where $p^d(x, q_m, t)$ is the desired level that the doctor wants to see (the middle of the range or close to the normal level).

C.5 Weak formulation of Liouville equation:

$$
\frac{dp}{dt} + \nabla \cdot (b(x,q) p(x,q,t)) = 0
$$

We have:

$$
\int_0^T \int_\Omega \left(\frac{dp}{dt} + \nabla \cdot (b(x,q) p(x,q,t))\right) w(x,q,t) dx dq dt = 0
$$

Distribution $w(x,q,t)$ we have:

$$
\int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t) dx dq dt + \int_0^T \int_\Omega (\nabla . (b(x,q) p(x,q,t))) w(x,q,t) dx dq dt = 0
$$

Using integral by parts, we have

$$\int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t)dxdqdt - \int_0^T \int_\Omega (b(x,q)p(x,q,t)) \cdot \nabla w(x,q,t)dxdqdt$$
$$+ \int_0^T \int_\Omega [b(x,q)p(x,q,t) \cdot \vec{n}]w = 0$$

Choose $w(x,q,t) = 0$ on $\partial\Omega$, we have:

$$\int_0^T \int_\Omega [b(x,q)p(x,q,t) \cdot \vec{n}]w = 0$$

Then the weak form

$$\int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t)dxdqdt - \int_0^T \int_\Omega (b(x,q)p(x,q,t)).\nabla w(x,q,t)dxdqdt = 0$$

We need to make the problem unconstrained using Lagrange multipliers:

$$L(p,w,u) = J(p,u) + \int_0^T \int_\Omega \left(\frac{dp}{dt} w(x,q,t) - (b(x,q)p(x,q,t)) \nabla \cdot w(x,q,t) \right) dxdqdt$$
$$L(p,w,u) = \frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d\left(x,q_m,t\right) \right)^2 dxdqdt + \frac{\beta}{2} \int_0^T (u(t))^2 dt$$
$$+ \int_0^T \int_\Omega \frac{dp}{dt} w(x,q,t)dxdqdt - \int_0^T \int_\Omega (b(x,q)p(x,q,t)) \cdot \nabla w(x,q,t)dxdqdt$$

C.6 Forward equations:

$$\frac{dL}{dw} = \lim_{\varepsilon \to 0} \frac{L(p, w + \varepsilon\widetilde{w}, u) - L(p,w,u)}{\varepsilon} = 0$$
$$\frac{dL(p,w,u)}{dw} = \frac{1}{\varepsilon} \left(\lim_{\varepsilon \to 0} \frac{\alpha}{2} \int_0^T \int_\Omega \left(p(x,q,t) - p^d\left(x,q_m,t\right) \right)^2 dxdqdt + \frac{\beta}{2} \int_0^T (u(t))^2 dt \right.$$

$$+\int_0^T\int_\Omega\left(\frac{dp}{dt}(w+\varepsilon\widetilde{w})(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot(w+\varepsilon\widetilde{w})(x,q,t)\right)dxdqdt$$

$$-\left(\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt\frac{\beta}{2}\int_0^T(u(t))^2dt\right.$$

$$\left.+\int_0^T\int_\Omega\left(\frac{dp}{dt}w(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot w(x,q,t)\right)dxdqdt\right)\Bigg)=0$$

$$=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\int_0^T\int_\Omega\left(\frac{dp}{dt}(w+\varepsilon\widetilde{w})(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot(w+\varepsilon\widetilde{w})(x,q,t)\right)dxdqdt\right.$$

$$\left.-\left(\int_0^T\int_\Omega\left(\frac{dp}{dt}w(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot w(x,q,t)\right)dxdqdt\right)\right)=0$$

$$=\frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\int_0^T\int_\Omega\left(\frac{dp}{dt}\varepsilon\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot\varepsilon\widetilde{w}(x,q,t)\right)dxdqdt\right)=0$$

$$=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla\cdot\widetilde{w}(x,q,t)\right)dxdqdt=0$$

$$=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-(b(x,q)p(x,q,t))\nabla.\widetilde{w}(x,q,t)+\int_0^T\int_\Omega[b(x,q)p(x,q,t).\vec{n}]w\right)dxdqdt=0$$

$$=\int_0^T\int_\Omega\left(\frac{dp}{dt}\widetilde{w}(x,q,t)-\nabla\cdot(b(x,q)p(x,q,t))\widetilde{w}(x,q,t)\right)dxdqdt=0$$

$$=\int_0^T\int_\Omega\left(\frac{dp}{dt}+\nabla\cdot(b(x,q)p(x,q,t))\right)\widetilde{w}(x,q,t)dxdqdt=0$$

Remove $\widetilde{w}(x,q,t)$, then we have

$$\frac{dp}{dt}+\nabla\cdot(b(x,q)p(x,q,t))=0$$

$$p(x,q,0)=p_0(x,q)=0$$

C.7 Adjoint equation:

$$
\begin{aligned}
\frac{dL(p,w,u)}{dp} &= \lim_{\varepsilon\to 0}\frac{L(p+\varepsilon\tilde{p},w,u)-L(p,w,u)}{\varepsilon}=0\\
&= \frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega\left((p+\varepsilon\tilde{p})(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt+\frac{\beta}{2}\int_0^T(u(t))^2dt\right.\\
&+\int_0^T\int_\Omega\frac{d(p+\varepsilon\tilde{p})}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega(b(x,q)(p+\varepsilon\tilde{p})(x,q,t)).\nabla w(x,q,t)dxdqdt\\
&-\left(\frac{\alpha}{2}\int_0^T\int_\Omega\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt+\frac{\beta}{2}\int_0^T(u(t))^2dt\right.\\
&\left.\left.+\int_0^T\int_\Omega\frac{dp}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega(b(x,q)p(x,q,t)).\nabla w(x,q,t)dxdqdt\right)\right)
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega\left((p+\varepsilon\tilde{p})(x,q,t)-p^d\left(x,q_m,t\right)\right)^2-\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt\right.\\
&\left.+\int_0^T\int_\Omega\left(\frac{d(p+\varepsilon\tilde{p}-p)}{dt}\right)w(x,q,t)dxdqdt-\int_0^T\int_\Omega(b(x,q)(p+\varepsilon\tilde{p}-p)(x,q,t))\cdot\nabla w(x,q,t)dxdqdt\right)
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega\left((p+\varepsilon\tilde{p})(x,q,t)-p^d\left(x,q_m,t\right)\right)^2-\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt\right.\\
&\left.+\varepsilon\int_0^T\int_\Omega\frac{d\tilde{p}}{dt}w(x,q,t)dxdqdt-\varepsilon\int_0^T\int_\Omega(b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt\right)
\end{aligned}
$$

$$
= \frac{1}{\varepsilon}\left(\lim_{\varepsilon\to 0}\frac{\alpha}{2}\int_0^T\int_\Omega\left((p+\varepsilon\tilde{p})(x,q,t)-p^d\left(x,q_m,t\right)\right)^2-\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2dxdqdt\right.
$$

$$+\varepsilon \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt - \varepsilon \int_0^T \int_\Omega (b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt \Bigg)$$

$$= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0} \frac{\alpha}{2} \int_0^T \int_\Omega (p+\varepsilon\tilde{p})^2 - 2pp^d - 2\varepsilon\tilde{p}p^d + \left(p^d\right)^2 - (p)^2 + 2pp^d - \left(p^d\right)^2 dxdqdt$$
$$+\varepsilon \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt - \varepsilon \int_0^T \int_\Omega (b(x,q)\tilde{p}(x,q,t)) \cdot \nabla w(x,q,t)dxdqdt \Bigg) = 0$$

$$= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0} \frac{\alpha}{2} \int_0^T \int_\Omega \left((p)^2 + 2p\varepsilon\tilde{p} + (\varepsilon\tilde{p})^2 - 2pp^d - 2\varepsilon\tilde{p}p^d + \left(p^d\right)^2 - (p)^2 + 2pp^d - \left(p^d\right)^2 \right) dxdqdt$$
$$+\varepsilon \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt - \varepsilon \int_0^T \int_\Omega (b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt \Bigg) = 0$$

$$= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0} \frac{\alpha}{2} \int_0^T \int_\Omega \left((p)^2 + 2p\varepsilon\tilde{p} + (\varepsilon\tilde{p})^2 - 2pp^d - 2\varepsilon\tilde{p}p^d + \left(p^d\right)^2 - (p)^2 + 2pp^d - \left(p^d\right)^2 \right) dxdqdt$$
$$+\varepsilon \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt - \varepsilon \int_0^T \int_\Omega (b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt \Bigg) = 0$$

$$= \frac{1}{\varepsilon}\Bigg(\lim_{\varepsilon\to 0} \frac{\alpha}{2} \int_0^T \int_\Omega \left(2p\varepsilon\tilde{p} + (\varepsilon)^2(\tilde{p})^2 - 2\varepsilon\tilde{p}p^d \right) dxdqdt$$
$$+\varepsilon \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt - \varepsilon \int_0^T \int_\Omega (b(x,q)\tilde{p}(x,q,t)) \cdot \nabla w(x,q,t)dxdqdt \Bigg) = 0$$
$$= \frac{\alpha}{2} \int_0^T \int_\Omega 2\left(p - p^d\right)\tilde{p}dxdqdt + \int_0^T \int_\Omega \frac{d\tilde{p}}{dt} w(x,q,t)dxdqdt$$

$$-\int_0^T\int_\Omega (b(x,q)\tilde{p}(x,q,t)).\nabla w(x,q,t)dxdqdt=0$$

$$=\alpha\int_0^T\int_\Omega \left(p-p^d\right)\tilde{p}dxdqdt-\int_\Omega\int_0^T \frac{dw}{dt}\tilde{p}(x,q,t)dxdqdt+\int_\Omega \tilde{p}(T)w(T)dxdq$$

$$-\int_\Omega \tilde{p}(0)w(0)dxdq-\int_0^T\int_\Omega (b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt=0$$

Choose $w(T)=0$

$$=\alpha\int_0^T\int_\Omega \left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)\tilde{p}dxdxdqdt-\int_\Omega\int_0^T \frac{dw}{dt}\tilde{p}(x,q,t)dxdqdt$$

$$-\int_0^T\int_\Omega (b(x,q)\tilde{p}(x,q,t))\cdot\nabla w(x,q,t)dxdqdt=0$$

$$=\int_0^T\int_\Omega \left(\alpha\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)-\frac{dw}{dt}-b(x,q).\nabla w(x,q,t)\right)\tilde{p}(x,q,t)\quad dxdqdt=0$$

Take

$$\alpha\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)-\frac{dw}{dt}-b(x,q).\nabla w(x,q,t)=0$$

Then, the adjoint equation:

$$\alpha\left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)=\frac{dw}{dt}+b(x,q).\nabla w(x,q,t)$$

$$w(x,q,T)=0$$

$$w(x,q)=0 \text{ on } \partial\Omega$$

C.8 optimality condition

Lagrange multipliers

$$L(p,w,u)=\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2 dxdqdt+\frac{\beta}{2}\int_0^T (u(t))^2dt$$
$$+\int_0^T\int_\Omega \frac{dp}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega (b(x,q)p(x,q,t)).\nabla w(x,q,t)dxdqdt$$

$$L(p,w,u)=\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2 dxdqdt+\frac{\beta}{2}\int_0^T (u(t))^2dt$$
$$+\int_0^T\int_\Omega \frac{dp}{dt}w(x,q,t)dxdqdt-\int_0^T\int_\Omega \left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx\right.\right.$$
$$\left.\left.-c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq-\gamma qu\right)p(x,q,t)\right).\nabla wdxdqdt$$

$$\frac{dL}{du}=\lim_{\varepsilon\to 0}\frac{L(p,w,u+\varepsilon\bar{u})-L(p,w,u)}{\varepsilon}=0$$
$$=\frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2 dxdqdt\right.$$
$$+\frac{\beta}{2}\int_0^T ((u+\varepsilon\bar{u})(t))^2dt+\int_0^T\int_\Omega \frac{dp}{dt}w(x,q,t)dxdqdt$$
$$-\int_0^T\int_\Omega \left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq\right.\right.$$
$$-\gamma q(u+\varepsilon\bar{u}))p(x,q,t))\cdot\nabla wdxdqdt)$$
$$-\left(\frac{\alpha}{2}\int_0^T\int_\Omega \left(p(x,q,t)-p^d\left(x,q_m,t\right)\right)^2 dxdqdt+\frac{\beta}{2}\int_0^T (u(t))^2dt+\int_0^T\int_\Omega^{dp} \frac{d}{dt}w(x,q,t)dxdqdt\right.$$
$$-\int_0^T\int_\Omega \left(\left(\mu_m\left(1-\frac{s}{q}\right)x-dx-c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h}-\mu_m(q-s)-bq\right.\right.$$
$$-\gamma qu)p(x,q,t))\cdot\nabla wdxdqdt)=0$$

$$\frac{dL}{du} = \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\int_0^T ((u+\varepsilon\bar{u})(t))^2 dt - \frac{\beta}{2}\int_0^T (u(t))^2 dt\right.$$

$$- \int_0^T \int_\Omega \left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq\right.\right.$$

$$- \gamma q(u+\varepsilon\bar{u}))p(x,q,t)) \cdot \nabla w dx dq dt$$

$$+ \int_0^T \int_\Omega \left(\left(\mu_m\left(1-\frac{s}{q}\right)x - dx - c\frac{k^n}{q^n+k^n}x, v_m\frac{q_m-q}{q_m-s}\frac{A}{A+v_h} - \mu_m(q-s) - bq\right.\right.$$

$$- \gamma qu)p(x,q,t)) \cdot \nabla w dx dq dt) = 0$$

$$= \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\int_0^T ((u+\varepsilon\bar{u}))^2 - u^2 dt - \int_0^T \int_\Omega ((0, -\gamma q\varepsilon\bar{u})p(x,q,t)) \cdot \nabla w dx dq dt\right)$$

$$= \int_0^T \beta u\bar{u} dt - \int_0^T \int_\Omega ((0, -\gamma q\bar{u})p(x,q,t)) \cdot \nabla w dx dq dt$$

$$= \frac{1}{\varepsilon}\lim_{\varepsilon\to 0}\left(\frac{\beta}{2}\int_0^T \left(u^2 + 2\varepsilon u\bar{u} + (\varepsilon\bar{u})^2 - u^2\right) dt - \int_0^T \int_\Omega ((0, -\gamma q\varepsilon\bar{u})p(x,q,t)) \cdot \nabla w dx dq dt\right)$$

$$\frac{\beta}{2}\int_0^T \left(2\varepsilon u\bar{u} + (\varepsilon\bar{u})^2\right) dt - \int_0^T \int_\Omega ((0, -\gamma q\varepsilon\bar{u})p(x,q,t)) \cdot \nabla w dx dq dt\Bigg)$$

Remove $\bar{u}$, then we have

$$\frac{dL}{du} = \int_0^T \beta u dt - \int_0^T \int_\Omega ((0, -\gamma q)p(x,q,t)) \cdot \nabla w dx dq dt$$

optimality condition

$$\int_0^T \beta u dt - \int_0^T \int_\Omega ((0, -\gamma q)p(x,q,t)) \cdot \nabla w dx dq dt$$

We can simplify as:

$$\int_0^T \beta u dt - \int_0^T \int_\Omega \left(-\gamma q p(x,q,t)\frac{dw}{dq}\right) dx dq dt = 0$$

C.9 Kurganov-Tadmor (KT) scheme

The semi discrete scheme for solving $\frac{df}{dt}+\frac{d}{dx}(bf)=0$, Using the Kurganov-Tadmor (KT) scheme.

Let (a,c) be a spatial domain. Where $a=x_0,x_1,x_2,\ldots,x_{n-1},x_n=c$ are grid points. Let $x_{i+\frac{1}{2}}=x_{\frac{1}{2}},x_{\frac{3}{2}},x_{\frac{5}{2}},\ldots,x_{n-\frac{1}{2}}$ for all $i=1,2,\ldots,n$ are the mid-point grids. Let $\bar{f}\left(x_i\right)=\frac{1}{h}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}}f(x)dx$ be the average value of f in $\left(x_{i-\frac{1}{2}},x_{i+\frac{1}{2}}\right)$. Then we have

$$\begin{aligned}\int_{x+\frac{1}{2}}^{x_{i+\frac{1}{2}}}\frac{df}{dt}+\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}}\frac{d}{dx}(bf)&=\frac{d}{dt}\frac{1}{h}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}}f\,dx+\frac{1}{h}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}}\frac{d}{dx}(bf)=0\\&=\frac{d}{dt}\bar{f}\left(x_i\right)+\frac{1}{h}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}}\frac{d}{dx}(bf)=0\end{aligned}$$

Using integration by parts, we have

$$=\frac{d}{dt}\bar{f}\left(x_i\right)+\frac{b_{i+\frac{1}{2}}\bar{f}\left(x_{i+\frac{1}{2}}\right)-b_{i-\frac{1}{2}}\bar{f}\left(x_{i-\frac{1}{2}}\right)}{h}=0$$

Now,

$$\frac{d}{dt}\bar{f}\left(x_i\right)=-\left(\frac{b_{i+\frac{1}{2}}\bar{f}\left(x_{i+\frac{1}{2}}\right)-b_{i-\frac{1}{2}}\bar{f}\left(x_{i-\frac{1}{2}}\right)}{h}\right)=\frac{-b_{i+\frac{1}{2}}\bar{f}\left(x_{i+\frac{1}{2}}\right)+b_{i-\frac{1}{2}}\bar{f}\left(x_{i-\frac{1}{2}}\right)}{h}$$
$$=\frac{-\mathcal{F}\left(x_{i+\frac{1}{2}}\right)+\mathcal{F}\left(x_{i-\frac{1}{2}}\right)}{h}$$

The second order approximation: Let

$$\begin{aligned}\mathcal{F}\left(x_{i+\frac{1}{2}}\right)&=b_{i+\frac{1}{2}}\bar{f}\left(x_{i+\frac{1}{2}}\right)\approx\mathcal{H}i+\frac{1}{2}(\bar{f})\\&=\frac{bi+\frac{1}{2}\bar{f}^{+}\left(x_{i+\frac{1}{2}}\right)+b_{i+\frac{1}{2}}\bar{f}^{-}\left(x_{i+\frac{1}{2}}\right)}{2}-\frac{\left|b_{i+\frac{1}{2}}\right|}{2}\left[\bar{f}^{+}\left(x_{i+\frac{1}{2}}\right)-\bar{f}^{-}\left(x_{i+\frac{1}{2}}\right)\right]\\\mathcal{F}\left(x_{i-\frac{1}{2}}\right)&=b_{i-\frac{1}{2}}\bar{f}\left(x_{i-\frac{1}{2}}\right)\approx\mathcal{H}i-\frac{1}{2}(\bar{f})\\&=\frac{bi-\frac{1}{2}\bar{f}^{+}\left(x_{i-\frac{1}{2}}\right)+b_{i-\frac{1}{2}}\bar{f}^{-}\left(x_{i-\frac{1}{2}}\right)}{2}-\frac{\left|b_{i-\frac{1}{2}}\right|}{2}\left[\bar{f}^{+}\left(x_{i-\frac{1}{2}}\right)-\bar{f}^{-}\left(x_{i-\frac{1}{2}}\right)\right]\end{aligned}$$

Where $\mathcal{H}_{i+\frac{1}{2}}(\bar{f})$ is an approximation to $\mathcal{F}\left(x_{i+\frac{1}{2}}\right)$.

We denote by $x_{i+\frac{1}{2}}$ and $x_{i-\frac{1}{2}}$ the left and right intermediate values. So,

$$\frac{d}{dt}\bar{f}\left(x_i\right) = \frac{-\left[b_{i+\frac{1}{2}}\bar{f}^{+}\left(x_{i+\frac{1}{2}}\right) + b_{i+\frac{1}{2}}\bar{f}^{-}\left(x_{i+\frac{1}{2}}\right)\right] + \left[b_{i-\frac{1}{2}}\bar{f}^{+}\left(x_{i-\frac{1}{2}}\right) + b_{i-\frac{1}{2}}\bar{f}^{-}\left(x_{i-\frac{1}{2}}\right)\right]}{2h}$$
$$+ \frac{\left|b_{i+\frac{1}{2}}\right|}{2h}\left[\bar{f}^{+}\left(x_{i+\frac{1}{2}}\right) - \bar{f}^{-}\left(x_{i+\frac{1}{2}}\right)\right] - \frac{\left|b_{i-\frac{1}{2}}\right|}{2h}\left[\bar{f}^{+}\left(x_{i-\frac{1}{2}}\right) - \bar{f}^{-}\left(x_{i-\frac{1}{2}}\right)\right]$$

Where,

$$\bar{f}^{+}\left(x_{i+\frac{1}{2}}\right) = \bar{f}\left(x_{i+1}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1}\right)$$
$$\bar{f}^{-}\left(x_{i+\frac{1}{2}}\right) = f\left(x_i\right) + \frac{h}{2}f'\left(x_i\right)$$

Similarly, for the negative half-points

$$\bar{f}^{+}\left(x_{i-\frac{1}{2}}\right) = \bar{f}\left(x_{i+1}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1}\right)$$
$$\bar{f}^{-}\left(x_{i-\frac{1}{2}}\right) = \bar{f}\left(x_i\right) + \frac{h}{2}\bar{f}'\left(x_i\right)$$

Note: To find $f'\left(x_i\right)$ we will be using minmod function.

Now, we discretize the time variable t into a series of time steps, such that $t_k = 0, 1, \ldots, M$ where $t_k = 0 + k\Delta t$ and $\Delta t = \frac{T}{M}$, since we discretized the time variable, we also need to write an approximation to $\frac{d}{dt}\bar{f}\left(x_{i,k}\right)$ using Euler scheme. $\frac{d}{dt}\bar{f}\left(x_{i,k}\right) \approx \frac{\bar{f}\left(x_{i,k+1}\right) - \bar{f}\left(x_{i,k}\right)}{\Delta t}$

$$\frac{\bar{f}\left(x_{i,k+1}\right) - \bar{f}\left(x_{i,k}\right)}{\Delta t} = -\left(\frac{b_{i+\frac{1}{2},k}\bar{f}\left(x_{i+\frac{1}{2},k}\right) - b_{i-\frac{1}{2},k}\bar{f}\left(x_{i-\frac{1}{2},k}\right)}{h}\right)$$
$$= \frac{-b_{i+\frac{1}{2},k}\bar{f}\left(x_{i+\frac{1}{2},k}\right) + b_{i-\frac{1}{2},k}\bar{f}\left(x_{i-\frac{1}{2},k}\right)}{h} \quad = \frac{-\mathcal{F}\left(x_{i+\frac{1}{2},k}\right) + \mathcal{F}\left(x_{i-\frac{1}{2},k}\right)}{h}$$

The second order approximation: Let

$$\mathcal{F}\left(x_{i+\frac{1}{2},k}\right) = b_{i+\frac{1}{2},k}\bar{f}\left(x_{i+\frac{1}{2},k}\right) \approx \mathcal{H}_{i+\frac{1}{2},k}(\bar{f})$$
$$= \frac{b_{i+\frac{1}{2},k}\bar{f}^{+}\left(x_{i+\frac{1}{2},k}\right) + b_{i+\frac{1}{2},k}\bar{f}^{-}\left(x_{i+\frac{1}{2},k}\right)}{2} - \frac{\left|b_{i+\frac{1}{2},k}\right|}{2}\left[\bar{f}^{+}\left(x_{i+\frac{1}{2},k}\right) - \bar{f}^{-}\left(x_{i+\frac{1}{2},k}\right)\right]$$
$$\mathcal{F}\left(x_{i-\frac{1}{2},k}\right) = b_{i-\frac{1}{2},k}\bar{f}\left(x_{i-\frac{1}{2},k}\right) \approx \mathcal{H}_{i-\frac{1}{2},k}(\bar{f})$$
$$= \frac{b_{i-\frac{1}{2},k}\bar{f}^{+}\left(x_{i-\frac{1}{2},k}\right) + b_{i-\frac{1}{2},k}\bar{f}^{-}\left(x_{i-\frac{1}{2},k}\right)}{2} - \frac{\left|b_{i-\frac{1}{2},k}\right|}{2} \mid \bar{f}^{+}\left(x_{i-\frac{1}{2},k}\right) - \bar{f}^{-}\left(x_{i-\frac{1}{2},k}\right)\Bigg]$$

We denote by $x_{i+\frac{1}{2}}$ and $x_{i-\frac{1}{2}}$ the left and right intermediate values. So,

$$\frac{\bar{f}\left(x_{i,k+1}\right) - \bar{f}\left(x_{i,k}\right)}{\Delta t}$$
$$= \frac{-\left[b_{i+\frac{1}{2},k}\bar{f}^{+}\left(x_{i+\frac{1}{2},k}\right) + b_{i+\frac{1}{2},k}\bar{f}^{-}\left(x_{i+\frac{1}{2},k}\right)\right] + \left[b_{i-\frac{1}{2},k}\bar{f}^{+}\left(x_{i-\frac{1}{2},k}\right) + b_{i-\frac{1}{2},k}\bar{f}^{-}\left(x_{i-\frac{1}{2},k}\right)\right]}{2h}$$
$$+ \frac{\left|b_{i+\frac{1}{2},k}\right|}{2h}\left[\bar{f}^{+}\left(x_{i+\frac{1}{2},k}\right) - \bar{f}^{-}\left(x_{i+\frac{1}{2},k}\right)\right] - \frac{\left|b_{i-\frac{1}{2},k}\right|}{2h}\left[\bar{f}^{+}\left(x_{i-\frac{1}{2},k}\right) - \bar{f}^{-}\left(x_{i-\frac{1}{2},k}\right)\right]$$

Where,

$$\bar{f}^{+}\left(x_{i+\frac{1}{2},k}\right) = \bar{f}\left(x_{i+1,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,k}\right)$$
$$\bar{f}^{-}\left(x_{i+\frac{1}{2},k}\right) = \bar{f}\left(x_{i,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,k}\right)$$

Similarly, for the negative half-points

$$\bar{f}^{+}\left(x_{i-\frac{1}{2},k}\right) = \bar{f}\left(x_{i+1,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,k}\right)$$
$$\bar{f}^{-}\left(x_{i-\frac{1}{2},k}\right) = \bar{f}\left(x_{i,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,k}\right)$$

Extension to two dimensions

$$\begin{aligned}
\frac{d}{dt}\bar{f}\left(x_{i,j}\right) =& -\left(\frac{b^1_{i+\frac{1}{2},j}\bar{f}\left(x_{i+\frac{1}{2},j}\right) - b^1_{i-\frac{1}{2},j}\bar{f}\left(x_{i-\frac{1}{2},j}\right)}{\Delta x}\right) - \left(\frac{b^2_{i,j+\frac{1}{2}}\bar{f}\left(x_{i,j+\frac{1}{2}}\right) - b^2_{i,j-\frac{1}{2}}\bar{f}\left(x_{i,j-\frac{1}{2}}\right)}{\Delta y}\right) \\
=& \frac{-b^1_{i+\frac{1}{2},j}\bar{f}\left(x_{i+\frac{1}{2},j}\right) + b^1_{i-\frac{1}{2},j}\bar{f}\left(x_{i-\frac{1}{2},j}\right)}{\Delta x} + \frac{-b^2_{i,j+\frac{1}{2}}\bar{f}\left(x_{i,j+\frac{1}{2}}\right) + b^2_{i,j-\frac{1}{2}}\bar{f}\left(x_{i,j-\frac{1}{2}}\right)}{\Delta y} \\
=& \frac{-\mathcal{F}_x\left(x_{i+\frac{1}{2},j}\right) + \mathcal{F}_x\left(x_{i-\frac{1}{2},j}\right)}{\Delta x} + \frac{\mathcal{F}_y\left(x_{i,j+\frac{1}{2}}\right) + \mathcal{F}_y\left(x_{i,j-\frac{1}{2}}\right)}{\Delta y}
\end{aligned}$$

The second order approximation: Let

$$\begin{aligned}
\mathcal{F}_x\left(x_{i+\frac{1}{2},j}\right) =& b^1_{i+\frac{1}{2},j}\bar{f}\left(x_{i+\frac{1}{2},j}\right) \approx \mathcal{H}_{i+\frac{1}{2},j}(\bar{f}) \\
=& \frac{b^1_{i+\frac{1}{2},j}\bar{f}^+\left(x_{i+\frac{1}{2},j}\right) + b^1_{i+\frac{1}{2},j}\bar{f}^-\left(x_{i+\frac{1}{2},j}\right)}{2} - \frac{\left|b^1_{i+\frac{1}{2},j}\right|}{2}\left[\bar{f}^+\left(x_{i+\frac{1}{2},j}\right) - \bar{f}^-\left(x_{i+\frac{1}{2},j}\right)\right] \\
\mathcal{F}_x\left(x_{i-\frac{1}{2},j}\right) =& b^1_{i-\frac{1}{2},j}\bar{f}\left(x_{i-\frac{1}{2},j}\right) \approx \mathcal{H}_{i-\frac{1}{2},j}(\bar{f}) \\
=& \frac{b^1_{i-\frac{1}{2},j}\bar{f}^+\left(x_{i-\frac{1}{2},j}\right) + b^1_{i-\frac{1}{2},j}\bar{f}^-\left(x_{i-\frac{1}{2},j}\right)}{2} - \frac{\left|b^1_{i-\frac{1}{2},j}\right|}{2}\left[\bar{f}^+\left(x_{i-\frac{1}{2},j}\right) - \bar{f}^-\left(x_{i-\frac{1}{2},j}\right)\right] \\
\mathcal{F}_y\left(x_{i,j+\frac{1}{2}}\right) =& b^2_{i,j+\frac{1}{2}}\bar{f}\left(x_{i,j+\frac{1}{2}}\right) \approx \mathcal{H}_{i,j+\frac{1}{2}}(\bar{f}) \\
=& \frac{b^2_{i,j+\frac{1}{2}}\bar{f}^+\left(x_{i,j+\frac{1}{2}}\right) + b^2_{i,j+\frac{1}{2}}\bar{f}^-\left(x_{i,j+\frac{1}{2}}\right)}{2} - \frac{\left|b^2_{i,j+\frac{1}{2}}\right|}{2}\left[\bar{f}^+\left(x_{i,j+\frac{1}{2}}\right) - \bar{f}^-\left(x_{i,j+\frac{1}{2}}\right)\right] \\
\mathcal{F}_y\left(x_{i,j-\frac{1}{2}}\right) =& b^2_{i,j-\frac{1}{2}}\bar{f}\left(x_{i,j-\frac{1}{2}}\right) \approx \mathcal{H}_{i,j-\frac{1}{2}}(\bar{f}) \\
=& \frac{b^2_{i,j-\frac{1}{2}}\bar{f}^+\left(x_{i,j-\frac{1}{2}}\right) + b^2_{i,j-\frac{1}{2}}\bar{f}^-\left(x_{i,j-\frac{1}{2}}\right)}{2} - \frac{\left|b^2_{i,j-\frac{1}{2}}\right|}{2}\left[\bar{f}^+\left(x_{i,j-\frac{1}{2}}\right) - \bar{f}^-\left(x_{i,j-\frac{1}{2}}\right)\right]
\end{aligned}$$

$$
\begin{aligned}
&\frac{d}{dt}\bar{f}\left(x_{i,j}\right) = \\
&\qquad \frac{-\left[b^1_{i+\frac{1}{2},j}\bar{f}^+\left(x_{i+\frac{1}{2},j}\right) + b^1_{i+\frac{1}{2},j}\bar{f}^-\left(x_{i+\frac{1}{2},j}\right)\right] + \left[b^1_{i-\frac{1}{2},j}\bar{f}^+\left(x_{i-\frac{1}{2},j}\right) + b^1_{i-\frac{1}{2},j}\bar{f}^-\left(x_{i-\frac{1}{2},j}\right)\right]}{\Delta x} \\
&\qquad + \frac{-\left[b^2_{i,j+\frac{1}{2}}\bar{f}^+\left(x_{i,j+\frac{1}{2}}\right) + b^2_{i,j+\frac{1}{2}}\bar{f}^-\left(x_{i,j+\frac{1}{2}}\right)\right] + \left[b^2_{i,j-\frac{1}{2}}\bar{f}^+\left(x_{i,j-\frac{1}{2}}\right) + b^2_{i,j-\frac{1}{2}}\left(x_{i,j-\frac{1}{2}}\right)\right]}{\Delta y} \\
&\qquad + \frac{\left|b^1_{i+\frac{1}{2},j}\right|}{2}\left[\bar{f}^+\left(x_{i+\frac{1}{2},j}\right) - \bar{f}^-\left(x_{i+\frac{1}{2},j}\right)\right] - \frac{\left|b^1_{i-\frac{1}{2},j}\right|}{2}\left[\bar{f}^+\left(x_{i-\frac{1}{2},j}\right) - \bar{f}^-\left(x_{i-\frac{1}{2},j}\right)\right] \\
&\qquad + \frac{\left|b^2_{i,j+\frac{1}{2}}\right|}{2}\left[\bar{f}^+\left(x_{i,j+\frac{1}{2}}\right) - \bar{f}^-\left(x_{i,j+\frac{1}{2}}\right)\right] - \frac{\left|b^2_{i,j-\frac{1}{2}}\right|}{2}\left[\bar{f}^+\left(x_{i,j-\frac{1}{2}}\right) - \bar{f}^-\left(x_{i,j-\frac{1}{2}}\right)\right]
\end{aligned}
$$

Where,

$$
\begin{aligned}
\bar{f}^+\left(x_{i+\frac{1}{2},j}\right) &= \bar{f}\left(x_{i+1,j}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,j}\right) \\
\bar{f}^-\left(x_{i+\frac{1}{2},j}\right) &= \bar{f}\left(x_{i,j}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j}\right) \\
\bar{f}^+\left(x_{i,j+\frac{1}{2}}\right) &= \bar{f}\left(x_{i,j+1}\right) - \frac{h}{2}\bar{f}'\left(x_{i,j+1}\right) \\
\bar{f}^-\left(x_{i,j+\frac{1}{2}}\right) &= \bar{f}\left(x_{i,j}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j}\right)
\end{aligned}
$$

And similarly, for the negative half-points

$$
\begin{aligned}
\bar{f}^+\left(x_{i-\frac{1}{2},j}\right) &= \bar{f}\left(x_{i+1,j}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,j}\right) \\
\bar{f}^-\left(x_{i-\frac{1}{2},j}\right) &= \bar{f}\left(x_{i,j}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j}\right) \\
\bar{f}^+\left(x_{i,j-\frac{1}{2}}\right) &= \bar{f}\left(x_{i,j+1}\right) - \frac{h}{2}\bar{f}'\left(x_{i,j+1}\right) \\
\bar{f}^-\left(x_{i,j-\frac{1}{2}}\right) &= \bar{f}\left(x_{i,j}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j}\right)
\end{aligned}
$$

Now, we discretize the time variable t into a series of time steps, such that $t_k = 0, 1, \ldots, M$ where $t_k = 0 + k\Delta t$ and $\Delta t = \frac{T}{M}$, since we discretized the time variable, we also need to write an approximation to $\frac{d}{dt}\bar{f}\left(x_{i,j,k}\right)$ using Euler scheme. $\frac{d}{dt}\bar{f}\left(x_{i,j,k}\right) = \frac{\bar{f}\left(x_{i,j,k+1}\right)-\bar{f}\left(x_{i,j,k}\right)}{\Delta t}$

$$
\begin{aligned}
&\frac{\bar{f}\left(x_{i,j,k+1}\right)-\bar{f}\left(x_{i,j,k}\right)}{\Delta t}\\
&= -\left(\frac{b^1_{i+\frac{1}{2},j,k}\bar{f}\left(x_{i+\frac{1}{2},j,k}\right) - b^1_{i-\frac{1}{2},j,k}\bar{f}\left(x_{i-\frac{1}{2},j,k}\right)}{\Delta x}\right)\\
&-\left(\frac{b^2_{i,j+\frac{1}{2},k}\bar{f}\left(x_{i,j+\frac{1}{2},k}\right) - b^2_{i,j-\frac{1}{2},k}\bar{f}\left(x_{i,j-\frac{1}{2},k}\right)}{\Delta y}\right)\\
&= \frac{-b^1_{i+\frac{1}{2},j,k}\bar{f}\left(x_{i+\frac{1}{2},j,k}\right) + b^1_{i-\frac{1}{2},j,k}\bar{f}\left(x_{i-\frac{1}{2},j,k}\right)}{\Delta x} + \frac{-b^2_{i,j+\frac{1}{2},k}\bar{f}\left(x_{i,j+\frac{1}{2},k}\right) + b^2_{i,j-\frac{1}{2},k}\bar{f}\left(x_{i,j-\frac{1}{2},k}\right)}{\Delta y}\\
&= \frac{-\mathcal{F}_x\left(x_{i+\frac{1}{2},j,k}\right) + \mathcal{F}_x\left(x_{i-\frac{1}{2},j,k}\right)}{\Delta x} + \frac{-\mathcal{F}_y\left(x_{i,j+\frac{1}{2},k}\right) + \mathcal{F}_y\left(x_{i,j-\frac{1}{2},k}\right)}{\Delta y}
\end{aligned}
$$

The second order approximation, Let

$$\begin{aligned}
\mathcal{F}_x\left(x_{i+\frac{1}{2},j,k}\right) &= b^1_{i+\frac{1}{2},j,k}\bar{f}\left(x_{i+\frac{1}{2},j,k}\right) \approx \mathcal{H}_{i+\frac{1}{2},j,k}(\bar{f}) \\
&= \frac{b^1_{i+\frac{1}{2},j,k}\bar{f}^+\left(x_{i+\frac{1}{2},j,k}\right) + b^1_{i+\frac{1}{2},j,k}\bar{f}^-\left(x_{i+\frac{1}{2},j,k}\right)}{2} \\
&- \frac{\left|b^1_{i+\frac{1}{2},j,k}\right|}{2}\left[\bar{f}^+\left(x_{i+\frac{1}{2},j,k}\right) - \bar{f}^-\left(x_{i+\frac{1}{2},j,k}\right)\right] \\
\mathcal{F}_x\left(x_{i-\frac{1}{2},j,k}\right) &= b^1 i - \frac{1}{2}, j, k\bar{f}\left(x_{i-\frac{1}{2},j,k}\right) \approx \mathcal{H}_{i-\frac{1}{2},j,k}(\bar{f}) \\
&= \frac{b^1 i - \frac{1}{2}, j, k\bar{f}^+\left(x_{i-\frac{1}{2},j,k}\right) + b^1 i - \frac{1}{2}, j, k\bar{f}^-\left(x_{i-\frac{1}{2},j,k}\right)}{2} \\
&- \frac{\left|b^1 i - \frac{1}{2}, j, k\right|}{2}\left[\bar{f}^+\left(x_{i-\frac{1}{2},j,k}\right) - \bar{f}^-\left(x_{i-\frac{1}{2},j,k}\right)\right] \\
\mathcal{F}_y\left(x_{i,j+\frac{1}{2},k}\right) &= b^2_{i,j+\frac{1}{2},k}\bar{f}\left(x_{i,j+\frac{1}{2},k}\right) \approx \mathcal{H}_{i,j+\frac{1}{2},k}(\bar{f}) \\
&= \frac{b^2 i, j + \frac{1}{2}, k\bar{f}^+\bar{f}\left(x_{i,j+\frac{1}{2},k}\right) + b^2 i, j + \frac{1}{2}, k\bar{f}^-\bar{f}\left(x_{i,j+\frac{1}{2},k}\right)}{2} \\
&- \frac{\left|b^2 i, j + \frac{1}{2}, k\right|}{2}\left[\bar{f}^+\left(x_{i,j+\frac{1}{2},k}\right) - \bar{f}^-\left(x_{i,j+\frac{1}{2},k}\right)\right] \\
\mathcal{F}\boldsymbol{y}\left(x_{i,j-\frac{1}{2},k}\right) &= b^2_{i,j-\frac{1}{2},k}\bar{f}\left(x_{i,j-\frac{1}{2},k}\right) \approx \mathcal{H}_{i,j-\frac{1}{2},k}(\bar{f}) \\
&= \frac{b^2 i, j - \frac{1}{2}, k\bar{f}^+\left(x_{i,j-\frac{1}{2},k}\right) + b^2_{i,j-\frac{1}{2},k}\bar{f}^-\left(x_{i,j-\frac{1}{2},k}\right)}{2} \\
&- \frac{\left|b^2 i, j - \frac{1}{2}, k\right|}{2}\left[\bar{f}^+\left(x_{i,j-\frac{1}{2},k}\right) - \bar{f}^-\left(x_{i,j-\frac{1}{2},k}\right)\right] \\
&\frac{\bar{f}\left(x_{i,j,k+1}\right) - \bar{f}\left(x_{i,j,k}\right)}{\Delta t}
\end{aligned}$$

$$
\begin{aligned}
&= \frac{-\left[b^1_{i+\frac{1}{2},j,k}\bar{f}^+\left(x_{i+\frac{1}{2},j,k}\right) + b^1_{i+\frac{1}{2},j,k}\bar{f}^-\left(x_{i+\frac{1}{2},j,k}\right)\right] + \left[b^1_{i-\frac{1}{2},j,k}\bar{f}^+\left(x_{i-\frac{1}{2},j,k}\right) + b^1_{i-\frac{1}{2},j,k}\bar{f}^-\left(x_{i-\frac{1}{2},j,k}\right)\right]}{\Delta x} \\
&+ \frac{-\left[b^2_{i,j+\frac{1}{2},k}\bar{f}^+\left(x_{i,j+\frac{1}{2},k}\right) + b^2_{i,j+\frac{1}{2},k}\bar{f}^-\left(x_{i,j+\frac{1}{2},k}\right)\right] + \left[b^2_{i,j-\frac{1}{2},k}\bar{f}^+\left(x_{i,j-\frac{1}{2},k}\right) + b^2_{i,j-\frac{1}{2},k}\bar{f}^-\left(x_{i,j-\frac{1}{2},k}\right)\right]}{\Delta y} \\
&+ \frac{\left|b^1_{i+\frac{1}{2},j,k}\right|}{2}\left[\bar{f}^+\left(x_{i+\frac{1}{2},j,k}\right) - \bar{f}^-\left(x_{i+\frac{1}{2},j,k}\right)\right] - \frac{\left|b^1_{i-\frac{1}{2},j,k}\right|}{2}\left[\bar{f}^+\left(x_{i-\frac{1}{2},j,k}\right) - \bar{f}^-\left(x_{i-\frac{1}{2},j,k}\right)\right] \\
&+ \frac{\left|b^2_{i,j+\frac{1}{2},k}\right|}{2}\left[\bar{f}^+\left(x_{i,j+\frac{1}{2},k}\right) - \bar{f}^-\left(x_{i,j+\frac{1}{2},k}\right)\right] - \frac{\left|b^2_{i,j-\frac{1}{2},k}\right|}{2}\left[\bar{f}^+\left(x_{i,j-\frac{1}{2},k}\right) - \bar{f}^-\left(x_{i,j-\frac{1}{2},k}\right)\right]
\end{aligned}
$$

Where,

$$
\begin{aligned}
\bar{f}^+\left(x_{i+\frac{1}{2},j,k}\right) &= \bar{f}\left(x_{i+1,j,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,j,k}\right) \\
\bar{f}^-\left(x_{i+\frac{1}{2},j,k}\right) &= \bar{f}\left(x_{i,j,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j,k}\right) \\
\bar{f}^+\left(x_{i,j+\frac{1}{2},k}\right) &= \bar{f}\left(x_{i,j+1,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i,j+1,k}\right) \\
\bar{f}^-\left(x_{i,j+\frac{1}{2},k}\right) &= \bar{f}\left(x_{i,j,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j,k}\right)
\end{aligned}
$$

And similarly, for the negative half-points

$$
\begin{aligned}
\bar{f}^+\left(x_{i-\frac{1}{2},j,k}\right) &= \bar{f}\left(x_{i+1,j,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i+1,j,k}\right) \\
\bar{f}^-\left(x_{i-\frac{1}{2},j,k}\right) &= \bar{f}\left(x_{i,j,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j,k}\right) \\
\bar{f}^+\left(x_{i,j-\frac{1}{2},k}\right) &= \bar{f}\left(x_{i,j+1,k}\right) - \frac{h}{2}\bar{f}'\left(x_{i,j+1,k}\right) \\
\bar{f}^-\left(x_{i,j-\frac{1}{2},k}\right) &= \bar{f}\left(x_{i,j,k}\right) + \frac{h}{2}\bar{f}'\left(x_{i,j,k}\right)
\end{aligned}
$$

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BIOGRAPHICAL STATEMENT

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