

University of Montana

## ScholarWorks at University of Montana

---

Graduate Student Theses, Dissertations, &  
Professional Papers

Graduate School

---

2004

### Asymptotic reductions of a model describing facilitated diffusion in membrane transport

Lucas A. Casady  
*The University of Montana*

Follow this and additional works at: <https://scholarworks.umt.edu/etd>

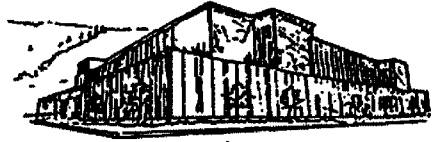
**Let us know how access to this document benefits you.**

---

#### Recommended Citation

Casady, Lucas A., "Asymptotic reductions of a model describing facilitated diffusion in membrane transport" (2004). *Graduate Student Theses, Dissertations, & Professional Papers*. 6639.  
<https://scholarworks.umt.edu/etd/6639>

This Thesis is brought to you for free and open access by the Graduate School at ScholarWorks at University of Montana. It has been accepted for inclusion in Graduate Student Theses, Dissertations, & Professional Papers by an authorized administrator of ScholarWorks at University of Montana. For more information, please contact [scholarworks@mso.umt.edu](mailto:scholarworks@mso.umt.edu).



Maureen and Mike  
**MANSFIELD LIBRARY**

The University of  
**Montana**

---

Permission is granted by the author to reproduce this material in its entirety, provided that this material is used for scholarly purposes and is properly cited in published works and reports.

**\*\*Please check "Yes" or "No" and provide signature\*\***

Yes, I grant permission



No, I do not grant permission

Author's Signature: *Luix Corbady*

Date: 5/26/04

Any copying for commercial purposes or financial gain may be undertaken only with the author's explicit consent.

---



ASYMPTOTIC REDUCTIONS OF A MODEL  
DESCRIBING FACILITATED DIFFUSION  
IN MEMBRANE TRANSPORT

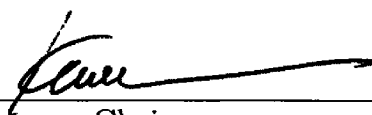
By  
Lucas A. Casady

M.A.T. Western Oregon University, U.S.A. 2002

B.Sc. Oregon State University, U.S.A. 1998

SUBMITTED IN PARTIAL FULFILLMENT OF THE  
REQUIREMENTS FOR THE DEGREE OF  
MASTER OF SCIENCE AT  
THE UNIVERSITY OF MONTANA  
MISSOULA, MONTANA  
MAY 2004

Approved by:



---

Chairperson



---

Dean, Graduate School

5-26-04

---

Date

UMI Number: EP37440

All rights reserved

**INFORMATION TO ALL USERS**

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI EP37440

Published by ProQuest LLC (2013). Copyright in the Dissertation held by the Author.

Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against  
unauthorized copying under Title 17, United States Code



ProQuest LLC.  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106 - 1346

# Abstract

Casady, Lucas A. M.Sc., May 2004

Mathematics

## **Asymptotic Reductions of a Model Describing Facilitated Diffusion in Membrane Transport**

Supervisor: Leonid V. Kalachev



Many nutrients that a cell needs are large and composed of lipid-insoluble molecules. These do not easily cross cell walls. In order to transport these large hydrophilic permeants, cells have specialized membrane-embedded proteins called carriers that by a conformational change, transport a specific permeant from one side of the membrane to the other. This mechanism is called facilitated diffusion.

In this thesis we will study the mechanisms of facilitated diffusion from a mathematical perspective. The goal of our study is to produce various asymptotically reduced models describing facilitated diffusion transport across membranes under various possible physiological conditions. These simplified models can later be used for parameter identification using experimental data. Also, such simplified models may be included as parts of more complex heterogeneous pharmacokinetics models.

# Table of Contents

<b>Abstract</b>	<b>ii</b>
<b>Table of Contents</b>	<b>iii</b>
<b>List of Tables</b>	<b>v</b>
<b>List of Figures</b>	<b>vi</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Model mechanism of facilitated diffusion transport . . . . .	3
1.2 Asymptotic Approximation Techniques . . . . .	7
1.2.1 Asymptotic Approximation Algorithm . . . . .	7
1.2.2 Conditions of the Asymptotic Approximation Algorithm . . . .	10
<b>2 Analysis of a simplified model</b>	<b>14</b>
2.1 Formulation of the model . . . . .	14
2.2 Analysis of Case 1 . . . . .	18
2.2.1 Re-scaling the equations . . . . .	18
2.2.2 The leading order approximation: Regular functions . . . . .	20
2.2.3 The leading order approximation: Boundary functions . . . . .	21
2.2.4 The regular functions' constant of integration . . . . .	23
2.2.5 Discussion . . . . .	23
2.3 Analysis of Case 2 . . . . .	26
2.3.1 The leading order approximation: Regular functions for Case 2	27
2.3.2 The first order approximation: Regular functions for Case 2 .	27
2.3.3 The leading order approximation: Boundary Functions for Case 2	28
2.3.4 Discussion . . . . .	29
2.4 Analysis of Case 3 . . . . .	30
2.4.1 The leading order approximation: Regular functions for Case 3	31

2.4.2	The leading order approximation: Boundary Functions for Case 3	31
2.4.3	Stability analysis for the regular functions . . . . .	32
2.4.4	Stability analysis for the boundary functions . . . . .	34
2.4.5	Discussion . . . . .	34
2.5	Analysis of Case 4 . . . . .	36
2.5.1	The leading order approximation: Regular functions for Case 4	37
2.5.2	The first order approximation: Regular functions for Case 4 .	37
2.5.3	The leading order approximation: Boundary Functions for Case 4	38
2.5.4	Discussion . . . . .	38
2.6	Analysis of Case 5 . . . . .	40
2.6.1	The leading order approximation: Regular functions for Case 5	41
2.6.2	The leading order approximation: Boundary Functions for Case 5	41
2.6.3	Stability analysis for the regular functions . . . . .	42
2.6.4	Stability analysis for the boundary functions . . . . .	44
2.6.5	Discussion . . . . .	44
2.7	Analysis of Case 6 . . . . .	46
2.7.1	The leading order approximation: Regular functions for Case 6	47
2.7.2	The leading order approximation: Boundary Functions for Case 6	47
2.7.3	Discussion . . . . .	50
2.8	Analyzing the simplified models . . . . .	52
2.8.1	Summary of Case 1 . . . . .	52
2.8.2	Summary of Case 2 . . . . .	52
2.8.3	Summary of Case 3 . . . . .	53
2.8.4	Summary of Case 4 . . . . .	53
2.8.5	Summary of Case 5 . . . . .	53
2.8.6	Summary of Case 6 . . . . .	54

<b>Bibliography</b>	<b>55</b>
---------------------	-----------



# List of Tables

- 2.8.1 Summary of Case 1, page 52
- 2.8.2 Summary of Case 2, page 52
- 2.8.3 Summary of Case 3, page 53
- 2.8.4 Summary of Case 4, page 53
- 2.8.5 Summary of Case 5, page 53
- 2.8.6 Summary of Case 6, page 54

# List of Figures

- Figure 1. Model of the cell membrane. Page 2.
- Figure 2. Diagram of Facilitated Diffusion Transport Mechanism. Page 6.
- Figure 3. Illustration of Asymptotic Analysis Approximation. Page 13.
- Figure 4. Concentrations of A and B vs Time for Case 1. Page 25.
- Figure 5. Concentrations of A and B vs Time for Case 2. Page 29.
- Figure 6. Concentrations of A and B vs Time for Case 3. Page 35.
- Figure 7. Concentrations of A and B vs Time for Case 4. Page 39.
- Figure 8. Concentrations of A and B vs Time for Case 5. Page 45.
- Figure 9. Concentrations of A and B vs Time for Case 6. Page 51.

# Chapter 1

## Introduction

Drugs come in all shapes and sizes, both physically and chemically. The way drugs are administered and absorbed varies as well (orally, rectally, pulmonarily, intravenously, etc.). However, regardless of how a drug is taken or what the drug is, all drugs follow the same life cycle. The drug must first be absorbed into the blood stream, distributed throughout the body by the blood, received and used at the site of action (a very small percentage of the administered drug), and/or excreted. [1,2]

Despite the same life cycle, drugs interact with cells and their membranes differently depending upon their molecular size, structure, and solubility. Initially almost all drugs are absorbed into the blood stream and are then distributed around the body in the water phase of the blood plasma. Since the entire blood volume circulates throughout the body in approximately one minute, the drug is distributed throughout the circulatory system relatively quickly. Approximately sixty percent of a person's total body weight is composed of water, 8.5 percent of which is blood. That leaves 51.5 percent of the total body weight being composed of water that is in the body tissues. Most drugs are readily transferred from the blood to the body fluid. If the structure of the drug molecules is such that they can penetrate the cells,

then they are absorbed into the cells as well [1,3].

Generally speaking, drug molecules can be classified into three categories. First are the molecules that do not diffuse from the blood into the body fluids. These molecules bind to proteins contained in the blood. After binding to the protein the molecule is too big to freely diffuse out of the bloodstream. Second are lipid-insoluble molecules. These molecules diffuse out of the bloodstream readily, but are not quickly absorbed into the cells. Cellular membranes are composed of a wall of fat molecules called phospholipids. The exterior and interior of the cellular membrane is made up of a densely packed layer of protein heads. The inside of the membrane is comprised of lipid chains that resemble tails attached to the protein head. (See Figure 1.) [1,4,5]

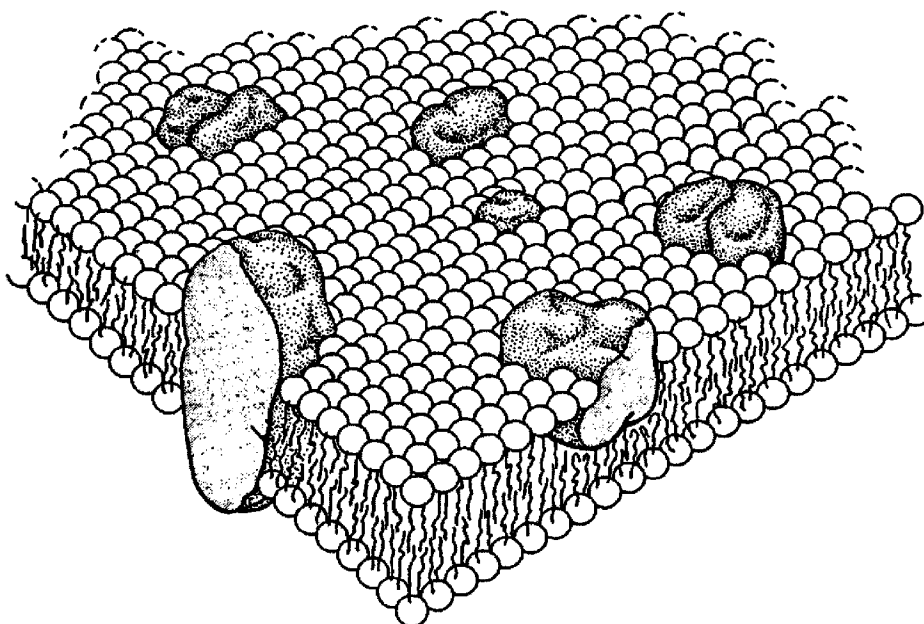


Figure 1. Model of the cell membrane. The surface of the membrane is made up of a densely packed layer of protein heads. The interior part of the membrane is comprised of lipid chains attached to the proteins. The large structures are large protein molecules [1].

Since the cellular walls are made up primarily of lipids, lipid-insoluble molecules do not readily diffuse across the membrane wall. The third type of drug molecules are those that are either lipid-soluble, or are so small that they pass through the tiny gaps (about 8 angstroms in diameter) in the membrane walls. In this thesis we are going to concern ourselves with the second type of drug molecules [1,5,6].

Many nutrients that a cell needs are large and composed of lipid-insoluble molecules. These do not easily cross cell walls. In order to transport these large hydrophilic permeants, cells have specialized membrane-embedded proteins called carriers that by a conformational change, transport a specific permeant from one side of the membrane to the other. This mechanism is called facilitated diffusion [3,7].

In this thesis we will study the mechanisms of facilitated diffusion from a mathematical perspective. The goal of our study is to produce various asymptotically reduced models describing facilitated diffusion transport across membranes under various possible physiological conditions. These simplified models can later be used for parameter identification using experimental data. Also, such simplified models may be included as parts of more complex heterogeneous pharmacokinetics models.

## **1.1 Model mechanism of facilitated diffusion transport**

The driving force of a permeant  $A$  across a membrane is either its own electrochemical gradient, or that of another permeant, which is competing with  $A$  for the protein-carrier. In some cases this may lead to counter-transport. If the driving concentration gradient goes to zero transport stops [7].

On the membrane surface the permeant molecule binds to the carriers at the

binding sites. The permeant-carrier complex goes through a conformational change and releases the permeant on the other side of the membrane. At this point the carrier is either “loaded” by a molecule of permeant B and reverses the process, or it is “loaded” by a resetting chemical such as potassium which is transported outside of the cell and released. The carrier may cross the membrane and return to the outside of the membrane surface empty[8].

During our analysis we will use the following notation:

- $A$  represents the permeant on the outside of the cell;
- $B$  represents the permeant on the inside of the cell;
- $G$  represents the resetting-chemical on the outside of the cell;
- $F$  represents the resetting-chemical on the inside of the cell;
- $P$  represents the protein-carrier:

$P_1$  is the protein-carrier on the “ $A$ -side” of the membrane and;

$P_2$  is the protein-carrier on the “ $B$ -side” of the membrane;

- $Q$  represents the permeant-carrier complex:

$Q_1$  is the  $AP_1$  complex and

$Q_2$  is the  $BP_2$  complex;

$Q_3$  is the  $GP_1$  complex and

$Q_4$  is the  $FP_2$  complex;

- $a, b, g, f, p_1, p_2, q_1, q_2$  represent the concentrations of  $A, B, G, F, P_1, P_2, Q_1,$  and  $Q_2$  respectively;
- $k_1^+$  and  $k_2^+$  represent the rate constants for the production of  $AP_1$  and  $BP_2$  complexes, respectively;
- $k_1^-$  and  $k_2^-$  represent the disassociation rate constants of the  $AP_1$  and the  $BP_2$  complexes, respectively;
- $k_3^+$  and  $k_3^-$  represent the rates of the conformational changes of the loaded carriers;
- $k_4^+$  and  $k_4^-$  represent the constant rates at which the carriers are reset;
- $k_5^+$  and  $k_6^+$  represent the rate constants for the production of  $FP_2$  and  $GP_1$  complexes, respectively;
- $k_5^-$  and  $k_6^-$  represent the disassociation rate constants of the  $FP_2$  and the  $GP_1$  complexes, respectively.

The above notation as well as schematic representation of facilitated diffusion transport model are illustrated in Figure 2.

In this figure the sequential stages consisting of the carrier loading and reloading processes are shown in detail. In stage I the protein-carrier picks up the permeant, leading to stage II. From stage II to stage III the complex reorients to release the permeant on the inside of the cell. In stage IV the protein-carrier picks up the resetting-chemical. From stage V to stage VI the complex reorients to release the resetting-chemical to the outside of the cell and the process repeats. Any of these

stages can be reversed by changes in the concentration gradient or by numerous other counter-transport mechanisms.

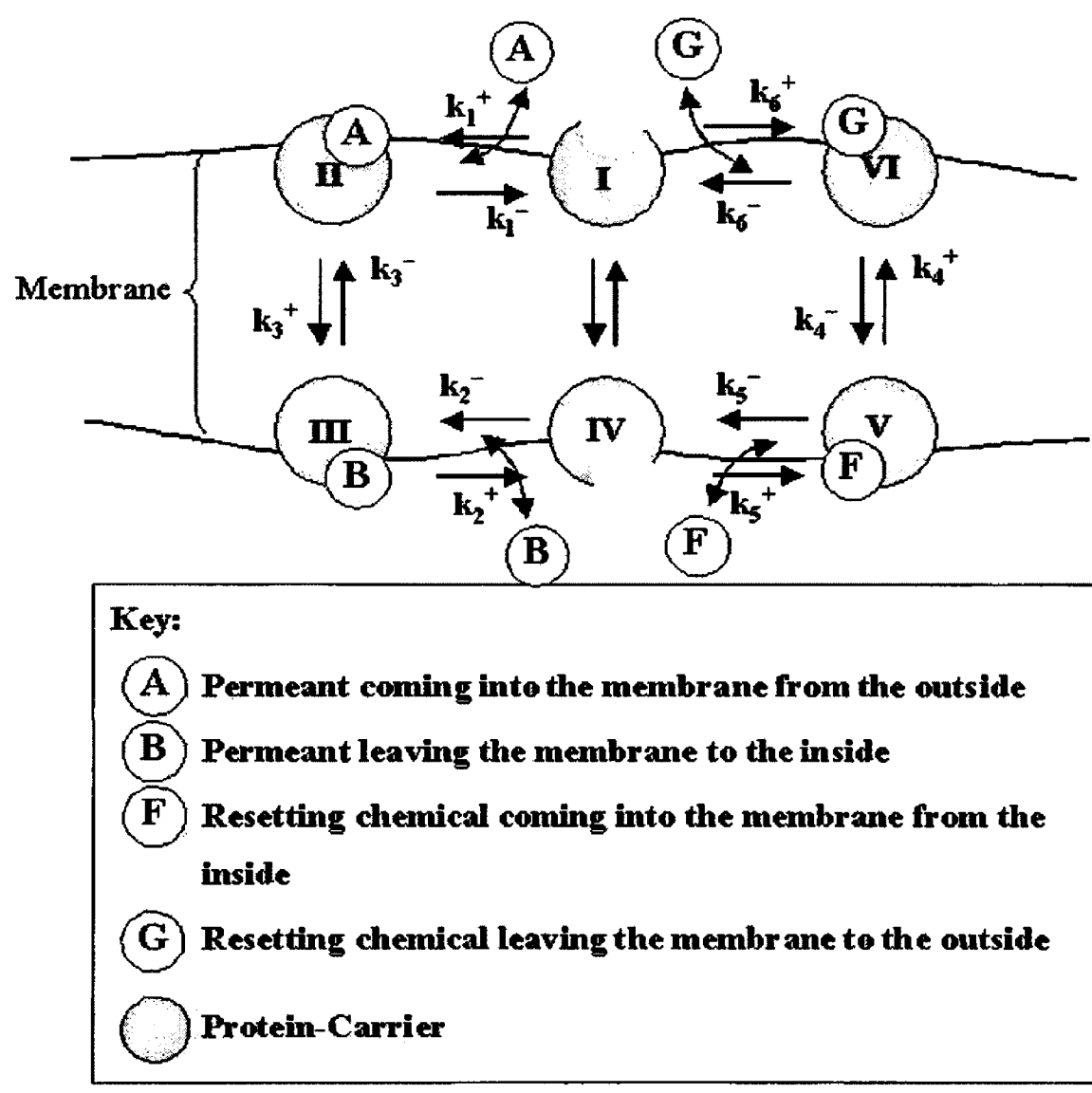


Figure 2. Diagram of Facilitated Diffusion Transport Mechanism [8].



## 1.2 Asymptotic Approximation Techniques

### 1.2.1 Asymptotic Approximation Algorithm

For mathematical analysis of the facilitated diffusion process we employ asymptotic approximation techniques [9]. We present an outline of the algorithm below.

Before proceeding, we should take a moment to rationalize this asymptotic approximation approach. When designing a mathematical model for any natural process or phenomenon one must weigh the pros and cons of a complex model against those of a more simple model. One tries to find the best balance between the two. The model must be complex enough to capture the dominant features of the process, yet simple enough to be accessible to the analytic and numeric methods available. For this reason, a good mathematical model is not going to model the physical reality perfectly, but adequately.

Imagine that we have a choice of two different models, one more complex but slightly more accurate than the other. We say that the more complex model, or extended model, is perturbed, and a simpler model is unperturbed. The difference between the two is that the perturbed one, compared to the unperturbed model, contains additional terms depending on usually small numerical parameters. By setting these parameters to zero we get the corresponding unperturbed model from the perturbed one. The perturbations can be categorized into two groups: *regular perturbations* and *singular perturbations*.

Consider two hypothetical models:

$$\text{model } A_0 : L_0 u = f_0,$$

$$\text{model } A_\epsilon : L_0 u + \epsilon L_1 u = f_0 + \epsilon f_1.$$

Here  $f_0$  and  $f_1$  are known functions,  $\epsilon$  is a small positive scalar parameter,  $u$  is

the unknown function, and  $L_0$  and  $L_1$  are general operators.  $A_0$  represents the simple unperturbed model and  $A_\epsilon$  represents the extended model. The terms  $\epsilon L_1 u$  and  $\epsilon f_1$  represent perturbations. We will denote the solution of  $A_0$  by  $u_0(t)$  and the solution of  $A_\epsilon$  by  $u_\epsilon(t)$ . Solutions are defined in domain  $D$ .

The problem  $A_\epsilon$  is called *regularly perturbed* in a domain  $D$  if

$$\sup_D \|u_\epsilon(t) - u_0(t)\| \rightarrow 0 \text{ as } \epsilon \rightarrow 0.$$

Otherwise, the problem  $A_\epsilon$  is called *singularly perturbed*.

In this thesis we will use the Euclidean Norm.

In general, problem  $A_\epsilon$  is not solvable directly. We will consider a function  $U(t, \epsilon)$  defined in a subdomain  $D_1$  of  $D$ . In particular cases,  $D_1$  might coincide with  $D$ .

The function  $U(t, \epsilon)$  is called an *asymptotic approximation* of the solution  $u_\epsilon(t)$  with respect to the parameter  $\epsilon$  in the subdomain  $D_1$  if

$$\sup_{D_1} \|u_\epsilon(t) - U(t, \epsilon)\| \rightarrow 0 \text{ as } \epsilon \rightarrow 0.$$

Moreover, if  $\sup_{D_1} \|u_\epsilon(t) - U(t, \epsilon)\| = O(\epsilon^k)$ , then we say that  $U(t, \epsilon)$  is the asymptotic approximation of  $u_\epsilon(t)$  in  $D_1$  to within accuracy of order  $\epsilon^k$ .

*Note:* The notation  $\alpha(\epsilon) = O(\epsilon^k)$  means that there exists numbers  $c, \epsilon_0 > 0$  such that for  $0 < \epsilon \leq \epsilon_0$  the inequality  $\|\alpha(\epsilon)\| \leq c\epsilon^k$  holds.

The asymptotic method is a method of constructing an asymptotic approximation  $U(t, \epsilon)$  for the solution  $u_\epsilon(t)$  of problem  $A_\epsilon$ . The advantage of this approach is

that often the construction of  $U_\epsilon(t)$  is easier than the construction of  $u_\epsilon(t)$ , i.e., the problems that comprise  $U_\epsilon(t)$  are simpler than the original problem for  $A_\epsilon$ .

In our case we will be able to formulate our model in terms of differential equations. Let us consider a general example:

$$\epsilon \frac{du}{dt} = F(u, t, \epsilon). \quad (1.2.1)$$

In each of the cases below we will construct uniform asymptotic approximation in  $D_1 = D = [0, T]$ ,  $T$  fixed, of the solution to the original problem in the form of a truncated power series in the powers of  $\epsilon$ :

$$\epsilon \frac{d\bar{u}}{dt} + \frac{d\Pi u}{dt} = \bar{F}(t, \epsilon) + \Pi F(\tau, \epsilon). \quad (1.2.2)$$

Here  $\tau = t/\epsilon$  is a stretched variable,

$$\bar{F}(t, \epsilon) = \bar{F}_0(t) + \epsilon \bar{F}_1(t) + \dots + \epsilon^k \bar{F}_k(t) + \dots \quad (1.2.3)$$

is the **regular part** of the expansion and,

$$\Pi F(\tau, \epsilon) = \Pi_0 F(\tau) + \epsilon \Pi_1 F(\tau) + \dots + \epsilon^k \Pi_k F(\tau) + \dots \quad (1.2.4)$$

is the **boundary layer part**. In what follows, we assume that  $\Pi_i F(\tau) \rightarrow 0$  as  $\tau \rightarrow \infty$ . This will guarantee that the boundary functions only play a role near the initial point. We then expand all the terms in power series in powers of  $\epsilon$ , and equate coefficients multiplying like powers of  $\epsilon$  separately for the **regular** and **boundary layer** functions.

In this thesis we will construct series in the powers of  $\epsilon$ ,

$$\sum_{i=0}^{\infty} \epsilon^i (\overline{F}_i(t, \epsilon) + \Pi_i F(\tau, \epsilon)), \quad (1.2.5)$$

such that the  $k$ th partial sum (truncated series),

$$U_k(t, \epsilon) = \sum_{i=0}^k \epsilon^i (\overline{F}_i(t, \epsilon) + \Pi_i F(\tau, \epsilon)), \quad (1.2.6)$$

will give the asymptotic approximation to the solution  $u_\epsilon(t)$  within an accuracy of order  $\epsilon^{k+1}$  in domain  $D_1$ .  $U_k(t, \epsilon)$  is then called the *asymptotic series* for the function  $u_\epsilon(t)$  (or the *asymptotic expansion* for  $u_\epsilon(t)$ ) in the domain  $D_1$  as  $\epsilon \rightarrow 0$ . For most applications and for most of the cases studied below we will be interested only in the leading order approximation.

## 1.2.2 Conditions of the Asymptotic Approximation Algorithm

Let us formulate one of the central theorems of asymptotic analysis for an ODE system used in pharmacokinetic modeling [9]:

$$\epsilon \frac{du}{dt} = F(u, v, t), \quad \frac{dv}{dt} = f(u, v, t), \quad 0 \leq t \leq T, \quad (1.2.7)$$

$$u(0, \epsilon) = u^0, \quad v(0, \epsilon) = v^0. \quad (1.2.8)$$

We assume that the functions  $F(u, v, t)$  and  $f(u, v, t)$  are continuous together with their derivatives with respect to  $u$  and  $v$  in some domain

$$G = \{\|u\| \leq a, \|v\| \leq a, 0 \leq t \leq T\}.$$

**Condition 1:**

Let  $F(\bar{u}, \bar{v}, t) = 0$  have an isolated root with respect to  $\bar{u} : \bar{u}(t) = \phi(\bar{v}(t), t)$ ,  $(\bar{v}(t), t) \in D = \{\|\bar{v}\| \leq a, 0 \leq t \leq T\}$ , and suppose that the corresponding reduced problem has a unique solution in the interval  $0 \leq t \leq T$ .

System (1.2.7) has an associated system:

$$\epsilon \frac{d\tilde{u}}{d\tau} = F(\tilde{u}, v, t), \tau \geq 0. \quad (1.2.9)$$

By virtue of **Condition 1**,  $\tilde{u} = \phi(v, t)$  is a steady state of system (1.2.7).

**Condition 2:**

Let the steady state  $\tilde{u} = \phi(v, t)$  of the associated system be asymptotically stable in the sense of Lyapunov, uniformly in  $(v, t) \in D$  as  $\tau \rightarrow \infty$  [11].

This means that for any  $\epsilon > 0$ , there exists a  $\delta = \delta(\epsilon) > 0$  such that if  $\|\tilde{u}(0) - \phi(v, t)\| < \delta$  then  $\|\tilde{u}(\tau) - \phi(v, t)\| < \epsilon$  for  $\tau \geq 0$ , and also  $\tilde{u} \rightarrow \phi(v, t)$  when  $\tau \rightarrow \infty$ .

Several roots of the equation  $F(u, v, t) = 0$  might satisfy **Condition 2**. However we want a solution  $\tilde{u}(\tau)$  that approaches the steady state. Therefore we stipulate condition 3:

**Condition 3:**

Let the solution  $\tilde{u}(\tau)$  of the problem for  $\tilde{u}$  with  $t = 0$  exist for  $\tau \geq 0$  and tend to the steady state  $\phi(v^0, 0)$  as  $\tau \rightarrow \infty$ . This means that  $u^0$  belongs to the domain of attraction of the steady state  $\phi(v^0, 0)$ .

## Tikhonov's Theorem

Under **Conditions 1-3** and for sufficiently small  $\epsilon$ , the original perturbed problem has a unique solutions  $u(t, \epsilon)$ ,  $v(t, \epsilon)$  such that the following limiting equalities hold:

$$\lim_{\epsilon \rightarrow 0} v(t, \epsilon) = \bar{v}(t) \text{ for } 0 \leq t \leq T,$$

$$\lim_{\epsilon \rightarrow 0} u(t, \epsilon) = \bar{u}(t) \text{ for } 0 \leq t \leq T.$$

These equalities show that in the limit the solution  $u(t, \epsilon)$ ,  $v(t, \epsilon)$  of the original problem tend to the solution of the reduced problem. Transition to the limit for  $v$  takes place for all  $t$  in the interval  $0 \leq t \leq T$ . Moreover this limiting process is uniform. Transition to the limit for  $u$  takes place for any  $t$  except  $t = 0$ . The limiting process for  $u$  will be uniform outside some small  $\delta$ -vicinity of the initial point. The subinterval  $[0, \delta]$ , where the fast change of the solution  $u(t, \epsilon)$  from the initial value to values close to  $\bar{u}(t)$  takes place, is called the *boundary layer*.

Thus  $\bar{v}(t)$  will be the asymptotic approximation to  $v(t, \epsilon)$  in the interval  $0 \leq t \leq T$ , and  $\bar{u}(t)$  will be the asymptotic approximation to  $u(t, \epsilon)$  for  $\delta \leq t \leq T$ , where  $\delta$  is asymptotically small. Possible behavior of the solution  $u(t, \epsilon)$  for various values of  $\epsilon$  for some specific singularly perturbed ODE problem can be seen in Figure 3 below.

We will use this and related results for our analysis in this thesis [9].

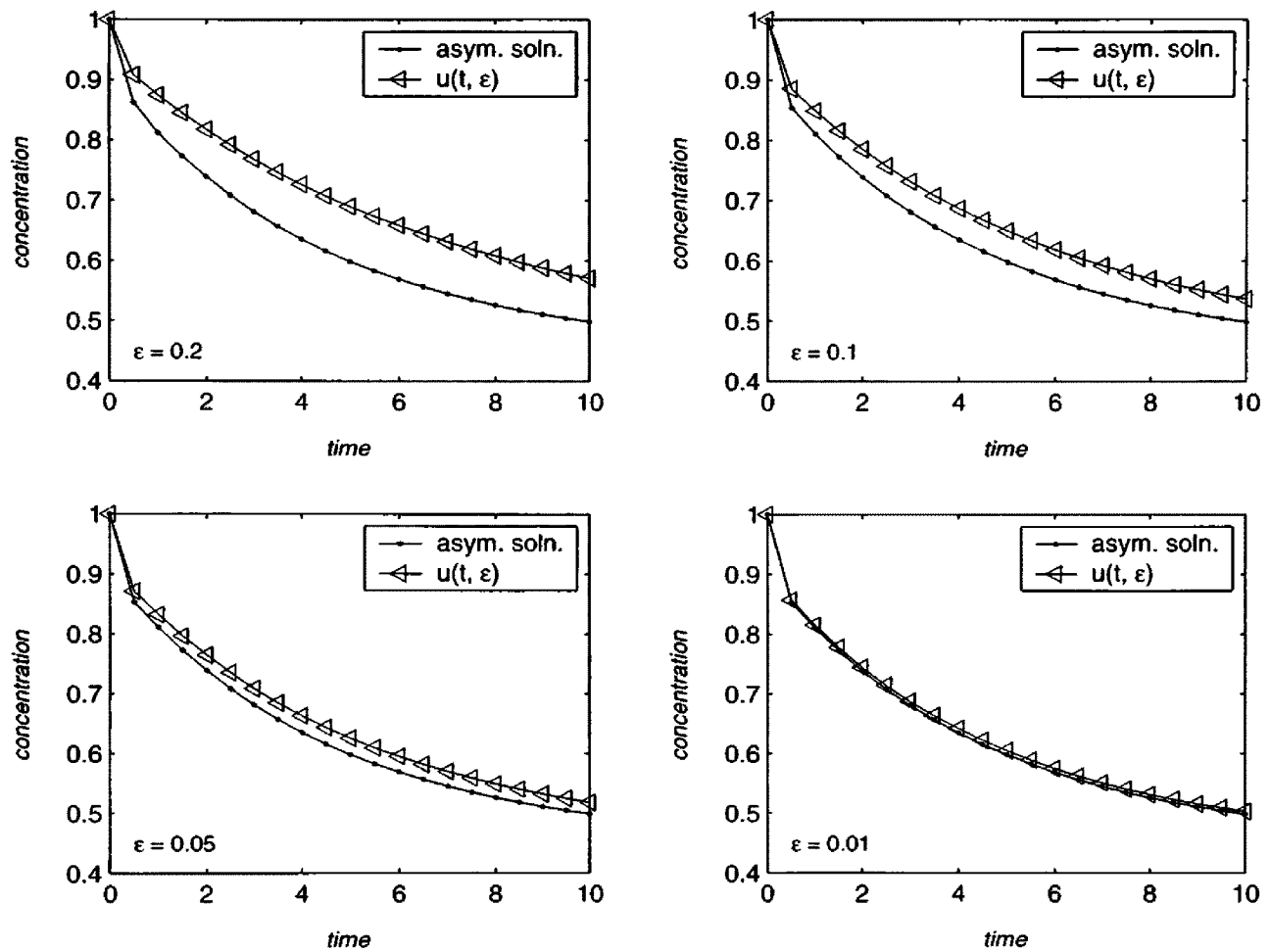


Figure 3. Comparison of the leading order asymptotic approximation with the numerical solutions of the singularly perturbed problem for various values of epsilon.

# Chapter 2

## Analysis of a simplified model

### 2.1 Formulation of the model

We start with the model that does not take into account possible asymmetry of the protein-carrier resetting process (see assumptions below), and focus just on the transport process of the permeant from the outside to the inside of the cell.

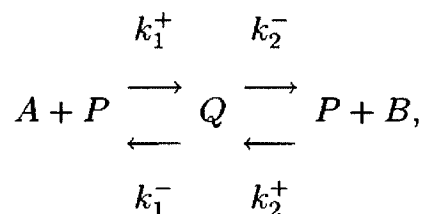
We make the following simplifying assumptions on the “resetting” process:

- $a^0 > p^0$ ,
- $P$  and  $Q$  cannot leave the membrane, and complex formation and disassociation only occurs at the membrane wall,
- $k_3^+ = k_3^- = k_4^\pm \gg k_1^\pm$  and  $k_2^\pm$  (note: since  $k_3^+ = k_3^- = k_4^\pm$ , we have  $Q_1 = Q_2 = Q$ , and  $P_1 = P_2 = P$ , so we assume instantaneous equilibrium redistribution of free and occupied protein carrier sites between the “inside” and “outside” boundaries of the membrane.).



Note: The third simplifying assumption that the conformational change is instantaneous is not a physically realistic assumption. In fact it has been shown experimentally that this conformational change is rate limiting. Nevertheless, these simplifying assumptions will provide us with a perspective from which to more simply draw some physically significant results. These results will then be able to be included as parts of more complex and realistic heterogeneous pharmacokinetics models.

We discuss the experimental setup for which the volumes on both sides of the membrane are the same and the initial conditions are chosen to satisfy:  $a(0) = a^0, b(0) = 0, p(0) = p^0, q(0) = 0$ . With these assumptions we get the following reaction scheme representing the model:



where  $A$  is the permeant,  $P$  is the carrier,  $Q$  is the permeant/carrier complex, and  $B$  is the permeant on the intracellular side of the membrane.

We will address the following cases:

- Case 1: The first forward reaction and the second forward reaction are both fast ( $k_1^+$  and  $k_2^+$  are large) and both reverse reactions are moderate ( $k_1^-$  and  $k_2^-$  are moderate),
- Case 2: The first forward reaction and the second reverse reaction are both fast ( $k_1^+$  and  $k_2^-$  are large) and the first reverse reaction and second forward reaction are moderate ( $k_1^-$  and  $k_2^+$  are moderate),

- Case 3: The first forward and first reverse reactions are both fast ( $k_1^+$  and  $k_1^-$  are large) and the second forward and second reverse reactions are moderate ( $k_2^+$  and  $k_2^-$  are moderate),
- Case 4: The first reverse and second forward reactions are both fast ( $k_1^-$  and  $k_2^+$  are large) and the first forward and second reverse reactions are both moderate ( $k_1^+$  and  $k_2^-$  are moderate),
- Case 5: The second forward and second reverse reactions are fast ( $k_2^+$  and  $k_2^-$  are large) and the first forward and first reverse reactions are moderate ( $k_1^+$  and  $k_1^-$  are moderate),
- Case 6: All the reaction rates are moderate and  $p^0/a^0$  is small.

Using the Law of Mass Action we write the system of differential equations for concentrations of the species:

$$\frac{da}{dt} = k_1^- q - k_1^+ ap, \quad (2.1.1)$$

$$\frac{db}{dt} = k_2^- q - k_2^+ bp, \quad (2.1.2)$$

$$\frac{dp}{dt} = k_1^- q - k_1^+ ap + k_2^- q - k_2^+ bp = \frac{da}{dt} + \frac{db}{dt}, \quad (2.1.3)$$

$$\frac{dq}{dt} = -(k_1^- q - k_1^+ ap + k_2^- q - k_2^+ bp) = -\left(\frac{da}{dt} + \frac{db}{dt}\right) = -\frac{dp}{dt}. \quad (2.1.4)$$

Equations (2.1.3) and (2.1.4) can be re-written as follows:

$$\frac{da}{dt} + \frac{db}{dt} - \frac{dp}{dt} = 0, \quad (2.1.5)$$

$$\frac{da}{dt} + \frac{db}{dt} + \frac{dq}{dt} = 0. \quad (2.1.6)$$

Solving (2.1.5), we get:  $a + b + p = \text{const.}$

Using initial conditions, we get that the constant is  $a^0 - p^0$ . This gives us:

$$p = a + b + p^0 - a^0. \quad (2.1.7)$$

Solving (2.1.6), we get:  $a + b + q = \text{const.}$

Using initial conditions, we get that the constant is  $a^0$ . Thus,

$$q = a^0 - a - b. \quad (2.1.8)$$

Since  $p$  and  $q$  are expressed in terms of  $a$  and  $b$  we only need to analyze equations (2.1.1) and (2.1.2), where  $p$  is given by equation (2.1.7) and  $q$  is given by (2.1.8).

## 2.2 Analysis of Case 1

We start with Case 1, assuming that the first forward ( $k_1^+$ ) and second forward ( $k_2^+$ ) reactions are both fast, and the other two reactions are moderate.

### 2.2.1 Re-scaling the equations

In (2.1.1) and (2.1.2) we make the following substitutions:  $a = \tilde{a}a_0$ ;  $b = \tilde{b}b_0$ ;  $t = \tilde{t}t_0$ ;  $p = \tilde{p}p_0$ ;  $q = \tilde{q}q_0$ . We obtain:

$$\begin{aligned}\frac{a_0 d\tilde{a}}{t_0 d\tilde{t}} &= k_1^- q_0 \tilde{q} - k_1^+ a_0 p_0 \tilde{a} \tilde{p}, \\ \frac{b_0 db}{t_0 dt} &= k_2^- q_0 \tilde{q} - k_2^+ b_0 p_0 \tilde{b} \tilde{p}.\end{aligned}$$

Multiplying by  $t_0$  and dividing the first equation by  $a_0$  and the second equation by  $b_0$ , we get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \frac{k_1^- q_0 t_0}{a_0} \tilde{q} - k_1^+ t_0 p_0 \tilde{a} \tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \frac{k_2^- q_0 t_0}{b_0} \tilde{q} - k_2^+ t_0 p_0 \tilde{b} \tilde{p}.\end{aligned}$$

Let us choose  $a_0 = b_0 = p_0 = q_0 = a^0$ . Then,

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= k_1^- t_0 \tilde{q} - k_1^+ t_0 \tilde{a} \tilde{p} a^0, \\ \frac{d\tilde{b}}{d\tilde{t}} &= k_2^- t_0 \tilde{q} - k_2^+ t_0 \tilde{b} \tilde{p} a^0.\end{aligned}$$

Since the first forward ( $k_1^+$ ) and the second forward ( $k_2^+$ ) reactions are both fast, and the other two reactions are slow, we can make the following choice of characteristic

time scale:  $t_0 = \frac{1}{k_1^-}$ . We now have:

$$\frac{d\tilde{a}}{d\tilde{t}} = \tilde{q} - \frac{k_1^+}{k_1^-} a^0 \tilde{a} \tilde{p},$$

$$\frac{d\tilde{b}}{d\tilde{t}} = \frac{k_2^-}{k_1^-} \tilde{q} - \frac{k_2^+}{k_1^-} a^0 \tilde{b} \tilde{p}.$$

Finally, we introduce the following substitutions:

$$\frac{1}{\epsilon} = \frac{k_1^+}{k_1^-} a^0; \quad \frac{\gamma}{\epsilon} = \frac{k_2^+}{k_1^-} a^0 \Rightarrow \gamma = \frac{k_2^+}{k_1^+}; \quad \beta = \frac{k_2^-}{k_1^-}, \quad 0 < \epsilon \ll 1 \text{ is a small parameter.}$$

We get:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} - \epsilon \tilde{q} = -\tilde{a} \tilde{p}, \quad (2.2.1)$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} - \epsilon \beta \tilde{q} = -\gamma \tilde{b} \tilde{p}. \quad (2.2.2)$$

Re-scaling equations (2.1.7) and (2.1.8) gives us:

$$\tilde{p} = \tilde{a} + \tilde{b} + \frac{p^0}{a^0} - 1, \quad (2.2.3)$$

$$\tilde{q} = 1 - (\tilde{a} + \tilde{b}). \quad (2.2.4)$$

Substituting equations (2.2.3) and (2.2.4) into (2.2.1) and (2.2.2), we obtain:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} - \epsilon(1 - \tilde{a} - \tilde{b}) = -\tilde{a}(\tilde{a} + \tilde{b} + \frac{p^0}{a^0} - 1),$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} - \epsilon\beta(1 - \tilde{a} - \tilde{b}) = -\gamma\tilde{b}(\tilde{a} + \tilde{b} + \frac{p^0}{a^0} - 1).$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ , and  $\tilde{b}(0) = 0$ .

To simplify notation we drop the tildes and substitute  $p^*$  for  $p^0/a^0$ :

$$\epsilon \frac{da}{dt} - \epsilon(1 - a - b) = -a(a + b + p^* - 1), \quad (2.2.5)$$

$$\epsilon \frac{db}{dt} - \epsilon\beta(1 - a - b) = -\gamma b(a + b + p^* - 1). \quad (2.2.6)$$

## 2.2.2 The leading order approximation: Regular functions

Setting  $\epsilon$  equal to zero, we get:

$$\bar{a}_0 + \bar{b}_0 = 1 - p^*. \quad (2.2.7)$$

If we divide (2.2.5) by  $\bar{a}_0$  and (2.2.6) by  $\gamma\bar{b}_0$  and take the difference of the two equations in the leading order approximation, we get:

$$\frac{1}{\bar{a}_0} \frac{d\bar{a}_0}{dt} - \frac{(1 - \bar{a}_0 - \bar{b}_0)}{\bar{a}_0} = \frac{1}{\gamma\bar{b}_0} \frac{d\bar{b}_0}{dt} - \frac{\beta(1 - \bar{a}_0 - \bar{b}_0)}{\bar{b}_0}. \quad (2.2.8)$$

Differentiating equation (2.2.7), we obtain  $\frac{da}{dt} = -\frac{db}{dt}$ .

Thus, we can simplify (2.2.8) to:

$$\left( \frac{1}{\bar{a}_0} + \frac{1}{\gamma\bar{b}_0} \right) \frac{d\bar{a}_0}{dt} = (1 - \bar{a}_0 - \bar{b}_0) \left( \frac{1}{\bar{a}_0} - \frac{\beta}{\gamma\bar{b}_0} \right).$$

Dividing both sides by  $\left( \frac{1}{\bar{a}_0} + \frac{1}{\gamma\bar{b}_0} \right)$  and re-arranging terms, we get:

$$\frac{d\bar{a}_0}{dt} = p^* \left( \frac{\gamma\bar{b}_0 - \beta\bar{a}_0}{\gamma\bar{b}_0 + \bar{a}_0} \right) \quad (2.2.9)$$

We can write (2.2.9) strictly in terms of  $\bar{a}_0$  since  $\bar{b}_0 = 1 - p^* - \bar{a}_0$ :

$$\frac{d\bar{a}_0}{dt} = p^* \left( \frac{1 - p^* - \bar{a}_0(1 + \frac{\beta}{\gamma})}{1 - p^* - \bar{a}_0(1 - \frac{1}{\gamma})} \right). \quad (2.2.10)$$

This is a separable ODE, and its implicit solution is:

$$\bar{a}_0 + \ln(\bar{a}_0(\beta + \gamma) + \gamma(p^* - 1)) \frac{(p^* - 1)(\beta + 1)\gamma}{(\gamma - 1)(\beta + \gamma)} = \frac{(\beta + \gamma)(p^*t + C_1)}{\gamma - 1}.$$

In order to find  $C_1$  we need an initial condition for  $\bar{a}_0$ , which we will find during construction of the boundary functions.

### 2.2.3 The leading order approximation: Boundary functions

For the boundary functions  $\Pi_0a$  and  $\Pi_0b$  from (2.2.5) and (2.2.6) we have:

$$\begin{aligned} \frac{d\Pi_0a}{d\tau} &= -(\bar{a}_0(0) + \Pi_0a)(\bar{a}_0(0) + \Pi_0a + \bar{b}_0(0) + \Pi_0b - (\bar{a}_0(0) + \bar{b}_0(0))), \\ \frac{d\Pi_0b}{d\tau} &= -\gamma(\bar{b}_0(0) + \Pi_0b)(\bar{a}_0(0) + \Pi_0a + \bar{b}_0(0) + \Pi_0b - (\bar{a}_0(0) + \bar{b}_0(0))). \end{aligned}$$

Simplifying these, we get:

$$\frac{d\Pi_0a}{d\tau} = -(\bar{a}_0(0) + \Pi_0a)(\Pi_0a + \Pi_0b), \quad (2.2.11)$$

$$\frac{d\Pi_0b}{d\tau} = -\gamma(\bar{b}_0(0) + \Pi_0b)(\Pi_0a + \Pi_0b). \quad (2.2.12)$$

After dividing both sides of (2.2.11) by  $(\bar{a}_0(0) + \Pi_0 a)$  and both sides of (2.2.12) by  $\gamma(\bar{b}_0(0) + \Pi_0 b)$ , and taking the difference, we get:

$$\frac{\gamma}{(\bar{a}_0(0) + \Pi_0 a)} \frac{d\Pi_0 a}{d\tau} = \frac{1}{(\bar{b}_0(0) + \Pi_0 b)} \frac{d\Pi_0 b}{d\tau}.$$

Integrating and taking exponents of both sides yields:

$$\bar{b}_0(0) + \Pi_0 b = C_2(\bar{a}_0(0) + \Pi_0 a)^\gamma. \quad (2.2.13)$$

Initial conditions in the leading order approximation are:

$$\bar{a}_0(0) + \Pi_0 a(0) = 1,$$

$$\bar{b}_0(0) + \Pi_0 b(0) = 0.$$

Substituting the initial conditions into (2.2.13) and solving for  $C_2$  we get:  $C_2 = 0$ .

Substituting this back into (2.2.13), we get:

$$\bar{b}_0(0) + \Pi_0 b(\tau) = 0. \quad (2.2.14)$$

As  $\tau \rightarrow \infty$  the  $\Pi_0$  term in (2.2.14) will vanish. This means that  $\bar{b}_0(0)$  must be zero, and hence, from equation (2.2.14) we obtain that  $\Pi_0 b(\tau) \equiv 0$ . Since  $\bar{a}_0(0) + \bar{b}_0(0) = 1 - p^*$  and  $\bar{b}_0(0) = 0$ , we know

$$\bar{a}_0(0) = 1 - p^*. \quad (2.2.15)$$

Thus,

$$\Pi_0 a(0) = p^*. \quad (2.2.16)$$



Substituting (2.2.15) back into (2.2.11) we get:

$$\frac{d\Pi_0 a}{d\tau} = -\Pi_0 a(1 - p^* + \Pi_0 a).$$

Separation of variables yields:  $\frac{\Pi_0 a}{\Pi_0 a - p^* + 1} = C_3 \cdot e^{(-\tau)} e^{(1-p^*)}$ .

Using initial condition (2.2.16) we find that  $C_3 = p^* e^{p^*-1}$ . Thus, we have:

$$\Pi_0 a(\tau) = \frac{p^* e^{-\tau}(1 - p^*)}{1 - p^* e^{-\tau}}. \quad (2.2.17)$$

We can see that the boundary functions go to zero as  $\tau \rightarrow \infty$ .

#### 2.2.4 The regular functions' constant of integration

Since we now know the initial condition (2.2.15) for  $\bar{a}_0$ , we can find  $C_1$  in the leading order regular function expression:

$$C_1 = \frac{(1 - p^*)}{(\beta + \gamma)^2} [(\gamma - 1)(\beta + \gamma) - \gamma(\beta + 1)[\ln(\beta(1 - p^*))]].$$

So, the implicit solution to the leading order regular function  $\bar{a}_0$  is:

$$\bar{a}_0 + \ln(\bar{a}_0(\beta + \gamma) + \gamma(p^* - 1)) \frac{(p^* - 1)(\beta + 1)\gamma}{(\gamma - 1)(\beta + \gamma)} = \quad (2.2.18)$$

$$p^* \frac{\beta + \gamma}{\gamma - 1} + (1 - p^*) \left[ 1 - \frac{(\beta + 1)\gamma}{(\gamma - 1)(\beta + \gamma)} \ln(\beta(1 - p^*)) \right].$$

#### 2.2.5 Discussion

The concentration of permeant  $A$  is modeled, in the leading order approximation, by the sum  $\bar{a}_0(t) + \Pi_0 a(\tau)$ , defined by (2.2.18) and (2.2.17). If the concentration of  $A$  is

large, i.e., as  $\bar{a}_0 \rightarrow 1$ ,

$$\frac{d\bar{a}_0}{dt} \rightarrow p^* \frac{p^*\gamma + \beta}{p^*\gamma - 1}.$$

This means that, as the concentration of  $A$  increases without bound, the rate of trans-membrane transport approaches a limit. Note that if we make the assumption that  $\gamma = \beta = 1$  (the membrane transport is perfectly symmetric), then we have:

$$\frac{d\bar{a}_0}{dt} = \left( \frac{p^*}{1 - p^*} \right) (1 - p^* - 2\bar{a}_0) = p^* - 2 \frac{p^*\bar{a}_0}{1 - p^*}.$$

This is a linear ODE and its solution is:

$$\bar{a}_0(t) = C \exp\left(-\frac{2p^*}{1 - p^*}t\right) + \frac{1 - p^*}{2}, \text{ which approaches } \frac{1 - p^*}{2} \text{ as } t \rightarrow \infty. \text{ This}$$

means that permeant  $A$  diffuses into and through the membrane until equilibrium is reached. The equilibrium concentrations of  $A$  and  $B$  are the same:

$$\bar{a}_0(\infty) = \bar{b}_0(\infty) = \frac{1 - p^*}{2}.$$

This process is illustrated in Figure 4.

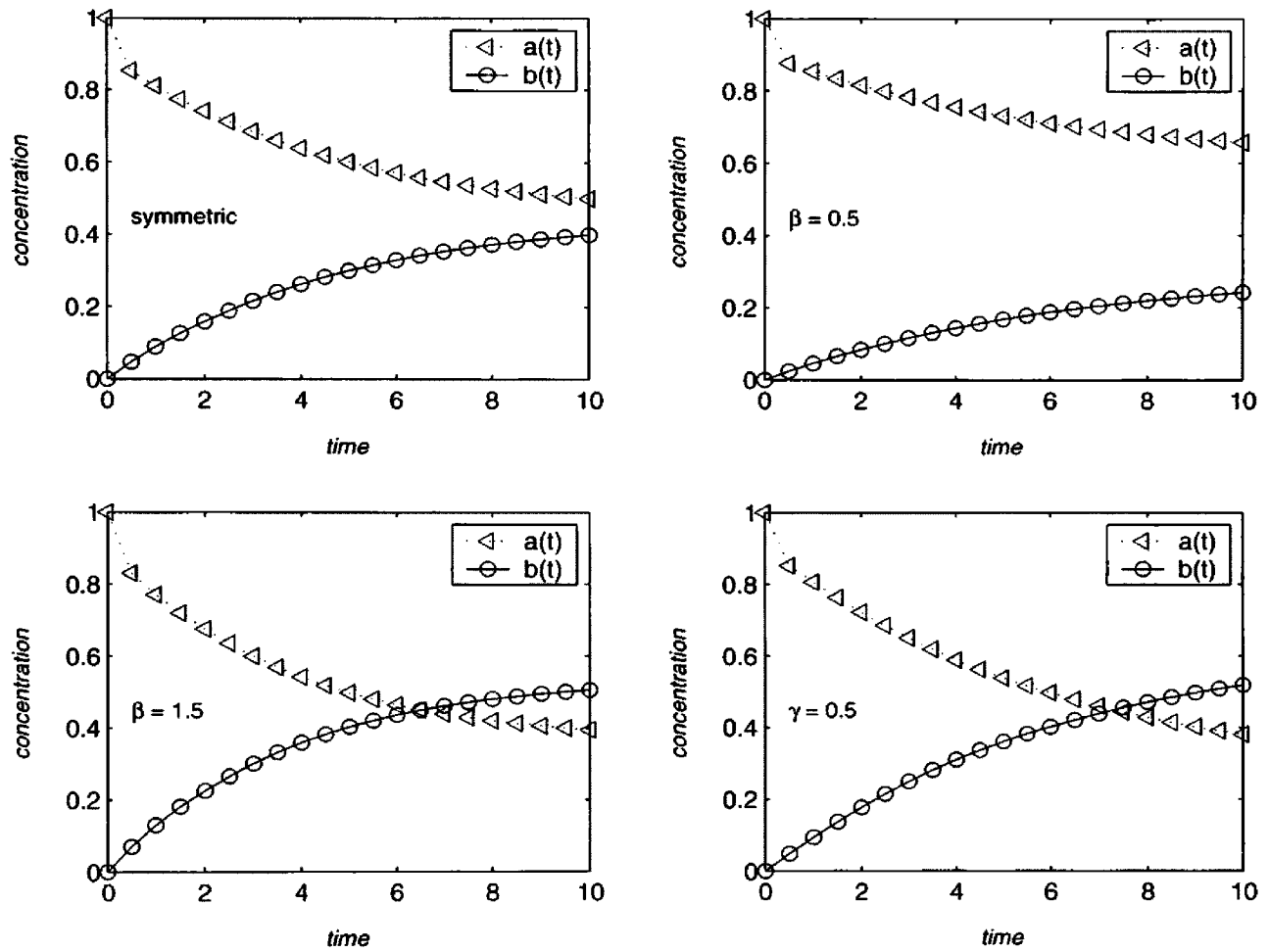


Figure 4. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = 0.01$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.3 Analysis of Case 2

For Case 2, where  $(k_1^+)$  and  $(k_2^-)$  are large, we make the following substitution:

$$t_0 = \frac{1}{k_1^-}.$$

Now we perform the same analysis as before and check how the model behavior changes. Going back to equations (2.1.1) and (2.1.2) and making the above substitution for  $t_0$  we get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \tilde{q} - \frac{k_1^+}{k_1^-} a^0 \tilde{a} \tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \frac{k_2^-}{k_1^-} \tilde{q} - \frac{k_2^+}{k_1^-} a^0 \tilde{b} \tilde{p}.\end{aligned}$$

Introducing parameters:

$$\frac{1}{\epsilon} = \frac{k_1^+}{k_1^-} a^0; \quad \frac{\beta}{\epsilon} = \frac{k_2^-}{k_1^-}; \quad \gamma = \frac{k_2^+}{k_1^-} a^0,$$

we get:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} - \epsilon \tilde{q} = -\tilde{a} \tilde{p}, \tag{2.3.1}$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} + \epsilon \gamma \tilde{b} \tilde{p} = \beta \tilde{q}.$$

We recall that  $\tilde{q} = 1 - \tilde{a} - \tilde{b}$  and  $\tilde{p} = (\tilde{a} + \tilde{b} + p^* - 1)$ , and substitute these into (2.3.1)

to obtain:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} - \epsilon(1 - \tilde{a} - \tilde{b}) = -\tilde{a}(\tilde{a} + \tilde{b} + p^* - 1), \tag{2.3.2}$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} + \epsilon \gamma \tilde{b}(\tilde{a} + \tilde{b} + p^* - 1) = \beta(1 - \tilde{a} - \tilde{b}). \tag{2.3.3}$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ ,  $\tilde{b}(0) = 0$ .

We will omit the tildes in what follows in order to simplify notation.

### 2.3.1 The leading order approximation: Regular functions for Case 2

Setting  $\epsilon$  equal to zero we obtain:

$$0 = -\bar{a}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1), \text{ and}$$

$$0 = \beta(1 - \bar{a}_0 - \bar{b}_0).$$

Solving these together we get  $\bar{a}_0(t) = 0$ , and

$$\bar{a}_0(t) + \bar{b}_0(t) = 1, \tag{2.3.4}$$

so  $\bar{b}_0(t) = 1$ .

Next, we calculate the first order approximation of the regular functions.

### 2.3.2 The first order approximation: Regular functions for Case 2

Collecting the regular terms of first order in  $\epsilon$  from equations (2.3.2) and (2.3.3) we get:

$$\frac{d\bar{a}_0}{dt} - 1 + \bar{a}_0 + \bar{b}_0 = -\bar{a}_0(\bar{a}_1 - \bar{b}_1) - \bar{a}_1(\bar{a}_0 + \bar{b}_0 + p^* - 1), \tag{2.3.5}$$

$$\frac{d\bar{b}_0}{dt} + \gamma\bar{b}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1) = -\beta(\bar{a}_1 + \bar{b}_1). \tag{2.3.6}$$

Since  $\bar{a}_0 = 0$  and  $\bar{b}_0 = 1$ , we know that  $\frac{d\bar{a}_0}{dt} = \frac{d\bar{b}_0}{dt} = 0$ , and therefore from equations (2.3.5) and (2.3.6) we obtain  $\bar{a}_1 = 0$  and  $\bar{b}_1 = \frac{-\gamma p^*}{\beta}$ .

### 2.3.3 The leading order approximation: Boundary Functions for Case 2

Using the standard procedure, we have:

$$\begin{aligned} \frac{d\Pi_0 a}{d\tau} &= -(\bar{a}_0(0) + \Pi_0 a)(\bar{a}_0(0) + \Pi_0 a + \bar{b}_0(0) + \Pi_0 b + p^* - 1) \\ &= -\Pi_0 a(p^* + \Pi_0 a + \Pi_0 b), \end{aligned} \quad (2.3.7)$$

$$\frac{d\Pi_0 b}{d\tau} = \beta(1 - (\bar{a}_0(0) + \Pi_0 a) - (\bar{b}_0(0) + \Pi_0 b)) = -\beta(\Pi_0 a + \Pi_0 b). \quad (2.3.8)$$

Initial conditions for the boundary functions in the leading order are

$$\Pi_0 a(0) = 1 - \bar{a}_0(0) = 1, \quad (2.3.9)$$

$$\Pi_0 b(0) = -\bar{b}_0(0) = -1. \quad (2.3.10)$$

The steady state of system (2.3.7), (2.3.8) is (0,0), and  $\det[J(0,0) - \lambda I] = 0$  yields eigenvalues:

$$\lambda_{1,2} = \frac{-(p^* + \beta) \pm \sqrt{(p^* + \beta)^2 - 4p^*\beta}}{2}.$$

Since the eigenvalues are real, distinct, and less than zero (due to the fact that  $p^*$  and  $\beta$  are positive) the steady state is a stable node. Therefore the boundary functions approach zero as  $\tau \rightarrow \infty$ .

### 2.3.4 Discussion

Since  $d\bar{a}_0/dt = d\bar{a}_1/dt = 0$  with  $\bar{a}_0(0) = \bar{a}_1(0) = 0$  and the steady state  $(0, 0)$  for the boundary functions is a stable node, we conclude that permeant  $A$  is absorbed into and through the membrane at a fast rate. This is clearly seen in Figure 5 below.

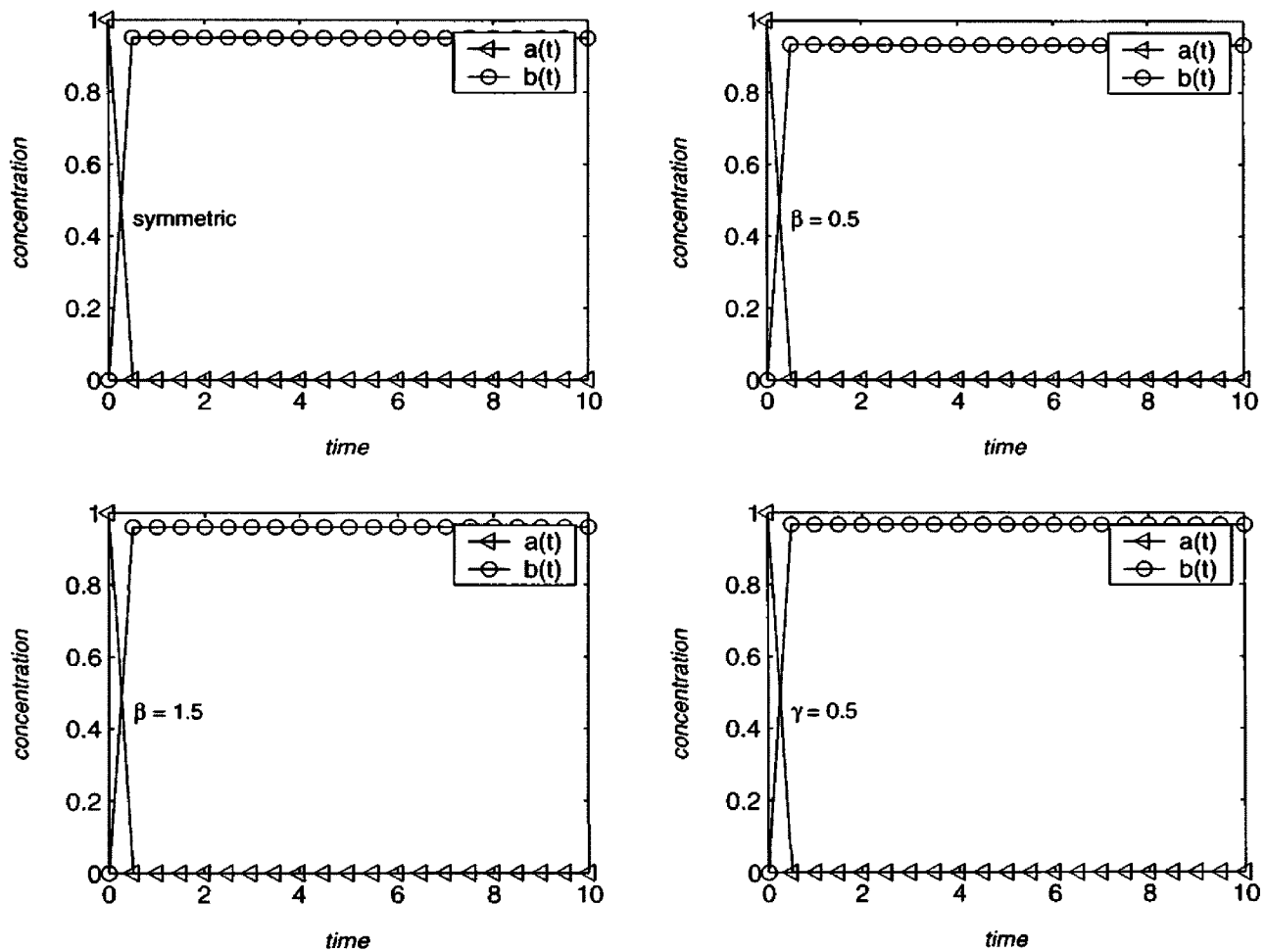


Figure 5. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = .001$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.4 Analysis of Case 3

For Case 3, where  $(k_1^+)$  and  $(k_1^-)$  are large, we make the following substitution:

$$t_0 = \frac{1}{k_2^-}.$$

Now we perform the same analysis as before and check how the model behavior changes. Going back to equations (2.1.1) and (2.1.2) and making the above substitution for  $t_0$ , we get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \frac{k_1^-}{k_2^-}\tilde{q} - \frac{k_1^+}{k_2^-}a^0\tilde{a}\tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \tilde{q} - \frac{k_2^+}{k_2^-}a^0\tilde{b}\tilde{p}.\end{aligned}$$

Introducing parameters:

$$\frac{1}{\epsilon} = \frac{k_1^+}{k_2^-}a^0; \quad \gamma = \frac{k_1^-}{k_2^-}; \quad \beta = \frac{k_2^+}{k_2^-}a^0,$$

we arrive at:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} = \gamma\tilde{q} - \tilde{a}\tilde{p}, \tag{2.4.1}$$

$$\frac{d\tilde{b}}{d\tilde{t}} = \tilde{q} - \beta\tilde{b}\tilde{p}.$$

We recall that  $\tilde{q} = 1 - \tilde{a} - \tilde{b}$  and  $\tilde{p} = (\tilde{a} + \tilde{b} + p^* - 1)$ . Substituting these into (2.4.1), we obtain:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} = \gamma(1 - \tilde{a} - \tilde{b}) - \tilde{a}(\tilde{a} + \tilde{b} + p^* - 1), \tag{2.4.2}$$

$$\frac{d\tilde{b}}{d\tilde{t}} = 1 - \tilde{a} - \tilde{b} - \beta\tilde{b}(\tilde{a} + \tilde{b} + p^* - 1). \tag{2.4.3}$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ ,  $\tilde{b}(0) = 0$ .



We omit the tildes in what follows in order to simplify notation.

### 2.4.1 The leading order approximation: Regular functions for Case 3

Setting  $\epsilon$  equal to zero in (2.4.2), we get:

$$\gamma(1 - \bar{a}_0 - \bar{b}_0) = \bar{a}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1). \quad (2.4.4)$$

Solving this for  $\bar{a}_0$ , we obtain,

$$\bar{a}_0 = \frac{(1 - (\gamma + p^* + \bar{b}_0)) \pm \sqrt{(1 - \gamma - p^* - \bar{b}_0)^2 - 4\gamma(\bar{b}_0 - 1)}}{2}. \quad (2.4.5)$$

We can substitute (2.4.5) into (2.4.3) to get an equation in terms of  $\bar{b}_0$  only. To find the correct sign in (2.4.5) we need to first discuss the boundary functions. Once we find the right sign, we will analyze the long term behavior of the regular functions.

### 2.4.2 The leading order approximation: Boundary Functions for Case 3

Using the standard asymptotic procedure we arrive at:

$$\begin{aligned} \frac{d\Pi_0 a}{d\tau} &= \gamma(1 - (\bar{a}_0(0) + \Pi_0 a) - (\bar{b}_0(0) + \Pi_0 b)) \\ &\quad - (\bar{a}_0(0) + \Pi_0 a)(\bar{a}_0(0) + \Pi_0 a + \bar{b}_0(0) + \Pi_0 b + p^* - 1), \end{aligned} \quad (2.4.6)$$

$$\frac{d\Pi_0 b}{d\tau} = 0. \quad (2.4.7)$$

Initial conditions in the leading order are:

$$\bar{a}_0(0) + \Pi_0 a(0) = 1, \quad (2.4.8)$$

$$\bar{b}_0(0) + \Pi_0 b(0) = 0. \quad (2.4.9)$$

Clearly  $\Pi_0 b(\tau) = \text{const.}$  Since  $\Pi_0 b \rightarrow 0$  as  $\tau \rightarrow \infty$ , the constant is zero and, therefore,  $\bar{b}_0(0) = 0$ . Thus, (2.4.6) becomes:

$$\frac{d\Pi_0 a}{d\tau} = \gamma(1 - (\bar{a}_0(0) + \Pi_0 a)) - (\bar{a}_0(0) + \Pi_0 a)(\bar{a}_0(0) + \Pi_0 a + p^* - 1), \quad (2.4.10)$$

From (2.4.4) we have  $\gamma(1 - \bar{a}_0(0)) = \bar{a}_0(0)(\bar{a}_0(0) + p^* - 1)$ . Using this we simplify (2.4.10) to:

$$\frac{d\Pi_0 a}{d\tau} = -\gamma\Pi_0 a - 2\bar{a}_0(0)\Pi_0 a - (\Pi_0 a)^2 - \Pi_0 a(p^* - 1), \quad (2.4.11)$$

with  $\bar{a}_0(0) = \frac{(1 - \gamma - p^*) + \sqrt{(1 - \gamma - p^*)^2 + 4\gamma}}{2}$ . Note that since we want  $\bar{a}_0(0) \geq 0$  (concentrations are non-negative), we choose the positive sign in (2.4.5).

### 2.4.3 Stability analysis for the regular functions

Solving (2.4.4) for  $\bar{b}_0$  yields

$$\bar{b}_0 = \frac{\gamma(1 - \bar{a}_0) - \bar{a}_0(\bar{a}_0 + p^* - 1)}{\bar{a}_0 + \gamma}. \quad (2.4.12)$$

Substituting (2.4.4) into equation (2.4.3), we can write:

$$\frac{d\bar{b}_0}{dt} = (\bar{a}_0 + \bar{b}_0 + p^* - 1)\left(\frac{\bar{a}_0}{\gamma} - \beta\bar{b}_0\right) = F(\bar{a}_0, \bar{b}_0). \quad (2.4.13)$$

The equilibrium points of equation (2.4.13), if they exist, must belong to null-clines,

$$\bar{b}_0 = 1 - \bar{a}_0 - p^*, \quad (2.4.14)$$

$$\bar{b}_0 = \frac{\bar{a}_0}{\beta\gamma}, \quad (2.4.15)$$

as well as the null-cline given by (2.4.12).

By setting (2.4.12) equal to (2.4.14) we can see that these null-clines do not cross, (since when we solve for  $\bar{a}_0$  we get that  $p^* = 0$  which is not possible). Therefore we have no meaningful steady states belonging to (2.4.14).

Setting (2.4.12) equal to (2.4.15) and solving for  $\bar{a}_0$  we get:

$$\bar{a}_0 = \frac{1 - (p^* + \gamma + \beta^{-1}) \pm \sqrt{(p^* + \gamma + \beta^{-1} - 1)^2 + 4\gamma(1 + (\beta\gamma)^{-1})}}{2 + 2(\beta\gamma)^{-1}}. \quad (2.4.16)$$

Since we are only interested in  $\bar{a}_0$  in the first quadrant, we choose the positive sign in (2.4.16). We denote this unique steady state by  $(\bar{a}_0^*, \bar{b}_0^*)$ .

Taking the derivative of the right hand side of equation (2.4.13) with respect to  $\bar{b}_0$ , we get:

$$\frac{dF}{d\bar{b}_0}(\bar{a}_0(\bar{b}_0), \bar{b}_0) = \left( \frac{d\bar{a}_0}{d\bar{b}_0} + 1 \right) \left( \frac{\bar{a}_0}{\gamma} - \beta\bar{b}_0 \right) + (\bar{a}_0 + \bar{b}_0 + p^* - 1) \left( \frac{1}{\gamma} \frac{d\bar{a}_0}{d\bar{b}_0} - \beta \right).$$

For stability we need  $\frac{dF}{d\bar{b}_0}(\bar{a}_0^*, \bar{b}_0^*) < 0$ .

Since at the steady state  $\bar{b}_0 = \frac{\bar{a}_0}{\beta\gamma}$ , the first product in the right-hand-side is zero.

We argue that  $\frac{d\bar{a}_0}{d\bar{b}_0} < 0$  by the *Implicit Function Theorem* [10] as follows. Let us re-write the implicit function representation (2.4.4) as

$$G(\bar{a}_0, \bar{b}_0) = \bar{a}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1) + \gamma(\bar{a}_0 + \bar{b}_0 - 1) = 0.$$

Invoking the *Implicit Function Theorem*,

$$\frac{d\bar{a}_0}{d\bar{b}_0} = -\frac{\partial G/\partial \bar{b}_0}{\partial G/\partial \bar{a}_0} = -\frac{\bar{a}_0 + \gamma}{2\bar{a}_0 + \bar{b}_0 + p^* - 1 + \gamma} < 0.$$

And finally, we can see from equation (2.4.4) that

$(\bar{a}_0 + \bar{b}_0 + p^* - 1)$  is positive. Therefore, we have that  $\frac{dF}{db_0} < 0$ , which means  $(\bar{a}_0^*, \bar{b}_0^*)$  is a stable steady state, and both  $\bar{a}_0$  and  $\bar{b}_0$  approach this steady state as  $t \rightarrow \infty$ .

#### 2.4.4 Stability analysis for the boundary functions

The steady states for the system (2.4.6) and (2.4.7) are:

$$(\Pi_0 a^*, \Pi_0 b^*)_1 = (0, 0) \text{ and}$$

$$(\Pi_0 a^*, \Pi_0 b^*)_2 = (1 - \gamma - p^* - 2\bar{a}_0(0), 0).$$

Since the abscissa of  $(\Pi_0 a^*, \Pi_0 b^*)_2$  is negative we are not interested in that steady state. Therefore the only physically viable steady state is  $(0, 0)$ .

We calculate:

$$\left(\frac{d\Pi_0 a}{d\tau}\right)' (\Pi_0 a^*, \Pi_0 b^*)_1 = 1 - \gamma - p^* - 2\bar{a}_0(0).$$

$$\text{Since } \bar{a}_0(0) = \frac{(1 - \gamma - p^*) + \sqrt{(1 - \gamma - p^*)^2 + 4\gamma}}{2},$$

we see that  $\left(\frac{d\Pi_0 a}{d\tau}\right)' (\Pi_0 a^*, \Pi_0 b^*)_1 < 0$ . Therefore  $(0, 0)$  is a stable steady state.

#### 2.4.5 Discussion

Recall that the only steady state for regular functions that had any physical significance was:

$$\bar{b}_0 = \frac{\bar{a}_0}{\beta\gamma},$$

with  $\bar{a}_0$  given by (2.4.16) with positive sign.

For symmetric membrane transport ( $\beta = \gamma = 1$ ) we have:

$$\bar{a}_0(\infty) = \bar{b}_0(\infty) = \frac{-(p^* + 1) + \sqrt{(p^* + 1)^2 + 8}}{4}.$$

The following sequence of graphs illustrate this result for various parameter values.

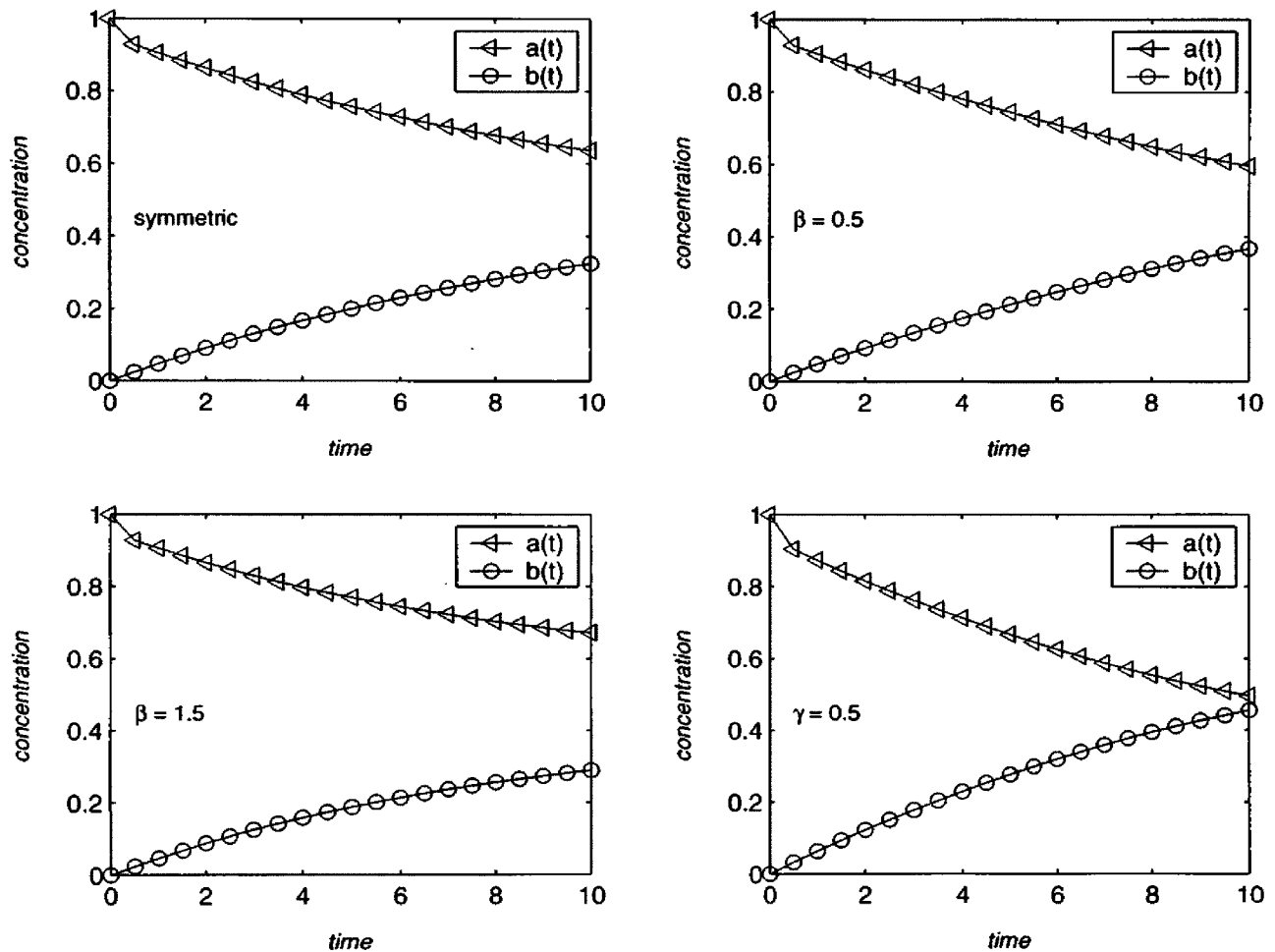


Figure 6. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = 0.01$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.5 Analysis of Case 4

For Case 4, where  $(k_1^-)$  and  $(k_2^+)$  are large, we make the following substitution:

$$t_0 = \frac{1}{k_2^-}.$$

Once again, we go back to equations (2.1.1) and (2.1.2) and make the new substitution for  $t_0$  and get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \frac{k_1^-}{k_2^-} \tilde{q} - \frac{k_1^+}{k_2^-} a^0 \tilde{a} \tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \tilde{q} - \frac{k_2^+}{k_2^-} a^0 \tilde{b} \tilde{p}.\end{aligned}$$

Introducing new parameters as follows:

$$\frac{1}{\epsilon} = \frac{k_2^+}{k_2^-} a^0; \quad \gamma = \frac{k_1^-}{k_2^-}; \quad \beta = \frac{k_1^+}{k_2^-} a^0,$$

we get:

$$\begin{aligned}\epsilon \frac{d\tilde{a}}{d\tilde{t}} + \epsilon \beta \tilde{a} \tilde{p} &= \gamma \tilde{q}, \\ \epsilon \frac{d\tilde{b}}{d\tilde{t}} - \epsilon \tilde{q} &= -\tilde{b} \tilde{p}.\end{aligned}\tag{2.5.1}$$

Recall that  $\tilde{q} = 1 - \tilde{a} - \tilde{b}$  and  $\tilde{p} = (\tilde{a} + \tilde{b} + p^* - 1)$ . We substitute these into (2.5.1) and get:

$$\epsilon \frac{d\tilde{a}}{d\tilde{t}} + \epsilon \beta \tilde{a} (\tilde{a} + \tilde{b} + p^* - 1) = \gamma (1 - \tilde{a} - \tilde{b}),\tag{2.5.2}$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} - \epsilon (1 - \tilde{a} - \tilde{b}) = -\tilde{b} (\tilde{a} + \tilde{b} + p^* - 1).\tag{2.5.3}$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ ,  $\tilde{b}(0) = 0$ .

We omit the tildes now.

### 2.5.1 The leading order approximation: Regular functions for Case 4

Setting  $\epsilon$  equal to zero we get:

$$0 = \gamma(1 - \bar{a}_0 - \bar{b}_0), \text{ and}$$

$$0 = -\bar{b}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1).$$

Solving these together we get  $\bar{b}_0 = 0$ , and

$$\bar{a}_0 + \bar{b}_0 = 1, \tag{2.5.4}$$

so  $\bar{a}_0 = 1$ .

Next we calculate the first order approximation of the regular functions.

### 2.5.2 The first order approximation: Regular functions for Case 4

Collecting the regular terms of first order in  $\epsilon$  from equations (2.5.2) and (2.5.3) we get:

$$\frac{d\bar{a}_0}{dt} + \beta\bar{a}_0(\bar{a}_0 + \bar{b}_0 + p^* - 1) = -\gamma(\bar{a}_1 + \bar{b}_1), \tag{2.5.5}$$

$$\frac{d\bar{b}_0}{dt} - 1 + \bar{a}_0 + \bar{b}_0 = -\bar{b}_0(\bar{a}_1 - \bar{b}_1) - \bar{b}_1(\bar{a}_0 + \bar{b}_0 + p^* - 1). \tag{2.5.6}$$

Since  $\bar{a}_0 = 1$  and  $\bar{b}_0 = 0$ , we know that  $(d\bar{a}_0/dt) = (d\bar{b}_0/dt) = 0$ , and therefore from equations (2.5.5) and (2.5.6) we obtain  $\bar{b}_1 = 0$  and  $\bar{a}_1 = \frac{-\beta p^*}{\gamma}$ .

### 2.5.3 The leading order approximation: Boundary Functions for Case 4

Using the standard procedure, we have:

$$\frac{d\Pi_0 a}{d\tau} = \gamma(1 - (\bar{a}_0(0) + \Pi_0 a) - (\Pi_0 a + \Pi_0 b)) = -\gamma(\Pi_0 a + \Pi_0 b), \quad (2.5.7)$$

$$\begin{aligned} \frac{d\Pi_0 b}{d\tau} &= -(\bar{b}_0(0) + \Pi_0 b)(\bar{a}_0(0) + \Pi_0 a + \bar{b}_0(0) + \Pi_0 b + p^* - 1) \\ &= -\Pi_0 b(\Pi_0 a + \Pi_0 b + p^*). \end{aligned} \quad (2.5.8)$$

Our boundary function initial conditions in the leading order are

$$\Pi_0 a(0) = 0, \quad (2.5.9)$$

$$\Pi_0 b(0) = 0. \quad (2.5.10)$$

The analysis of this case is similar to that of Case 2. As in Case 2, the steady state of system (2.5.7), (2.5.8) is (0,0) and  $\det[J(0,0) - \lambda I] = 0$  yields eigenvalues:

$$\lambda_{1,2} = \frac{-(p^* + \gamma) \pm \sqrt{(p^* + \gamma)^2 - 4p^*\gamma}}{2}.$$

Since the eigenvalues are real, distinct, and less than zero (because  $p^*$  and  $\gamma$  are positive) the steady state is a stable node. Therefore the boundary functions, obtained as solutions of (2.5.7)-(2.5.10), are identically zero.

### 2.5.4 Discussion

Since  $d\bar{a}_0/dt = d\bar{a}_1/dt = 0$  with  $\bar{a}_0(0) = 1$ ,  $\bar{a}_1(0) = -\beta p^*/\gamma$ , and the steady state (0,0) for the boundary functions is a stable node, we conclude that the concentration



of permeant  $A$  changes very little. This means that  $A$  is not absorbed into and transported through the membrane. This is illustrated in the graphs below.

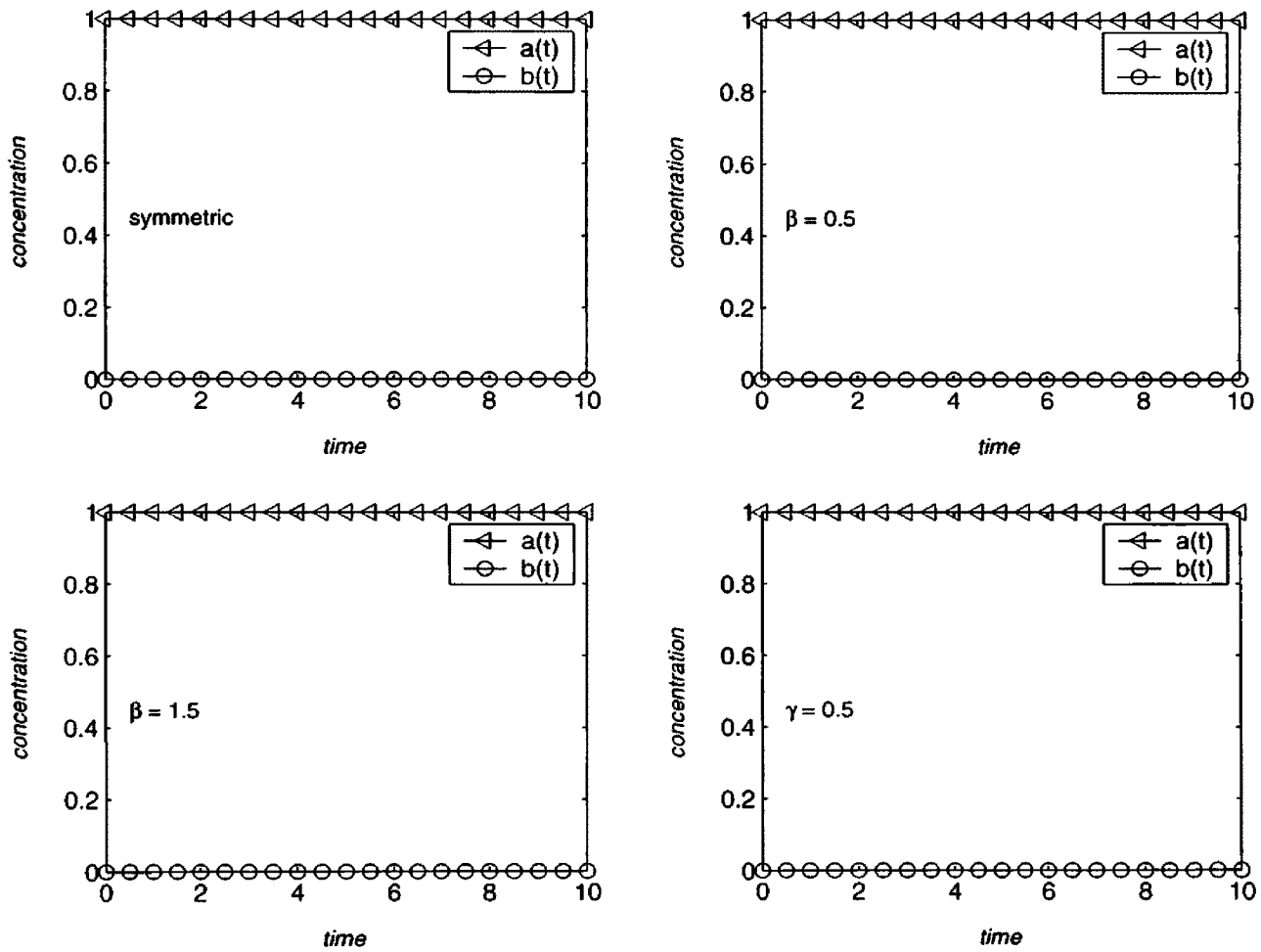


Figure 7. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = 0.01$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.6 Analysis of Case 5

For Case 5, where  $(k_2^+)$  and  $(k_2^-)$  are large, we make the following substitution:

$$t_0 = \frac{1}{k_1^-}.$$

Now we perform the same analysis as before and check how the model behavior changes. Going back to equations (2.1.1) and (2.1.2) and making the above substitution for  $t_0$ , we get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \tilde{q} - \frac{k_1^+}{k_1^-} a^0 \tilde{a} \tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \frac{k_2^-}{k_1^-} \tilde{q} - \frac{k_2^+}{k_1^-} a^0 \tilde{b} \tilde{p}.\end{aligned}$$

Making substitutions:

$$\frac{1}{\epsilon} = \frac{k_2^-}{k_1^-}; \quad \frac{\gamma}{\epsilon} = \frac{k_2^+}{k_1^-} a^0; \quad \beta = \frac{k_1^+}{k_1^-} a^0,$$

we get:

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \tilde{q} - \beta \tilde{a} \tilde{p}, \\ \epsilon \frac{d\tilde{b}}{d\tilde{t}} &= \tilde{q} - \gamma \tilde{b} \tilde{p}.\end{aligned}$$

We recall that  $\tilde{q} = 1 - \tilde{a} - \tilde{b}$  and  $\tilde{p} = (\tilde{a} + \tilde{b} + p^* - 1)$ . We substitute these in the above system and get:

$$\frac{d\tilde{a}}{d\tilde{t}} = 1 - \tilde{a} - \tilde{b} - \beta \tilde{a}(\tilde{a} + \tilde{b} + p^* - 1), \quad (2.6.1)$$

$$\epsilon \frac{d\tilde{b}}{d\tilde{t}} = 1 - \tilde{a} - \tilde{b} - \gamma \tilde{b}(\tilde{a} + \tilde{b} + p^* - 1). \quad (2.6.2)$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ ,  $\tilde{b}(0) = 0$ .

In what follows we simplify notation by omitting the tildes.

### 2.6.1 The leading order approximation: Regular functions for Case 5

Setting  $\epsilon$  equal to zero in (2.6.2) we get:

$$\gamma \bar{b}_0 (\bar{a}_0 + \bar{b}_0 + p^* - 1) = 1 - \bar{a}_0 - \bar{b}_0. \quad (2.6.3)$$

Solving this for  $\bar{b}_0$  we obtain:

$$\bar{b}_0 = \frac{(-\gamma(\bar{a}_0 + p^* - 1) - 1) \pm \sqrt{(\gamma(\bar{a}_0 + p^* - 1) + 1)^2 - 4\gamma(\bar{a}_0 - 1)}}{2}. \quad (2.6.4)$$

We can substitute (2.6.4) into (2.6.1) to get an equation in terms of  $\bar{a}_0$  only. To find the correct sign in (2.6.4) we need to first discuss the boundary functions. Once we find the right sign, we will analyze the long term behavior of the regular functions.

### 2.6.2 The leading order approximation: Boundary Functions for Case 5

Using the standard procedure for the leading order boundary functions, we obtain:

$$\frac{d\Pi_0 a}{d\tau} = 0, \quad (2.6.5)$$

$$\begin{aligned} \frac{d\Pi_0 b}{d\tau} &= 1 - (\bar{a}_0(0) + \Pi_0 a) - (\bar{b}_0(0) + \Pi_0 b) \\ &\quad - \gamma(\bar{b}_0(0) + \Pi_0 b)(\bar{a}_0(0) + \Pi_0 a + \bar{b}_0(0) + \Pi_0 b + p^* - 1). \end{aligned} \quad (2.6.6)$$

The initial conditions in the leading order approximation are:

$$\bar{a}_0(0) + \Pi_0 a(0) = 1, \quad (2.6.7)$$

$$\bar{b}_0(0) + \Pi_0 b(0) = 0. \quad (2.6.8)$$

Clearly  $\Pi_0 a = \text{const}$ . Since  $\Pi_0 a \rightarrow 0$  as  $\tau \rightarrow \infty$ ,  $\text{const} = 0$  and therefore,  $\bar{a}_0(0) = 1$ .

Thus (2.6.6) becomes:

$$\frac{d\Pi_0 b}{d\tau} = -(\bar{b}_0(0) + \Pi_0 b) - \gamma(\bar{b}_0(0) + \Pi_0 b)(\bar{b}_0(0) + \Pi_0 b + p^*). \quad (2.6.9)$$

From (2.6.3) we have  $\gamma\bar{b}_0(0)(\bar{b}_0(0) + p^*) = -\bar{b}_0(0)$ . Using this we simplify (2.6.9):

$$\frac{d\Pi_0 b}{d\tau} = -\Pi_0 b - 2\gamma\bar{b}_0(0)\Pi_0 b - \gamma(\Pi_0 b)^2 - \gamma\Pi_0 b p^*, \quad (2.6.10)$$

with  $\bar{b}_0(0) = -(\gamma p^* + 1)$  or  $\bar{b}_0(0) = 0$ . Since we need  $\bar{b}_0(0) \geq 0$ , we choose  $\bar{b}_0(0) = 0$ .

Then,

$$\frac{d\Pi_0 b}{d\tau} = -\Pi_0 b - \gamma\Pi_0 b(\Pi_0 b + p^*).$$

Separation of variables yields:  $\frac{\Pi_0 b}{\gamma\Pi_0 b + \gamma p^* + 1} = \text{const} \cdot e^{(-\tau)} e^{(\gamma p^* + 1)}$ .

It follows from  $\bar{b}_0(0) = 0$  and the initial conditions in (2.6.8) that  $\Pi_0 b(0) = 0$ . Thus, we obtain that  $\Pi_0 b(\tau) \equiv 0$ .

### 2.6.3 Stability analysis for the regular functions

Solving (2.6.3) for  $\bar{a}_0$  yields,

$$\bar{a}_0 = 1 - \bar{b}_0 \left( 1 + \frac{\gamma p^*}{1 + \gamma \bar{b}_0} \right). \quad (2.6.11)$$

Substituting equation (2.6.3) into equation (2.6.1), we can write:

$$\frac{d\bar{a}_0}{dt} = (\bar{a}_0 + \bar{b}_0 + p^* - 1)(\gamma\bar{b}_0 - \beta\bar{a}_0) = F(\bar{a}_0, \bar{b}_0). \quad (2.6.12)$$

The equilibrium points of equation (2.6.12), if they exist, must belong to null-clines,

$$\bar{a}_0 = 1 - \bar{b}_0 - p^*, \quad (2.6.13)$$

$$\bar{a}_0 = \frac{\gamma \bar{b}_0}{\beta}, \quad (2.6.14)$$

as well as to the null-cline given by (2.6.11).

By setting (2.6.11) equal to (2.6.13), we can see that these null-clines do not cross (since when we solve for  $\bar{b}_0$  we get  $p^* = 0$  which is not possible). Therefore we have no meaningful steady states belonging to (2.6.13).

Setting (2.6.11) equal to (2.6.14) and solving for  $\bar{b}_0$  we get:

$$\bar{b}_0 = \frac{-(\gamma + \beta(1 + \gamma p^* - \gamma)) \pm \sqrt{(\gamma + \beta(1 + \gamma p^* - \gamma))^2 + 4\beta(\gamma^2 + \gamma\beta)}}{2(\gamma^2 + \gamma\beta)}. \quad (2.6.15)$$

Since only non-negative concentrations are possible, we choose the positive sign in (2.6.15). We denote this unique steady state by  $(\bar{a}_0^*, \bar{b}_0^*)$ .

Taking the derivative of the right hand side of equation (2.6.12) in with respect to  $\bar{a}_0$ , we get:

$$\frac{dF}{d\bar{b}_0}(\bar{a}_0(\bar{b}_0), \bar{b}_0) = \left( \frac{d\bar{b}_0}{d\bar{a}_0} + 1 \right) (\gamma \bar{b}_0 - \beta \bar{a}_0) + (\bar{a}_0 + \bar{b}_0 + p^* - 1) \left( \gamma \frac{d\bar{b}_0}{d\bar{a}_0} - \beta \right).$$

For stability we need  $\frac{dF}{d\bar{a}_0}(\bar{a}_0^*, \bar{b}_0^*) < 0$ .

Since  $\bar{a}_0 = (\gamma \bar{b}_0)/\beta$ , the first product in the right-hand-side is zero.

Similar to Case 3 we may show that  $d\bar{a}_0/d\bar{b}_0 < 0$  by the *Implicit Function Theorem*

[10] And finally, we can see from equation (2.6.3) that  $(\bar{a}_0 + \bar{b}_0 + p^* - 1)$  is positive.

Therefore, we have that  $(dF/d\bar{a}_0)' < 0$ , which means  $(\bar{a}_0^*, \bar{b}_0^*)$  is a stable steady state, and both  $\bar{a}_0$  and  $\bar{b}_0$  approach this steady state as  $t \rightarrow \infty$ .

## 2.6.4 Stability analysis for the boundary functions

Since in this case the system of differential equations was directly solvable, stability analysis is not necessary. Recall the solution of system (2.6.5) and (2.6.6) is:

$$\Pi_0 a(\tau) \equiv \Pi_0 b(\tau) \equiv 0.$$

Therefore (0,0) is trivially a stable steady state.

## 2.6.5 Discussion

Recall that the only steady state for regular functions that had any physical significance was:

$$\bar{a}_0 = \frac{\gamma \bar{b}_0}{\beta},$$

with  $\bar{b}_0$  given by (2.6.15) (with positive sign).

For symmetric membrane transport ( $\beta = \gamma = 1$ ) we have:

$$\bar{a}_0(\infty) = \bar{b}_0(\infty) = \frac{-(1 + p^*) + \sqrt{((1 + p^*)^2 + 8)}}{4}.$$

The following sequence of graphs shows this result for various parameter values.

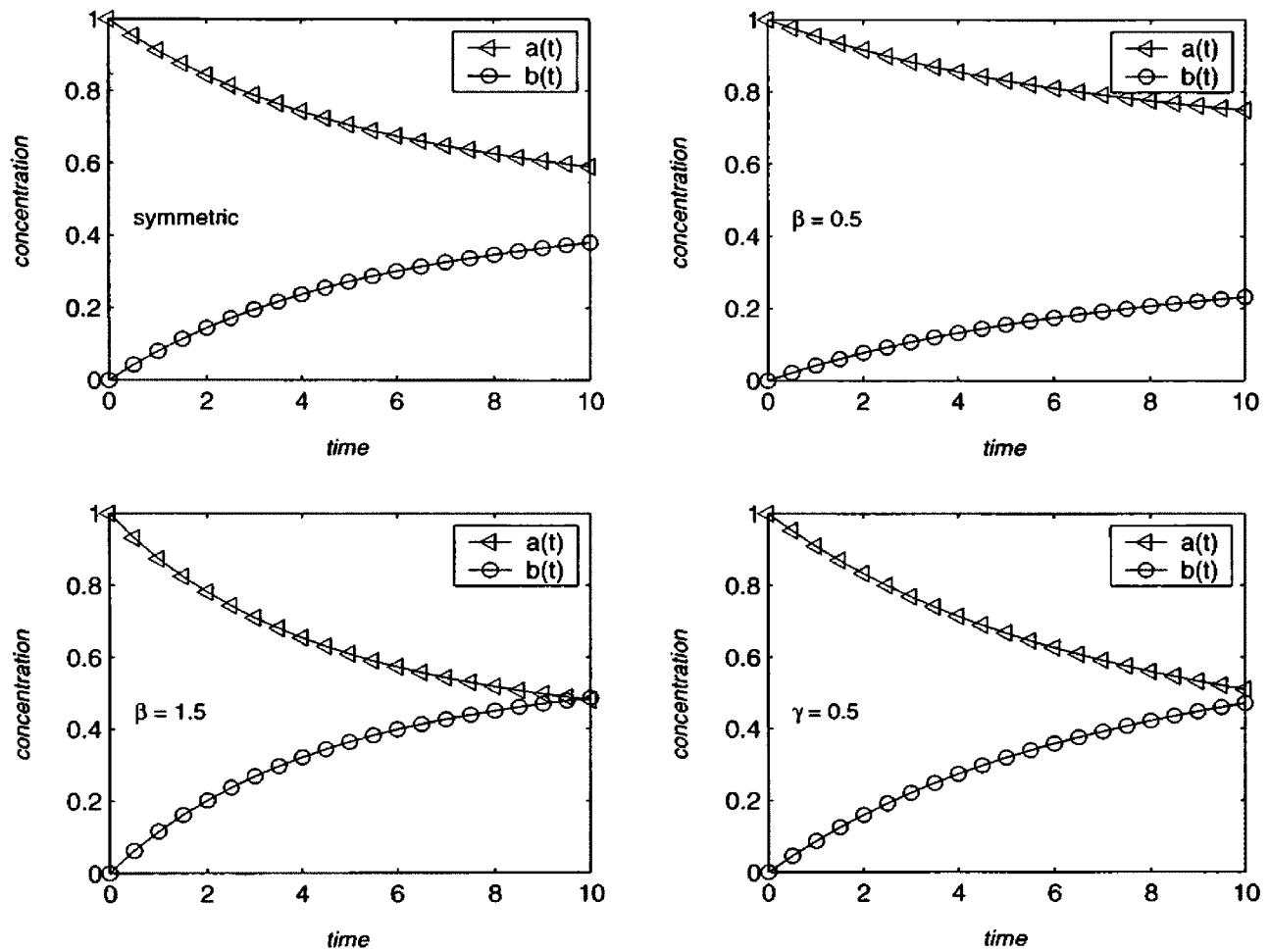


Figure 8. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = 0.01$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.7 Analysis of Case 6

For Case 6 we make the following substitution:  $t_0 = \frac{1}{k_1^+ p^0} \gg \frac{1}{k_1^+ a^0}$ . We obtain,

$$\begin{aligned}\frac{d\tilde{a}}{d\tilde{t}} &= \frac{k_1^- \tilde{q}}{k_1^+ p^0} - \frac{a^0}{p^0} \tilde{a} \tilde{p}, \\ \frac{d\tilde{b}}{d\tilde{t}} &= \frac{k_2^- \tilde{q}}{k_1^+ p^0} - \frac{k_2^+ a^0}{k_1^+ p^0} \tilde{b} \tilde{p}.\end{aligned}$$

Since the rate constants are all of the same order, their ratios are all of order  $O(1)$ .

We make the following substitutions:

$$\frac{1}{\epsilon} = \frac{a^0}{p^0} = \frac{1}{p^*} ; \beta = \frac{k_2^-}{k_1^+ a^0} ; \alpha = \frac{k_2^+}{k_1^+} ; \gamma = \frac{k_1^-}{k_1^+ a^0}.$$

We have:

$$\frac{d\tilde{a}}{d\tilde{t}} = \frac{\gamma}{\epsilon} \tilde{q} - \frac{1}{\epsilon} \tilde{a} \tilde{p}, \tag{2.7.1}$$

$$\frac{d\tilde{b}}{d\tilde{t}} = \frac{\beta}{\epsilon} \tilde{q} - \frac{\alpha}{\epsilon} \tilde{b} \tilde{p}.$$

Recall that  $q = 1 - \tilde{a} - \tilde{b}$  and  $p = (\tilde{a} + \tilde{b} + \epsilon - 1)$ . We substitute these into (2.7.1)

and get:

$$\epsilon \left( \frac{d\tilde{a}}{d\tilde{t}} + \tilde{a} \right) = (\gamma + \tilde{a})(1 - \tilde{a} - \tilde{b}), \tag{2.7.2}$$

$$\epsilon \left( \frac{d\tilde{b}}{d\tilde{t}} + \alpha \tilde{b} \right) = (\beta + \alpha \tilde{b})(1 - \tilde{a} - \tilde{b}). \tag{2.7.3}$$

The re-scaled initial conditions are:  $\tilde{a}(0) = 1$ ,  $\tilde{b}(0) = 0$ .

Below we omit the tildes.



### 2.7.1 The leading order approximation: Regular functions for Case 6

Setting  $\epsilon$  equal to zero we get:

$$\bar{a}_0 + \bar{b}_0 = 1. \quad (2.7.4)$$

Dividing (2.7.2) by  $(\gamma + \bar{a}_0)$ , dividing (2.7.3) by  $(\beta + \alpha\bar{b}_0)$ , and taking the difference of the two equations we arrive at:

$$\frac{1}{\gamma + \bar{a}_0} \left( \frac{d\bar{a}_0}{dt} + \bar{a}_0 \right) = \frac{1}{\beta + \alpha\bar{b}_0} \left( \frac{d\bar{b}_0}{dt} + \alpha\bar{b}_0 \right). \quad (2.7.5)$$

It follows from (2.7.4) that  $\frac{d\bar{a}_0}{dt} = -\frac{d\bar{b}_0}{dt}$ .

So, we simplify (2.7.5) to obtain:

$$\left( \frac{1}{\gamma + \bar{a}_0} + \frac{1}{\beta + \alpha\bar{b}_0} \right) \frac{d\bar{a}_0}{dt} = \frac{-\bar{a}_0}{\gamma + \bar{a}_0} + \frac{\alpha\bar{b}_0}{\beta + \alpha\bar{b}_0}.$$

Dividing both sides by  $\left( \frac{1}{\gamma + \bar{a}_0} + \frac{1}{\beta + \alpha\bar{b}_0} \right)$  and using a little algebra, we get:

$$\frac{d\bar{a}_0}{dt} = \frac{-\bar{a}_0\beta + \alpha\gamma\bar{b}_0}{\gamma + \beta + \bar{a}_0 + \alpha\bar{b}_0}.$$

This can be written strictly in terms of  $\bar{a}_0$  since  $\bar{b}_0 = 1 - \bar{a}_0$ :

$$\frac{d\bar{a}_0}{dt} = \frac{-\bar{a}_0\beta + \alpha\gamma(1 - \bar{a}_0)}{\gamma + \beta + \bar{a}_0 + \alpha(1 - \bar{a}_0)}. \quad (2.7.6)$$

This is a separable ODE with an implicit solution and is solved similar to Case 1.

### 2.7.2 The leading order approximation: Boundary Functions for Case 6

Using the standard procedure we write:

$$\frac{d\Pi_0 a}{d\tau} = (\gamma + \bar{a}_0(0) + \Pi_0 a)(1 - \bar{a}_0(0) - \bar{b}_0(0) - \Pi_0 a - \Pi_0 b),$$

$$\frac{d\Pi_0 b}{d\tau} = (\beta + \alpha \bar{b}_0(0) + \alpha \Pi_0 b)(1 - \bar{a}_0(0) - \bar{b}_0(0) - \Pi_0 a - \Pi_0 b).$$

Applying equation (2.7.4), we simplify this to obtain:

$$\frac{d\Pi_0 a}{d\tau} = -(\gamma + \bar{a}_0(0) + \Pi_0 a)(\Pi_0 a + \Pi_0 b), \quad (2.7.7)$$

$$\frac{d\Pi_0 b}{d\tau} = -(\beta + \alpha \bar{b}_0(0) + \alpha \Pi_0 b)(\Pi_0 a + \Pi_0 b). \quad (2.7.8)$$

Now we divide equation (2.7.7) by  $(\gamma + \bar{a}_0(0) + \Pi_0 a)$ , divide equation (2.7.8) by  $(\beta + \alpha \bar{b}_0(0) + \alpha \Pi_0 b)$ , and take the difference:

$$\left( \frac{1}{(\gamma + \bar{a}_0(0) + \Pi_0 a)} \right) \left( \frac{d\Pi_0 b}{d\tau} \right) = \left( \frac{1}{(\beta + \alpha \bar{b}_0(0) + \alpha \Pi_0 b)} \right) \left( \frac{d\Pi_0 a}{d\tau} \right). \quad (2.7.9)$$

Integrating both sides, we get:

$$\gamma + \bar{a}_0(0) + \Pi_0 a = C_1(\beta + \alpha \bar{b}_0(0) + \alpha \Pi_0 b). \quad (2.7.10)$$

Initial conditions in the leading order approximation are:

$$\bar{a}_0(0) + \Pi_0 a(0) = 1 \quad (2.7.11)$$

$$\bar{b}_0(0) + \Pi_0 b(0) = 0.$$

Substituting our initial conditions (2.7.11) into equation (2.7.10), we find that  $C_1 = \frac{\gamma + 1}{\beta}$ .

As  $\tau \rightarrow \infty$  the  $\Pi$ -functions must go to zero. Using the fact that  $\bar{a}_0(0) = 1 - \bar{b}_0(0)$  we can re-write (2.7.10) as  $\tau \rightarrow \infty$  in the form:

$$\gamma + 1 - \bar{b}_0(0) = \gamma + 1 + \frac{\alpha}{\beta}(\gamma + 1)(\bar{b}_0(0)).$$

Factoring leads to,

$$0 = \bar{b}_0(0)(1 + \frac{\alpha}{\beta}(\gamma + 1))$$

Therefore  $\bar{b}_0(0) = 0$  and  $\bar{a}_0(0) = 1$ . We can use this to re-write (2.7.7) and (2.7.8) as:

$$\frac{d\Pi_0 a}{d\tau} = -(\gamma + 1 + \Pi_0 a)(\Pi_0 a + \Pi_0 b), \quad (2.7.12)$$

$$\frac{d\Pi_0 b}{d\tau} = -(\beta + \alpha\Pi_0 b)(\Pi_0 a + \Pi_0 b). \quad (2.7.13)$$

Dividing (2.7.12) by (2.7.13) and solving by separation of variables, we arrive at the relation:

$$\gamma + 1 + \Pi_0 a = C_2(\beta + \alpha\Pi_0 b). \quad (2.7.14)$$

Initial conditions for the  $\Pi$ -functions in the leading order approximation are:

$$\Pi_0 a(0) = 0, \quad (2.7.15)$$

$$\Pi_0 b(0) = 0.$$

Substituting (2.7.15) into (2.7.14) we find  $C_2 = \frac{\gamma + 1}{\beta}$ .

Using the expression for  $C_2$  in equation (2.7.14), and solving for  $\Pi_0 b$ , we obtain:

$$\Pi_0 b = \frac{\beta}{\alpha(\gamma + 1)}(\gamma + 1 + \Pi_0 a) - \frac{\beta}{\alpha} = \frac{\beta\Pi_0 a}{\alpha(\gamma + 1)}. \quad (2.7.16)$$

Therefore:

$$\frac{d\Pi_0 a}{d\tau} = -(\gamma + 1 + \Pi_0 a)(\Pi_0 a + \frac{\beta\Pi_0 a}{\alpha(\gamma + 1)}). \quad (2.7.17)$$

Solving (2.7.17) by separation of variables yields:

$$\Pi_0 a(\tau) = \frac{C_3 \exp(-(\gamma + 1 + \beta/\alpha)\tau)(\gamma + 1)}{1 - C_3 \exp(-(\gamma + 1 + \beta/\alpha)\tau)}.$$

Using initial conditions (2.7.15) we see that  $\Pi_0 a(\tau) \equiv 0$ . Thus from (2.7.16) we have that  $\Pi_0 b(\tau) \equiv 0$  as well.

### 2.7.3 Discussion

Looking at equation (2.7.6) we see that if the concentration of  $A$  is kept large, i.e.,  $\bar{a}_0$  is close to one,

$$\frac{d\bar{a}_0}{dt} \rightarrow \frac{-\beta}{\gamma + \beta + 1}.$$

This means that, as the concentration of  $A$  increases without bound, the rate of facilitated diffusion transport approaches a limit.

Note that if we make the assumption that  $\gamma = \beta = \alpha = 1$ , we have:

$$\frac{d\bar{a}_0}{dt} = \frac{-\bar{a}_0 + (1 - \bar{a}_0)}{2 + \bar{a}_0 + (1 - \bar{a}_0)} = \frac{-2\bar{a}_0 + 1}{3}.$$

This is a linear ODE with solution:

$$\bar{a}_0 = C \cdot \exp(-2t/3) + 1/2, \text{ which approaches } 1/2 \text{ as } t \rightarrow \infty.$$

This means that permeant  $A$  diffuses into and through the membrane until half of the permeant is on the intracellular side of the membrane and the remainder stays outside the cell. At this point equilibrium is reached. This is illustrated in the figures below.

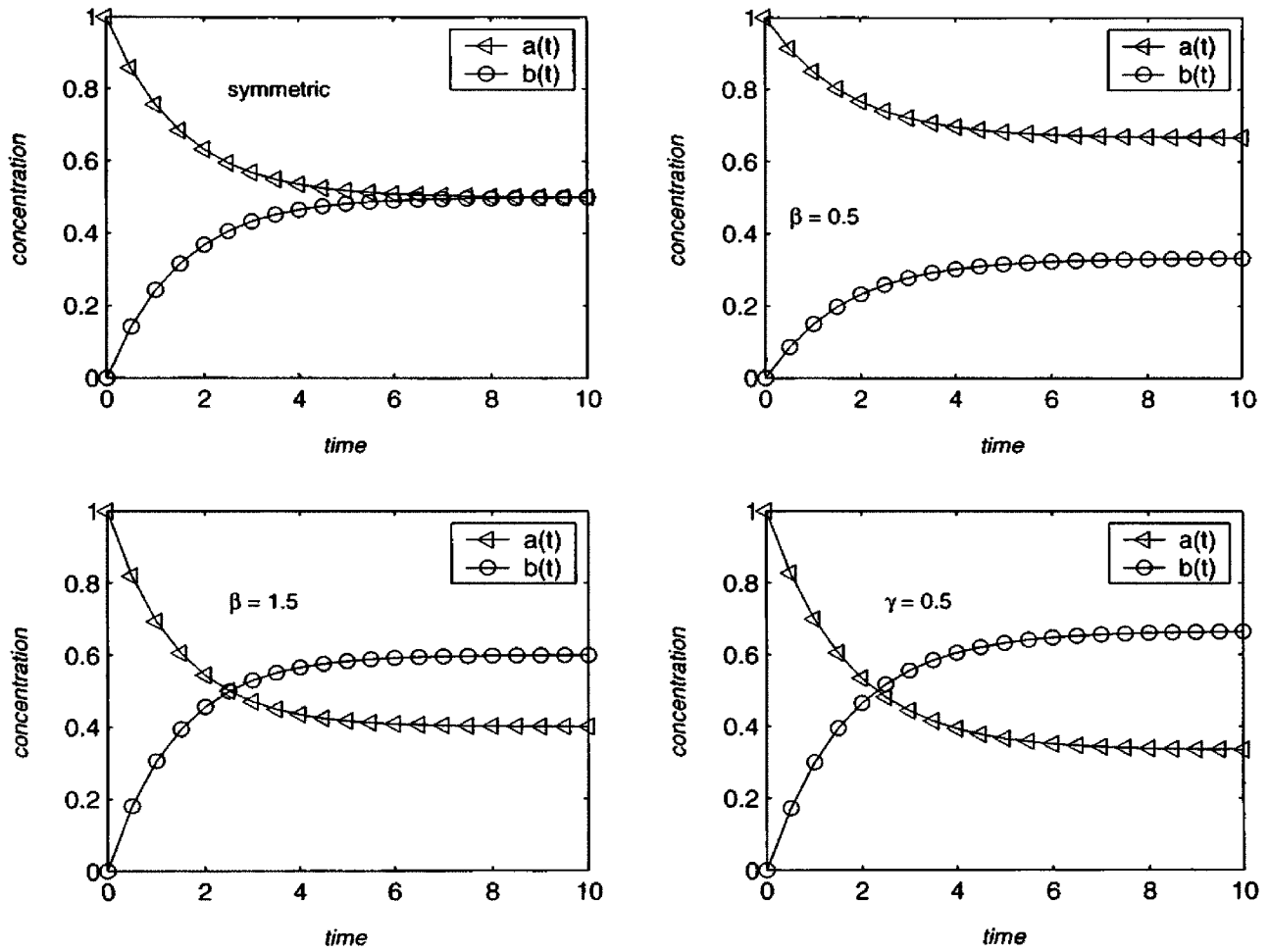


Figure 9. Graphs of  $a(t)$  and  $b(t)$  for various values of  $\beta$  and  $\gamma$  with  $\epsilon = 0.01$ ,  $a^0 = 1$ , and  $p^0 = 0.1$ . If the value of  $\beta$  or  $\gamma$  is not specified it was set equal to 1.

## 2.8 Analyzing the simplified models

We summarize our findings in the following tables. In tables 2.8.1 and 2.8.6 we present the reduced equations describing the rate of change of A and B depending on the current concentrations of A and B. In tables 2.8.2 through 2.8.5 we present approximate solutions for cases 2-5.

### 2.8.1 Summary of Case 1

Large	Small	Parameters	Absorbtion of Permeant A
$k_1^+, k_2^+$	$k_1^-, k_2^-$	$\beta = \frac{k_2^-}{k_1^-}, \gamma = \frac{k_2^+}{k_1^+}$	Initially fast absorption, then moderate absorbtion

Equations:

$$\frac{d\bar{a}_0}{dt} = p^* \left( \frac{\gamma\bar{b}_0 - \beta\bar{a}_0}{\gamma\bar{b}_0 + \bar{a}_0} \right),$$

$$\frac{d\bar{b}_0}{dt} = -\frac{d\bar{a}_0}{dt}.$$

### 2.8.2 Summary of Case 2

Large	Small	Parameters	Absorbtion of Permeant A
$k_1^+, k_2^-$	$k_1^-, k_2^+$	$\beta = \frac{k_2^-}{k_1^+ a^0}, \gamma = \frac{k_2^+}{k_1^- a^0}$	Nearly instantaneous absorption, through the membrane.

Equations:

$$\bar{a}_0 = 0,$$

$$\bar{b}_0 = 1.$$

### 2.8.3 Summary of Case 3

Large	Small	Parameters	Absorbtion of Permeant A
$k_1^+, k_1^-$	$k_2^+, k_2^-$	$\beta = \frac{k_2^+ a^0}{k_2^-}, \gamma = \frac{k_1^-}{k_1^+ a^0}$	Initially fast absorption, then moderate absorption.

Equations:

$$\bar{a}_0 = \frac{1 - (p^* + \gamma + \beta^{-1}) + \sqrt{(p^* + \gamma + \beta^{-1} - 1)^2 + 4\gamma(1 + (\beta\gamma)^{-1})}}{2 + 2(\beta\gamma)^{-1}},$$

$$\bar{b}_0 = \frac{1 - (p^* + \gamma + \beta^{-1}) + \sqrt{(p^* + \gamma + \beta^{-1} - 1)^2 + 4\gamma(1 + (\beta\gamma)^{-1})}}{2 + 2(\beta\gamma)}.$$

### 2.8.4 Summary of Case 4

Large	Small	Parameters	Absorbtion of Permeant A
$k_1^-, k_2^+$	$k_1^+, k_2^-$	$\beta = \frac{k_1^+ a^0}{k_2^-}, \gamma = \frac{k_1^-}{k_2^+ a^0}$	Little to no absorption

Equations:

$$\bar{a}_0 = 1,$$

$$\bar{b}_0 = 0.$$

### 2.8.5 Summary of Case 5

Large	Small	Parameters	Absorbtion of Permeant A
$k_2^+, k_2^-$	$k_1^+, k_1^-$	$\beta = \frac{k_1^+ a^0}{k_1^-}, \gamma = \frac{k_2^+ a^0}{k_2^-}$	Slow absorption.

Equations:

$$\bar{b}_0 = \frac{-(\gamma + \beta(1 + \gamma p^* - \gamma)) + \sqrt{(\gamma + \beta(1 + \gamma p^* - \gamma))^2 + 4\beta(\gamma^2 + \gamma\beta)}}{2\beta(\gamma + \beta)},$$

$$\bar{a}_0 = \frac{-(\gamma + \beta(1 + \gamma p^* - \gamma)) + \sqrt{(\gamma + \beta(1 + \gamma p^* - \gamma))^2 + 4\beta(\gamma^2 + \gamma\beta)}}{2(\gamma^2 + \gamma\beta)}.$$

### 2.8.6 Summary of Case 6

Rate Constants	Parameters	Absorbtion of Permeant A
all moderate	$\beta = \frac{k_2^-}{k_1^+ a^0}, \gamma = \frac{k_1^-}{k_1^+ a^0}, \alpha = \frac{k_2^+}{k_1^+}$	Moderate absorption.

Equations:

$$\frac{d\bar{a}_0}{dt} = \frac{-\bar{a}_0\beta + \alpha\gamma\bar{b}_0}{\gamma + \beta + \bar{a}_0 + \alpha\bar{b}_0},$$

$$\frac{d\bar{b}_0}{dt} = -\frac{d\bar{a}_0}{dt}.$$



# Bibliography

1. Julien, Robert M. (1981). *A Primer of Drug Action*. New York: W. H. Freeman and Company.
2. Pratt, William B., and Taylor, Palmer. (1990). *Principles of Drug Action—The Basis of Pharmacology*. New York: Churchill Livingstone.
3. Stein, Wilfred D. (1990). *Channels, Carriers, and Pumps: An Introduction to Membrane Transport*. San Diego: Academic Press, Inc.
4. Silverman, Richard B. (1992). *The Organic Chemistry of Drug Design and Drug Action*. New York: Academic Press, Inc.
5. Ansel, Howard C., and Popovich, Nicholas G. (1990). *Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lea & Febiger.
6. Shargel, Leon., and Yu, Andrew B.C. (1985). *Applied Biopharmaceutics and Pharmacokinetics*. Norwalk: Appleton-Century-Crofts.
7. van Rossum, Jacques M. (1977). *Kinetics of Drug Action*. New York: Springer-Verlag.
8. Bridges, Richard. Personal communication. February 13, 2004.

9. Vasil'eva, Adelaida B., and Butuzov, Valentin F., and Kalachev, Leonid V. (1995). *The Boundary Function Method for Singular Perturbation Problems*. Philadelphia: Society for Industrial and Applied Mathematics.
10. Krantz, Steven G. (1991). *Real Analysis and Foundations*. Boston: CRC Press, Inc.
11. Verhulst, Ferdinand. (2000). *Nonlinear Differential Equations and Dynamical Systems*. New York: Springer-Verlag.