CHAPTER

Continuum models of drug transport to multiple cell-type population

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List of Nomenclature

a_k	coefficient defined in the text
Bi	Biot number
C	volume-averaged drug concentration
C_∞	volume-averaged drug concentration of the reservoir in contact with the EC boundary
c	intrinsic volume-averaged drug concentration
D_{eff}	effective diffusivity of drug mass within the EC space
f_k	volume fraction of the k-th kind of cell
h_k	reaction term of the k-th kind of cell
$\mathbf{j}$	mass flux vector
j	mass flux
K	mass transfer coefficient at the EC boundary
L, W, H	dimensions of the parallelepiped-shaped tissue
m	drug mass
N	number of cell types in the tissue
$\mathbf{n}$	outward normal unit vector
$\mathbf{r}$	position vector
t	time
t_d	delivery time
V	volume
x, y, z	rectangular coordinates

Greek symbols

ε	porosity
μ_k	mass transfer rate at the k-th cell

Subscript

0	boundary of the EC space at $x = 0$
∞	undisturbed
C	cellular
CV	control volume

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EC extra-cellular
IC intra-cellular
k *k*-th cell type in the tissue
L boundary of the EC space at $x = L$
T total

Superscript

rev representative elementary volume
$\sim$ dimensionless

5.1 Introduction

The principal aim underlying the development of drugs and their administration is to elicit some subcellular level biochemical reaction (often occurring within the cells). Mathematical and pharmacokinetic models have been developed in order to aid researchers by determining the conditions that will control successful delivery of the drug to its target (or the conditions that will limit unintended reactions). Often the models evaluate the transport of the drug at the tissue scale; for example, in order to determine the maximum penetration depth (at some prescribed drug concentration) from the location of administration into poorly vascularized tissue.

Because at the tissue scale it is prohibitively computationally expensive to model the kinetics of the drug within and about each individual cell, continuum representations of the physical domain are employed (Fig. 5.1A). The continuum level representation should capture the effects of the important local physics involved at the cellular level; at least these should include the transport of the drug through the extracellular medium, the drug penetration across the cell membrane into the intracellular space, and reactions between the drug and the cell cytosol. To this end, a three-compartment model (Dordal et al., 1995) has been adopted in many tissue scale continuum models of drug delivery. The underlying concept, depicted in Fig. 5.1B, is that the drug exists in three distinct phases: the free drug in extracellular (EC) space, the free drug in the intracellular (IC) space, and the bound drug of the IC space that is represented as the product of reaction internal to the cell.

For completeness, we present a brief review of the most common three-compartment models of drug delivery in tissue composed of a single cell-type population in this section. The associated important physiological processes are discussed and these are linked to the most common mathematical expressions. The three-compartment model representation of the conservation of drug mass may be expressed by a coupled set of equations. The conservation of mass in the EC space is represented by the partial differential equation (PDE, for short):

$$\frac{\partial C_{EC}}{\partial t} = \nabla.\mathbf{j}(C_{EC}) - F(C_{EC}, C_{IC}) \tag{5.1}$$

The conservation of drug mass in the IC space is represented by the ordinary differential equation (ODE):

$$\frac{\partial C_{IC}}{\partial t} = F(C_{EC}, C_{IC}) - R(C_{IC}, P) \tag{5.2}$$

The product of the reaction within the cell is represented by the ODE:

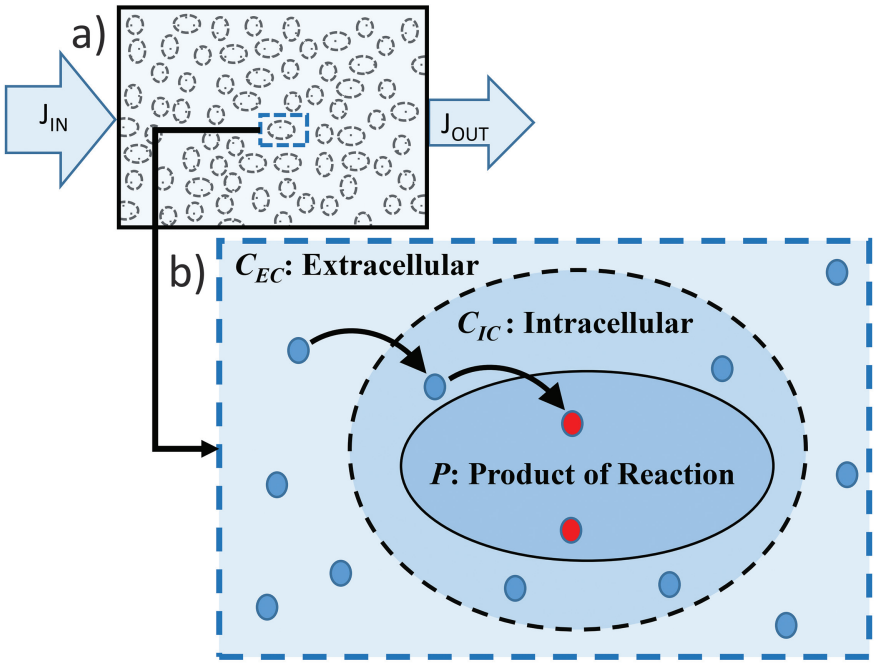

FIG. 5.1

(A) Depiction of continuum representation of drug delivery at the tissue scale. (B) Depiction of the three compartment model.

$$\frac{\partial P}{\partial t} = R(C_{IC}, P) \tag{5.3}$$

Here C_{EC} and C_{IC} are the total volume-averaged EC and IC drug concentrations, respectively. The flux of the drug within the EC space is usually modeled by simple diffusion or by a combination of diffusion and advection resulting from some interstitial flow velocity, $\mathbf{v}$:

$$\mathbf{j}(C_{EC}) = D\nabla C_{EC} + \mathbf{v}C_{EC} \tag{5.4}$$

Because the EC space is a porous domain, an effective diffusion coefficient, D, is used to account for the tortuous pathway through the fluid-filled space. In the discussion that follows only the diffusion of drug in the EC space is considered.

The function $F(C_{EC}, C_{IC})$ represents the net transport of the drug from the EC space to the IC space and reverse. When the intrinsic drug concentrations are modeled, the functions describing the transmembrane transport must account for the difference in the volumes of the IC space and the EC space. In single cell-type population models, when intrinsic drug concentrations are used, the functions representing the transmembrane transport of the EC space in Eq. (5.1) scales linearly to the function used in the intracellular space of Eq. (5.2) by the ratio of intracellular volume to EC volume.

A conversion of the drug inside the cell to some product P is often the intention of the drug therapy. Within the cell, the rate of this conversion is described by the reaction between the drug and the cell's internal organelles, $R(C_{IC}, P)$.

The sections that follow summarize some common mathematical representations of transmembrane transport and internal reactions that are used in single-cell-type PK models. In the discussion that follows a total volume-averaged concentration is used. The distinction between total volume-averaged concentration and intrinsic concentration is described in Section 5.2.1.

5.1.1 Transmembrane transport

The function $F(C_{EC}, C_{IC})$ must represent the nature of transport across the barrier function of the cell membrane (which is specific to the cell type and the molecular properties of the drug). The previous work (Yang and Hinner, 2015) provides a detailed review of how some molecules traverse this barrier. Generally, the continuum models describe this transmembrane transport in terms of the EC and IC drug concentrations.

5.1.1.1 Diffusion-based transmembrane transport models

For many drugs (small nonpolar ions, for example), the observed rate of transport across the cell membrane (from the EC space to the IC space) is linearly dependent on the drug concentration gradient across the membrane (Vendel et al., 2019a; El-Kareh and Secomb, 2003). Mathematical models describe the flux of free molecules across the cell membrane by Fickian diffusion. In this way the instantaneous rate of drug transport from the EC space to the IC space is represented by

$$F(C_{EC}, C_{IC}) = k_{12} C_{EC} - k_{21} C_{IC} \tag{5.5}$$

The parameter k_{12} is a constant representing the rate of mass transfer from the EC space to the IC space and k_{21} represents the rate constant in the reverse direction. These values may be determined experimentally and depend on the permeability of the cell wall to the drug, the density of the cells in the tissue, and whether partitioning is considered. It should also be noted that the magnitudes of these rates depend on whether the drug is represented by total volume-averaged concentration as in Jackson (2003) and Clarelli et al. (2020) or by intrinsic drug concentration as in Groh et al. (2014) and Mahnic-Kalamiza et al. (2014). In the analytical model that is developed in the second half of this chapter, only diffusion-based transmembrane transport is considered.

5.1.1.2 Facilitated diffusion transmembrane transport models

For some polar molecules (glucose, for example), the observed rate of transmembrane transport is saturable (limited) with respect to the transmembrane concentration gradient. This is in contrast with simple diffusion that is linearly related to this gradient. The transmembrane transport of such molecules is facilitated by a limited number of specialized carrier proteins (Yang and Hinner, 2015) and continuum models often describe the rate of facilitated transfer in terms of Michaelis–Menten kinetics (Vendel et al., 2019a; El-Kareh and Secomb, 2000). A relatively simple expression of facilitated passive transmembrane transport is presented in a study by Huang et al. (2011):

$$F(C_{EC}, C_{IC}) = \left(\frac{\mathrm{V}_{\max}}{K_M + C_{EC}}\right) C_{EC} - \left(\frac{\mathrm{V}_{\max}}{K_M + C_{IC}}\right) C_{IC} \tag{5.6}$$

Here the reaction velocity, V_{max}, indicates that the rate of transport across the cell wall is limited by the number of available transporters. The Michaelis constant, K_M, describes the strength of the interaction between the drug and the transporter. Its value is representative of the steady concentration value on one side of the membrane when one-half of the transporters are occupied and the other side of the membrane is highly diluted (Vivian and Polli, 2014). The nonlinearity of Eq. (5.6) makes it difficult to find the analytical solution, and so numerical methods are used to determine the solutions to Eq. (5.1) for drugs that rely on facilitated diffusion.

5.1.1.3 Rapid transmembrane transport approximation

Some models represent the transport across the cell wall as occurring instantaneously so that at any time the internal and external concentrations of the drug in its free unbound state are equal $C_{IC} = C_{EC} = C$ (local mass equilibrium—LME). This approximation allows the three-compartment model of Eqs. (5.1)–(5.3) to be represented by a two-compartment model that does not distinguish between EC and IC drug concentrations:

$$\begin{aligned} \frac{\partial C}{\partial t} &= \nabla . \mathbf{j}(C) - \mathrm{R}(C,P) \\ \frac{\partial P}{\partial t} &= R(C,P) \end{aligned} \tag{5.7}$$

This simplification holds when the transport of the drug across the cell membrane occurs on a much shorter timescale than those of the internal reactions. At shorter timescales, this two-compartment approximation fails to capture the time lag associated with the barrier function of the cell wall.

5.1.2 Reaction terms and binding models

Pharmacological continuum models often use the concept of binding (Clarelli et al., 2020) to represent the reactions between the drug and its environment. When the drug is free to diffuse and interact with its environment, the drug is in its unbound state, or free state. The drug may be in its free state within the EC medium and also within the interior of the cell. The drug molecule is designed to reach specific receptors within the interior of the cell (sometimes on the exterior cell wall). These receptors are referred to as specific binding sites; the drug that is bound to these is considered to be in its specific bound state. It is in this state that the drug can produce its intended effect. A comprehensive discussion of binding and signaling is presented in the book by Lauffenburger and Linderman (1993). For the purposes of this chapter, we use the principle of binding to represent the intracellular drug reactions and we present two simple and common reactions that have been used in the three-compartment models of drug delivery to cells.

5.1.2.1 Nonreversible first-order drug target binding model

In some previous studies of the delivery of drugs in cancer treatments (Jackson, 2003) the drug in its intracellular free state binds to the internal organelles of the cell in an irreversible manner. The idea is that once a sufficient concentration of the drug is in its bound state, the cancer cell will die and experimental observations show that this model is valid for specific cases (Dordal et al., 1995). Here the drug reaction rate is proportional to the concentration of the free drug in the cell cytosol:

$$\frac{\partial P}{\partial t} = R(C_{IC}) = k_{on} C_{IC} \tag{5.8}$$

The concentration of the drug in its specific bound state in the cell cytosol, P, is the drug's intended target. The parameter k_{on} is the binding rate constant of the drug in the cell and its value may be determined experimentally (Dordal et al., 1995). This type of reaction will be applied in the multiple cell-type population model introduced in Section 5.2.1.

5.1.2.2 Slow reversible nonlinear drug-target-binding models

For many drugs, the relationship between the rate of targeted binding and the drug concentration is not linear. Furthermore, these drugs bind to their receptors in a reversible manner so that some of the bound drug may return to its free state. These models consider that the rate of the binding is limited by the number of available binding sites. This representation has been used in three-compartment models (Clarelli et al., 2020; Groh et al., 2014) and is represented by

$$\frac{\partial P}{\partial t} = R(C_{IC}) = k_{on} C_{IC}(P_0 - P) - k_{off} P \tag{5.9}$$

Here k_{on} and k_{off} are the drug's association rate and disassociation rate constants, respectively. The maximum concentration of binding sites within the cell, P_0, limits the reaction and it is assumed that this value does not change during the reaction.

Sometimes instead of interacting with the intended specific binding site, the drug may interact with unintended receptors or other molecules (either in the EC space or within the interior of the cell) so the drug is bound and unable to interact with its intended receptors. Here the drug molecule would be considered to be in its nonspecific bound state. Recent drug delivery studies have accounted for both specific and nonspecific binding by including two reaction terms: one to account for specific binding rates and the other to account for nonspecific binding (McGinty and Pontrelli, 2016; Chakravarty et al., 2019).

While these models are of great interest, the nonlinearity of the reaction term provides a challenge to determine the exact mathematical solution; thus numerical methods of solution are generally employed.

5.1.2.3 Mathematical expressions of drug administration

In practice, the drug may be administered to the tissue via the circulatory system. When the vasculature is not well distributed, some studies use an advection boundary condition along the external boundaries where the tissue is in contact with the arterial supply. For example in the works by Vendel et al. (2019b, 2020) such a boundary condition is used to represent the transfer of the drug across the blood–brain barrier into the EC space:

$$D^* \frac{\partial C_{EC}}{\partial n}\bigg| = K(C_b - C_{EC}) \tag{5.10}$$

Here n is the direction of the outward pointing unit vector $\mathbf{n}$ normal to the boundary surface of the EC space, K is representative of the drug's permeability to the interface (also called mass transfer coefficient), and C_b is the concentration of the drug in the blood plasma which in those studies is modeled to be transient decaying in time.

When the drug is delivered to highly micro-vascularized tissues, a volumetric source term is sometimes used to account for the delivery from the microcirculatory system to the tissue's EC space (Jackson, 2003; El-Kareh and Secomb, 2000):

$$\dot{m}_b = \Gamma \cdot (C_b - C_{EC}) \tag{5.11}$$

where Γ is a term that is related to the permeability of the molecule in the vascular walls and to the density of the vascular network in the tissue (whose magnitude can vary by position).

In applications that use a polymer matrix as an applicator (such as a drug eluting stent), the drug is conserved within the applicator matrix as well as within the tissue domains. The transfer of the unbound drug to the EC medium is represented at the interface by boundary conditions both of mass flux type (Chakravarty et al., 2019) and of advection type (McGinty and Pontrelli, 2016):

$$\begin{aligned} D_0 \frac{\partial C_0}{\partial n} &= D \frac{\partial C_{EC}}{\partial n} + \upsilon C_{EC} \\ D \frac{\partial C_{EC}}{\partial n} &= K(C_0 - C_{EC}) \end{aligned} \tag{5.12}$$

Here D_0 and C_0 correspond to the effective diffusion coefficient and the concentration of the drug in the substrate, respectively, the parameter υ allows for partitioning of the drug at the interface.

5.1.3 Extension to multiple cell-type populations

The models reviewed so far have considered the delivery of drugs to cell populations comprised of only a single cell type. In many applications, drugs are delivered to a region of tissue composed of different cell types (for example, healthy and diseased cells) that may react differently to the drug administered. The concept of the extension of the three-compartment model to a multiple cell-type population is depicted in Fig. 5.2.

The mathematical representation of such a system would require that each cell type be assigned its own unique transmembrane transport term and its own unique reaction term. The extension of the three-compartment conservation of drug mass of Eqs. (5.1)–(5.3) to a population of N different cell types is accomplished by summing the components of the three-compartment model for each cell type:

$$\begin{aligned} \frac{\partial C_{EC}}{\partial t} &= \nabla \cdot \mathbf{j}(C_{EC}) - \sum_{i=1}^{N} F_i(C_{EC}, C_i) \\ \left.\begin{aligned} \frac{\partial C_i}{\partial t} &= F_i(C_{EC}, C_i) - R_i(C_i) \\ \frac{\partial P_i}{\partial t} &= R_i(C_i) \end{aligned}\right\} & \; i = 1 \ldots N \end{aligned} \tag{5.13}$$

Delivery to multiple cell-type populations attempts to capture the transient dynamics of the concentration of infected cells, of noninfected cells, and of the virus (Nowak et al., 1996). In order to capture the spread of the virus through a population of bacteria, the diffusion of the virus within the EC space has also been considered (You and Yin, 1999). Versions of this model reviewed all use the rapid transmembrane transport approximation so that they do not capture the barrier function of the cell membrane. These models focus on the conservation of the number of cell types. The manner in which

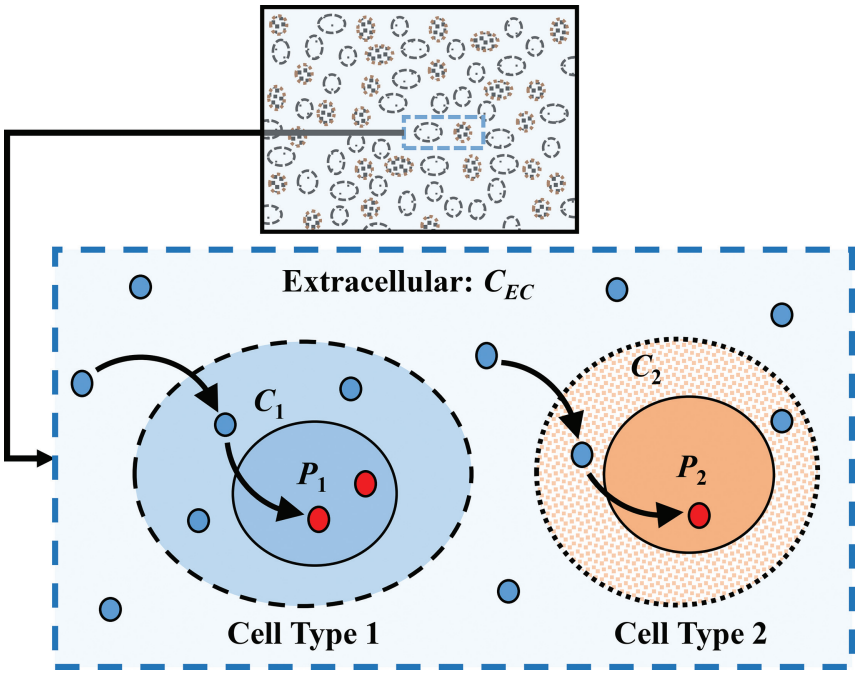

FIG. 5.2

Depiction of the extension of the three-compartment model of Fig. 5.1 to a multiple cell-type population.

the virus spreads to the cell (represented by the reaction term) has been shown to be nonlinear and irreversible making this application a poor candidate for expression by Eq. (5.13).

Multiple cell-type populations have also been considered in tumor growth models (Casciari et al., 1992); these consider that the rate of tumor cell growth is dependent on the available nutrient concentration. In their most general form, the coupled equations account for the different domains of the tumor (for example, EC space, space occupied by live cells, and space occupied by nonliving cells). These models consider that the volume fraction of each of these domains can each be represented by conservative equations and that there are reaction terms accounting for the dependence on different chemical nutrients. In its most general form, the model considers multiple phases and multiple chemical species (Roose et al., 2007; Casciari et al., 1992). Many applications of these models consider only a single chemical species and only two phases of tumor; for example, those presented by Breward et al. (2002) and Flegg and Nataraj (2019) which consider the conservation of only two phases (i) cell and (ii) EC fluid and only models the conservation of the single nutrient, i.e., oxygen. The focus of these models is to predict the distribution of tumor cell concentration (and not the distribution of drugs in the different cell types) so that the tumor growth models do not lend themselves readily to Eq. (5.13).

A drug resistance study by Jackson and Byrne (2000) modeled the diffusion of drug through a tumorous tissue composed of two cell types for which one cell type has a much stronger reaction to a drug than the other. However, that study did not account for the reduction of the drug mass in the EC space that results in the uptake of the drug by the cells; again that is because the focus of that study was the

conservation of the cells and not of the drug. Thus that study's approach also does not address the expressions posed by Eq. (5.13).

A three-compartment model of a multiple cell-type population has been considered in a previous study of the cellular uptake drug following exposure to electric fields (Argus et al., 2017). In that study the cells respond to the application of the electric pulse in two ways: in cell type 1 the permeability increases are transient and in cell type 2 the permeability increases are constant. The drug is free to diffuse through the EC space and transmembrane transport is modeled by Fickian diffusion. The governing equations for this two cell-type population are represented by

$$\begin{aligned}\frac{\partial C_{EC}}{\partial t} &= D\nabla^2 C_{EC} - \left(k_{12}C_{EC} - k_{21}e^{-t/\tau}C_1\right) - \left(k_{13}C_{EC} - k_{13}C_2\right)\\ \frac{\partial C_1}{\partial t} &= k_{12}C_{EC} - k_{21}e^{-t/\tau}C_1\\ \frac{\partial C_2}{\partial t} &= k_{13}C_{EC} - k_{13}C_2\end{aligned} \tag{5.14}$$

Here subscripts 1 and 2 indicate the cell types, and C_1 and C_2 are their respective total volume-averaged drug concentrations. Due to the complexity arising from the transient nature of the permeability of cell type 1 and because in that study the transport coefficients k_{12}, k_{21}, k_{13}, and k_{31}vary by position in a 2D domain, this problem was solved numerically (Argus et al., 2017). That study did not consider any drug reactions and is therefore not directly relatable to the greater problem posed by Eq. (5.13).

While the extension of the three-compartment model from single to multiple cell-type populations may seem obvious, there is a scarcity of its development in the literature. The focus of the remaining chapter is to provide this extension by first presenting the derivation of the equations conserving the drug mass. For each cell type, transmembrane transport is represented by the Fickian diffusion based model of Section 5.1.1.1. The reaction rates of each cell type are represented by nonreversible first-order binding of Section 5.1.2.1.

5.2 Formulation of the problem

Let us consider a portion of a biological medium of total volume V_T in a control volume (CV), as depicted in Fig. 5.3. The region is comprised of an EC space of volume V_{EC}, of volume V_C occupied by different cell types dispersed in it, having volumes of $V_1, V_2 \ldots, V_k \ldots, V_N$ (k denotes the k-th type of cell; think to healthy cell, tumor cell, inflamed cells, etc.).

Each type of cell responds to the therapy in a different way, so the mass transfers from the EC to the cell of type k, and vice versa. In the following derivation the rate of transmembrane mass transfer is dictated by the individual cell type's mass transfer coefficient, μ_k. Also, though the problem here is presented for an arbitrary number N of cell types, the derivation of the solution proposed in Section 5.3 is restricted to $N = 3$.

The tissue, taken as a whole, here is represented as a nonhomogeneous continuum by appropriately defining average variables over a sufficiently large volume, termed as "representative elementary volume" (rev, for short) (de Monte et al., 2013). The volume of the total space (V_T) is made of the volume occupied by the EC space (V_{EC}) and the volume occupied by the cells:

$$V_T = V_{EC} + V_C \tag{5.15a}$$

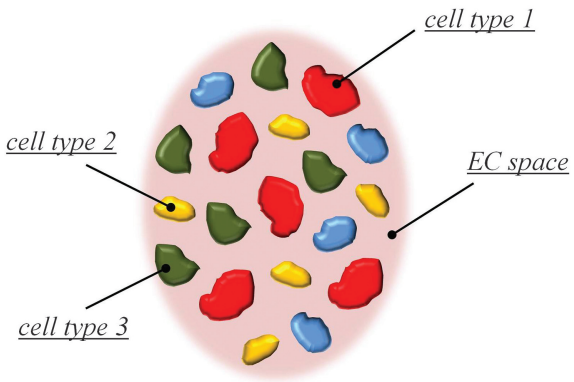

FIG. 5.3

The control volume CV (cross section in 2D) with individual cells of different types (different colors) immersed in the EC medium.

The volume occupied by the cells is composed of the volumes occupied by the different cell types:

$$V_C = V_1 + V_2 + \ldots + V_N \tag{5.15b}$$

The "*porosity*" is defined here as the fraction of the total volume that is composed of the EC space:

$$\varepsilon \equiv \frac{V_{EC}}{V_T} = \frac{V_{EC}}{V_{EC} + V_C} \tag{5.15c}$$

The volume occupied by all cell types is then $V_C = (1-\varepsilon)V_T$. The fraction of the cellular volume occupied by cell type "k" is defined as

$$f_k \equiv \frac{V_k}{V_C} = \frac{1}{(1-\varepsilon)}\frac{V_k}{V_T}, \quad k = 1, 2, \ldots, N. \tag{5.15d}$$

In this derivation it is assumed that the porosity, the volume fraction of the cell types and their corresponding volumes are spatially uniform and constant.

5.2.1 Concentrations and volume-averaged variables

The drug concentration in the liquid phase (EC space), c_{EC}, is defined as

$$c_{EC} = \frac{dm_{EC}}{dV_{EC}}, \tag{5.16}$$

where dm_{EC} is the elemental mass of drug in the EC differential volume dV_{EC}.

The concentration c_{EC} depends on $\mathbf{r}_{EC} \in V_{EC}$, where $\mathbf{r}_{EC}$ is the position vector of a point within the EC space. It can also depend on the time.

In addition, as the cellular space consists of N different types of cells, the intrinsic drug concentration in the k-th cell may be taken as

$$c_k = \frac{dm_k}{dV_k}, \quad k = 1, 2, \ldots, N \tag{5.17}$$

where dm_k is the elemental mass of drug contained into the k-th elemental volume dV_k. Also, the concentration c_k depends on $\mathbf{r}_k \in V_k$, where $\mathbf{r}_k$ is the position vector of a point within the k-th cell.

Now, there are two different ways of averaging over a volume. One is based on the volume of each phase contained in the rev, that is, $V_{EC}^{(rev)}$ for the EC space (which is a portion of the rev, i.e., ε) and $V_k^{(rev)}$ for the k-th cell [which is the $(1-\varepsilon)f_k$ fraction of the rev]. Another is based on the total volume of the rev (incorporating both fluid and cellular domains), given by

$$V^{(rev)} = V_{EC}^{(rev)} + V_C^{(rev)} = V_{EC}^{(rev)} + \sum_{k=1}^{N} V_k^{(rev)} \tag{5.18}$$

(The length scale of the rev is much larger than the pore scale given by the average size of the pores, but considerably smaller than the length scale over which macroscopic changes of physical quantities, such as drug concentration, have to be considered.) For example, we can take a volume average of c_{EC} as defined in Eq. (5.2) with respect to the corresponding phase volume $V_{EC}^{(rev)}$ or over the total volume $V^{(rev)}$ (de Monte et al., 2013). Thus it results in, respectively,

$$\langle c_{EC} \rangle_{EC} = \frac{1}{V_{EC}^{(rev)}} \underbrace{\int\limits_{V_{EC}^{(rev)}} c_{EC} dV_{EC}^{(rev)}}_{m_{EC}^{(rev)}} \tag{5.19a}$$

$$\langle c_{EC} \rangle = \frac{1}{V^{(rev)}} \int\limits_{V^{(rev)}} c_{EC} dV^{(rev)} = \frac{1}{V^{(rev)}} \underbrace{\int\limits_{V_{EC}^{(rev)}} c_{EC} dV_{EC}^{(rev)}}_{m_{EC}^{(rev)}} \tag{5.19b}$$

where $m_{EC}^{(rev)}$ is the mass of drug contained in the $V_{EC}^{(rev)}$ volume. However, it is assumed that the result of averaging over a volume is independent of the size of the rev (Nield and Bejan, 2013).

Eq. (5.19a) gives the so-called intrinsic volume-averaged concentration of c_{EC} as well as the companion Eq. (5.19b) yields its volume-averaged concentration. Comparing these two equations gives $\langle c_{EC} \rangle = \varepsilon \langle c_{EC} \rangle_{EC}$. It is of great concern to note that the averaging operation of c_{EC} performed through the above integrals provides the value of the drug concentration in the EC space at the centroid of the rev, which can fall in the EC or cellular domain. Therefore, if $\mathbf{r}$ denotes the position vector of the rev centroid, both $\langle c_{EC} \rangle$ and $\langle c_{EC} \rangle_{EC}$ depend on the same $\mathbf{r}$.

Similarly, we can take an average of c_k as defined by Eq. (5.17) with respect to the corresponding phase volume $V_k^{(rev)}$ or over the total volume $V^{(rev)}$ (de Monte et al., 2013). In such a way, it is found that, respectively,

$$\langle c_k \rangle_k = \frac{1}{V_k^{(rev)}} \underbrace{\int\limits_{V_k^{(rev)}} c_k dV_k^{(rev)}}_{m_k^{(rev)}} \quad k = 1, 2, \ldots, N \tag{5.20a}$$

$$\langle c_k \rangle = \frac{1}{V^{(rev)}} \int_{V^{(rev)}} c_k dV^{(rev)} = \frac{1}{V^{(rev)}} \underbrace{\int_{V_k^{(rev)}} c_k dV_k^{(rev)}}_{m_k^{(rev)}} \qquad k = 1,2,\ldots,N \tag{5.20b}$$

where $m_k^{(rev)}$ is the mass of drug contained in the $V_k^{(rev)}$ volume of the k-th cell. Also, comparing the above two equations gives $\langle c_k \rangle = (1-\varepsilon) f_k \langle c_k \rangle_k$.

The averaging operation of c_k gives the value of drug concentration within the k-th cell at the centroid of the rev, where a drug concentration in the EC space also exists. Therefore, each spatial point of the biological domain contains simultaneously $N+1$ phases: an EC phase with a volume fraction of ε and a k-th cellular phase ($k = 1,2, \ldots, N$) with a volume fraction of $(1-\varepsilon) f_k$.

For the sake of simplicity and brevity, in this chapter c_{EC} and c_k will be used to denote the intrinsic volume-averaged concentrations in place of $\langle c_{EC} \rangle_{EC}$ and $\langle c_k \rangle_k$, respectively. Similarly, C_{EC} and C_k will be utilized to indicate the volume-averaged concentrations in place of $\langle c_{EC} \rangle$ and $\langle c_k \rangle$, respectively. Therefore,

$$C_{EC} = \varepsilon c_{EC}, \quad C_k = f_k (1-\varepsilon) c_k, \quad k = 1,2,\ldots,N \tag{5.21}$$

5.2.2 Governing equations

The rate of variation of drug concentration in either type of cell is given by

$$\underbrace{[(1-\varepsilon) f_k] \frac{\partial c_k}{\partial t}}_{\text{mass storage}} = \underbrace{\frac{\Delta A_k \chi_k}{(\Delta V_T)_k} (c_{EC} - c_k)}_{\text{local mass transfer}} \underbrace{- [(1-\varepsilon) f_k] \; h_k c_k}_{\text{reaction term}} \qquad k = 1,2,\ldots,N \tag{5.22a}$$

where the diffusive terms are neglected as the cells are here considered to be lumped bodies because of their microscopic dimensions. In addition, χ_k (positive) is the mass transfer coefficient (having units of m s^{-1}) at the interface of the k-th cell/EC space (it is related to the permeability of the cell membrane to the drug). Also, $(\Delta V_T)_k = \Delta V_k / [(1-\varepsilon) f_k]$ is the total volume related to the ΔV_k volume of a mean cell type k as well as ΔA_k is its surface area; and h_k (positive) is a reaction coefficient (s^{-1}) that accounts for the drug absorption (metabolism) inside the volume occupied by cell type k. In particular, the first-order irreversible chemical reaction, i.e., $h_k c_k$, has the effect of reducing the free drug within the space occupied by the cells.

Eq. (5.22a) states that all mass transfer to/from either of the cell types at the microscopic level is modeled *across the cell membrane* so that the transmembrane transport is proportional to the difference in the intrinsic drug concentrations on either side of the cell wall, say $c_{EC} - c_k$. For the sake of compactness, a coefficient μ_k (s^{-1}) may be defined as $\mu_k = \chi_k (\Delta A_k / \Delta V_k)$. Therefore, Eq. (5.22a) becomes

$$\frac{\partial c_k}{\partial t} = \mu_k (c_{EC} - c_k) - h_k c_k \quad k = 1,2,\ldots,N \tag{5.22b}$$

Strictly speaking, the mass transfer rates μ_k depend on space and time, that is, $\mu_k = \mu_k(\mathbf{r}, t)$. However, in many biological applications, due to the spatio-temporal scale and relative magnitude analysis, this dependence can in general be omitted, and the coefficients μ_k can be considered uniform and time-independent.

The rate change in drug concentration within the EC space is subject to diffusion along the concentration gradient as well as the mass transfer from the EC to the different cell types and vice versa. The drug mass balance equation within the EC space is represented as

$$\underbrace{\varepsilon \frac{\partial c_{EC}}{\partial t}}_{\text{mass storage}} = \underbrace{\varepsilon D_{eff} \nabla^2 c_{EC}}_{\text{diffusive term}} - \sum_{k=1}^{N} \underbrace{\frac{\Delta A_k \chi_k}{(\Delta V_T)_k}(c_{EC} - c_k)}_{\text{local mass transfer with the } k-\text{th cell}} \tag{5.23a}$$

where D_{eff} is the effective diffusivity of the drug within the EC space. This is related to the conventional diffusivity (i.e., when the porous structure is absent) through the tortuosity of pathways for diffusion and a viscosity function accounting for local boundaries and viscosity (de Monte et al., 2013). Bearing in mind that $(\Delta V_T)_k = \Delta V_k/[(1-\varepsilon)f_k]$ and $\mu_k = \chi_k(\Delta A_k/\Delta V_k)$, Eq. (5.23a) becomes

$$\frac{\partial c_{EC}}{\partial t} = D_{eff} \nabla^2 c_{EC} - \left(\frac{1-\varepsilon}{\varepsilon}\right) \sum_{k=1}^{N} \mu_k (c_{EC} - c_k) f_k \tag{5.23b}$$

where the ratio $(1-\varepsilon)/\varepsilon = V_C/V_{EC}$.

By using the total volume-averaged concentrations defined in Section 5.2.1, Eqs. (5.22) and (5.23) become, respectively,

$$\frac{\partial C_k}{\partial t} = a_k C_{EC} - (\mu_k + h_k) C_k \quad k = 1, 2, \ldots, N \tag{5.24a}$$

$$\frac{\partial C_{EC}}{\partial t} = D_{eff} \nabla^2 C_{EC} - \sum_{k=1}^{N} (a_k C_{EC} - \mu_k C_k) \tag{5.24b}$$

where the coefficients a_k are uniform and constant, and may be taken as

$$a_k = \mu_k \left(\frac{1-\varepsilon}{\varepsilon} f_k\right), \quad k = 1, 2, \ldots, N \tag{5.25}$$

The boundary condition associated with the PDE Eq. (5.24b) is, in a generalized case (McMasters et al., 2019; for an analogous heat diffusive problem),

$$D_{eff} \frac{\partial C_{EC}}{\partial n} = j(\mathbf{r}, t) + K[C_\infty(\mathbf{r}, t) - C_{EC}(\mathbf{r}, t)] \tag{5.26a}$$

where $\mathbf{r}$ is the location of the boundary in a specific coordinate system. Also, $j(\mathbf{r}, t)$ is the surface mass flux applied to the EC boundary surface that is assumed to be a function of both position and time. K denotes the mass transfer coefficient with the adjacent reservoir at concentration $C_\infty(\mathbf{r}, t)$ depending in general on position and time.

The initial conditions for Eqs. (5.24a) and (5.24b) are, respectively,

$$\begin{aligned} &C_k(\mathbf{r}, t=0) = 0 \qquad k = 1, 2, \ldots, N, \\ &C_{EC}(\mathbf{r}, t=0) = 0 \end{aligned} \tag{5.26b}$$

as the biological domain does not contain any drug initially. Contrary to Eq. (5.26a), **r** appearing in Eq. (5.26b) denotes the position of any point within the tissue.

When the mass transfer coefficient K is very large ($K \to \infty$) in Eq. (5.26a), the result is a nonhomogeneous boundary condition of the first kind, that is, $C_{EC}(\mathbf{r},t) = C_{\infty}(\mathbf{r},t)$. On the contrary, when K is very small ($K \to 0$), a nonhomogeneous boundary condition of the second kind is obtained, i.e., $D_{eff}(\partial C_{EC}/\partial n) = j(\mathbf{r},t)$.

5.3 Method of solution

From a mathematical viewpoint, Eqs. (5.24a) ($k = 1, 2, \ldots, N$) and (5.24b) are a set of $N+1$ coupled, linear, homogeneous, PDEs (N of them are of first order; while only one is of second order) with constant and uniform coefficients, whose unknowns are $C_1, C_2, \ldots, C_N$ and C_{EC}.

To solve this system of PDEs by an exact analytical procedure, the starting point is to uncouple the $N+1$ PDEs by using the method proposed by de Monte and Haji-Sheikh (2017a,b) for an analogous heat diffusive-type problem.

5.3.1 Uncoupling procedure

The goal of the uncoupling procedure is to derive a PDE in the sole unknown $C_{EC}(\mathbf{r},t)$. Once this transient concentration distribution is calculated, the other concentrations $C_{EC}(\mathbf{r},t)$ ($k = 1,2,\ldots,N$) may be obtained by integrating Eq. (5.24a) that is a well-established linear ODE of first order. The related initial condition is defined through the former of the two Eqs. (5.26b).

The starting point is to sum up Eqs. (5.24a) and (5.24b) yielding the following equation:

$$\frac{\partial C_{EC}}{\partial t} + \sum_{k=1}^{N} h_k C_k + \sum_{k=1}^{N} \frac{\partial C_k}{\partial t} = D_{eff} \nabla^2 C_{EC} \tag{5.27}$$

Then, the concentration C_{EC} can be derived from Eq. (5.24a) as follows:

$$C_{EC} = \frac{\mu_k + h_k}{a_k} C_k + \frac{1}{a_k} \frac{\partial C_k}{\partial t} \quad k = 1,2,\ldots,N \tag{5.28}$$

Before proceeding to uncouple the governing equations, it is important to understand the relationships between the concentrations C_k and C_{EC} by analyzing Eq. (5.28). For this purpose, this equation may conveniently be rewritten as

$$\begin{aligned} C_{EC}(\mathbf{r},t) &= \underbrace{\left(\frac{\mu_k + h_k}{a_k}\right)}_{A_k} \cdot \left[C_k + \underbrace{\left(\frac{1}{\mu_k + h_k}\right)}_{\tau_k^{(c)}} \frac{\partial C_k}{\partial t} \right] \\ &\approx A_k C_k \left(\mathbf{r}, t + \tau_k^{(c)}\right) \quad k = 1,2,\ldots,N \end{aligned} \tag{5.29}$$

where the quantity between square brackets may be seen as a first-order approximation of $C_k(\mathbf{r}, t+\tau_k^{(c)})$ when using a Taylor series expansion. Also, Eq. (5.29) exhibits a time lag (or relaxation time) between the concentration of the EC space and the concentration C_k as well as an amplification or damping. These quantities are listed below, respectively, as

$$\tau_k^{(c)} = \frac{1}{\mu_k + h_k} \quad k = 1, 2, \ldots, N \tag{5.30a}$$

$$A_k = \frac{\mu_k + h_k}{a_k} = \frac{1}{\tau_k^{(c)} a_k} = \frac{\mu_k + h_k}{\mu_k} \left[\frac{\varepsilon}{(1-\varepsilon) f_k} \right] \quad k = 1, 2, \ldots, N \tag{5.30b}$$

where Eq. (5.25) was used in the latter. As $\tau_k^{(c)}$ is always positive, Eq. (5.29) states that the concentration C_k is delayed with respect to the concentration C_{EC}. As regards A_k, it can be less or greater than 1 and, hence, the concentration C_k can be amplified or damped with respect to C_{EC}. However, when using the intrinsic volume-averaged concentrations, the coefficient A_k simplifies to $A_k = (\mu_k + h_k)/\mu_k$ and, hence, reduces to 1 when the reaction coefficient h_k is zero.

Then, by using Eq. (5.30a), Eq. (5.28) can be rewritten as

$$C_{EC} = \frac{1}{\tau_k^{(c)} a_k} C_k + \frac{1}{a_k} \frac{\partial C_k}{\partial t} \quad k = 1, 2, \ldots, N \tag{5.31}$$

The uncoupling procedure consists of N steps in a cascade sequence that are illustrated in the following sections. Either step reduces the number of unknowns appearing in the EC mass balance equation defined by Eq. (5.27) but increases the order of this PDE up to $N+2$. As already said in Section 5.2, the problem is presented for an arbitrary number N of cell types but the derivation of the solution is restricted to only $N = 3$.

5.3.1.1 First step: Elimination of C_1

The goal of this step is to get a PDE in N unknowns, namely, C_2, …, C_N, and C_{EC}. To obtain it, the starting point is to substitute Eq. (5.31) for $k = 1$ in Eq. (5.27). It results in

$$\left(1 + \frac{1}{\tau_1^{(c)} a_1}\right) \frac{\partial C_1}{\partial t} + \frac{1}{a_1} \frac{\partial^2 C_1}{\partial t^2} + \sum_{k=2}^{N} \frac{\partial C_k}{\partial t} + \sum_{k=1}^{N} h_k C_k = D_{eff} \left[\frac{1}{\tau_1^{(c)} a_1} \nabla^2 C_1 + \frac{1}{a_1} \frac{\partial}{\partial t} \left(\nabla^2 C_1 \right) \right], \tag{5.32}$$

that is a PDE of the third order in N unknowns, i.e., C_1, C_2, …, C_N.

Eq. (5.32) is, however, not appropriate from a mathematical viewpoint as the boundary condition Eq. (5.26a) is prescribed only for the concentration C_{EC}, not for C_1. The diffusive phenomenon is in fact not considered within the cells. For this reason, it is convenient to derive a PDE where the concentration gradient regards only C_{EC}. To get it, one can rewrite Eq. (5.31) for $k = 1$ as

$$C_1 = \tau_1^{(c)} a_1 C_{EC} - \tau_1^{(c)} \frac{\partial C_1}{\partial t} \tag{5.33}$$

Substitution of Eq. (5.33) into Eq. (5.32) and bearing in mind Eq. (5.25) yields

$$\begin{aligned}
&\left(1+\tau_1^{(c)}a_1\right)\frac{\partial C_{EC}}{\partial t}+\tau_1^{(c)}\frac{\partial^2 C_{EC}}{\partial t^2}+h_1\tau_1^{(c)}a_1 C_{EC}-h_1\tau_1^{(c)}\frac{\partial C_1}{\partial t}+\sum_{k=2}^{N}\frac{\partial C_k}{\partial t}+\sum_{k=2}^{N}h_k C_k\\
&\quad=D_{eff}\left(\nabla^2 C_{EC}+\tau_1^{(c)}\frac{\partial}{\partial t}\nabla^2 C_{EC}\right)\\
&\quad\quad+\underbrace{\frac{\partial}{\partial t}\left[\left(1+\frac{1}{\tau_1^{(c)}a_1}\right)\tau_1^{(c)}\frac{\partial C_1}{\partial t}+\frac{\tau_1^{(c)}}{a_1}\frac{\partial^2 C_1}{\partial t^2}-D_{eff}\left(\frac{1}{a_1}\nabla^2 C_1+\frac{\tau_1^{(c)}}{a_1}\frac{\partial}{\partial t}\nabla^2 C_1\right)\right]}_{=-\tau_1^{(c)}\left\{\sum_{k=2}^{N}\frac{\partial C_k}{\partial t}+\sum_{k=1}^{N}h_k C_k\right\}}
\end{aligned}\tag{5.34}$$

where the quantity between square brackets on the RHS can be calculated by using Eq. (5.32).

Then, by some algebra, it results in

$$\begin{aligned}
&\left(1+\tau_1^{(c)}a_1\right)\frac{\partial C_{EC}}{\partial t}+\tau_1^{(c)}h_1 a_1 C_{EC}+\tau_1^{(c)}\frac{\partial^2 C_{EC}}{\partial t^2}+\sum_{k=2}^{N}h_k C_k\\
&\quad+\sum_{k=2}^{N}\left(1+\tau_1^{(c)}h_k\right)\frac{\partial C_k}{\partial t}+\tau_1^{(c)}\sum_{k=2}^{N}\frac{\partial^2 C_k}{\partial t^2}=D_{eff}\left[\nabla^2 C_{EC}+\tau_1^{(c)}\frac{\partial}{\partial t}\left(\nabla^2 C_{EC}\right)\right]
\end{aligned}\tag{5.35}$$

that is a PDE of third order in N unknowns, namely, C_2, …, C_N and C_{EC}.

Eq. (5.35) is similar to Eq. (5.27). In detail, there are six additional terms and all of them are multiplied by a factor of $\tau_1^{(c)}$. Also, if $N=1$, that is only one type of cells interacts with the EC space, Eq. (5.35) simplifies to

$$\left(1+\tau_1^{(c)}a_1\right)\frac{\partial C_{EC}}{\partial t}+\tau_1^{(c)}\frac{\partial^2 C_{EC}}{\partial t^2}+\tau_1^{(c)}h_1 a_1 C_{EC}=D_{eff}\left[\nabla^2 C_{EC}+\tau_1^{(c)}\frac{\partial}{\partial t}\left(\nabla^2 C_{EC}\right)\right]\tag{5.36}$$

whose only unknown is C_{EC}.

5.3.1.2 Second step: Elimination of C_2

The objective of this step is to derive a PDE in $N-1$ unknowns, namely, C_3, …, C_N and C_{EC}, in place of the N unknowns appearing in Eq. (5.35). To obtain it, the starting point is to substitute Eq. (5.31) for $k=2$ in Eq. (5.35) yielding

$$\begin{aligned}
&\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2\right)\frac{1}{\tau_2^{(c)}a_2}\frac{\partial C_2}{\partial t}+\left[\left(1+\tau_1^{(c)}a_1\right)+\left(1+\tau_2^{(c)}a_2\right)\frac{\tau_1^{(c)}}{\tau_2^{(c)}}\right]\frac{1}{a_2}\frac{\partial^2 C_2}{\partial t^2}\\
&\quad+\frac{\tau_1^{(c)}}{a_2}\frac{\partial^3 C_2}{\partial t^3}+\left(h_1\tau_1^{(c)}a_1\right)\left(\frac{1}{\tau_2^{(c)}a_2}C_2+\frac{1}{a_2}\frac{\partial C_2}{\partial t}\right)\\
&\quad+\left[\sum_{k=3}^{N}\frac{\partial C_k}{\partial t}+\tau_1^{(c)}\sum_{k=2}^{N}h_k\frac{\partial C_k}{\partial t}+\tau_1^{(c)}\sum_{k=3}^{N}\frac{\partial^2 C_k}{\partial t^2}+\sum_{k=2}^{N}h_k C_k\right]\\
&=D_{eff}\left[\frac{1}{\tau_2^{(c)}a_2}\nabla^2 C_2+\left(\frac{1}{a_2}+\frac{\tau_1^{(c)}}{\tau_2^{(c)}a_2}\right)\frac{\partial}{\partial t}\nabla^2 C_2+\frac{\tau_1^{(c)}}{a_2}\frac{\partial^2}{\partial t^2}\nabla^2 C_2\right]
\end{aligned}\tag{5.37}$$

that is a PDE of fourth order in $N-1$ unknowns, i.e., C_2, …, C_N.

Similar to what was said in the previous paragraph, Eq. (5.37) is not appropriate from a mathematical viewpoint as the boundary condition Eq. (5.26a) is assigned only to the EC concentration C_{EC}, not to C_2. For this reason, one can rewrite Eq. (5.32) for $k=2$ as

$$C_2 = \tau_2^{(c)} a_2 C_{EC} - \tau_2^{(c)} \frac{\partial C_2}{\partial t} \tag{5.38}$$

Substitution of Eq. (5.38) into Eq. (5.37), after lengthy algebra, yields

$$\begin{aligned}
&\left[\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2\right)+\tau_1^{(c)}\tau_2^{(c)}(h_1a_1+h_2a_2)\right]\frac{\partial C_{EC}}{\partial t}+\left[\left(1+\tau_1^{(c)}a_1\right)\tau_2^{(c)}+\left(1+\tau_2^{(c)}a_2\right)\tau_1^{(c)}\right]\frac{\partial^2 C_{EC}}{\partial t^2}\\
&+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^3 C_{EC}}{\partial t^3}+\left(\tau_1^{(c)}h_1a_1+\tau_2^{(c)}h_2a_2\right)C_{EC}+\sum_{k=3}^{N}\left(1+\tau_1^{(c)}h_k\right)\frac{\partial C_k}{\partial t}+\tau_1^{(c)}\sum_{k=3}^{N}\frac{\partial^2 C_k}{\partial t^2}+\sum_{k=3}^{N}h_kC_k\\
&-\left(\frac{\tau_1^{(c)}h_1a_1}{\mu_2}+h_2\tau_2^{(c)}\right)\frac{\partial C_2}{\partial t}-\left(\frac{\tau_1^{(c)}h_1a_1}{\mu_2}\tau_2^{(c)}+\tau_1^{(c)}\tau_2^{(c)}h_2\right)\frac{\partial^2 C_2}{\partial t^2}=\\
&=D_{eff}\left[\nabla^2C_{EC}+\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\frac{\partial}{\partial t}\nabla^2C_{EC}+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^2}{\partial t^2}\nabla^2C_{EC}\right]\\
&+\frac{\partial}{\partial t}\left\{\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2\right)\frac{1}{a_2}\frac{\partial C_2}{\partial t}+\left[\left(1+\tau_1^{(c)}a_1\right)\tau_2^{(c)}+\left(1+\tau_2^{(c)}a_2\right)\tau_1^{(c)}\right]\frac{1}{a_2}\frac{\partial^2 C_2}{\partial t^2}\right.\\
&\left.+\frac{\tau_1^{(c)}\tau_2^{(c)}}{a_2}\frac{\partial^3 C_2}{\partial t^3}-D_{eff}\left[\frac{1}{a_2}\nabla^2C_2+\frac{\left(\tau_1^{(c)}+\tau_2^{(c)}\right)}{a_2}\frac{\partial}{\partial t}\nabla^2C_2+\frac{\tau_1^{(c)}\tau_2^{(c)}}{a_2}\frac{\partial^2}{\partial t^2}\nabla^2C_2\right]\right\}
\end{aligned} \tag{5.39}$$

where the quantity between braces on the RHS can be calculated using Eq. (5.37).

After some algebra, it is obtained that

$$\begin{aligned}
&\left[\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2\right)+\tau_1^{(c)}\tau_2^{(c)}(h_1a_1+h_2a_2)\right]\frac{\partial C_{EC}}{\partial t}+\left[\tau_1^{(c)}\tau_2^{(c)}(a_1+a_2)+\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\right]\frac{\partial^2 C_{EC}}{\partial t^2}\\
&+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^3 C_{EC}}{\partial t^3}+\left(\tau_1^{(c)}h_1a_1+\tau_2^{(c)}h_2a_2\right)C_{EC}+\sum_{k=3}^{N}h_kC_k+\sum_{k=3}^{N}\left(1+\tau_1^{(c)}h_k+\tau_2^{(c)}h_k\right)\frac{\partial C_k}{\partial t}\\
&+\sum_{k=3}^{N}\left[h_k\tau_1^{(c)}\tau_2^{(c)}+\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\right]\frac{\partial^2 C_k}{\partial t^2}+\tau_1^{(c)}\tau_2^{(c)}\sum_{k=3}^{N}\frac{\partial^3 C_k}{\partial t^3}\\
&=D_{eff}\left[\nabla^2C_{EC}+\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\frac{\partial}{\partial t}\nabla^2C_{EC}+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^2}{\partial t^2}\nabla^2C_{EC}\right]
\end{aligned} \tag{5.40}$$

Eq. (5.40) is a PDE of fourth order in $N-1$ unknowns, namely, C_3, …, C_N and C_{EC}. Also, this equation is similar to Eq. (5.35). In detail, all the additional terms are multiplied by a factor of $\tau_2^{(c)}$. In addition, if $N=2$, that is only two different types of cells exchange drug with the EC space, Eq. (5.40) is reduced to

$$\begin{aligned}
&\left[\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2\right)+\tau_1^{(c)}\tau_2^{(c)}(h_1a_1+h_2a_2)\right]\frac{\partial C_{EC}}{\partial t}\\
&+\left[\left(\tau_1^{(c)}+\tau_2^{(c)}\right)+\tau_1^{(c)}\tau_2^{(c)}(a_1+a_2)\right]\frac{\partial^2 C_{EC}}{\partial t^2}+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^3 C_{EC}}{\partial t^3}+\left(\tau_1^{(c)}h_1a_1+\tau_2^{(c)}h_2a_2\right)C_{EC}\\
&=D_{eff}\left[\nabla^2C_{EC}+\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\frac{\partial}{\partial t}\nabla^2C_{EC}+\tau_1^{(c)}\tau_2^{(c)}\frac{\partial^2}{\partial t^2}\nabla^2C_{EC}\right]
\end{aligned} \tag{5.41}$$

whose only unknown is C_{EC}.

5.3.1.3 Third step: Elimination of C_3

Applying the same procedure shown in the previous two paragraphs results in

$$
\begin{aligned}
&\left\{\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2+\tau_3^{(c)}a_3\right)+\left[\begin{array}{l}\tau_1^{(c)}\tau_2^{(c)}(h_1a_1+h_2a_2)+\tau_1^{(c)}\tau_3^{(c)}(h_1a_1+h_3a_3)\\+\tau_2^{(c)}\tau_3^{(c)}(h_2a_2+h_3a_3)\end{array}\right]\right\}\frac{\partial C_{EC}}{\partial t}\\
&\quad+\left(\tau_1^{(c)}h_1a_1+\tau_2^{(c)}h_2a_2+\tau_3^{(c)}h_3a_3\right)C_{EC}\\
&\quad+\left\{\begin{array}{l}\left(\tau_1^{(c)}+\tau_2^{(c)}+\tau_3^{(c)}\right)+\left[\tau_1^{(c)}\tau_2^{(c)}(a_1+a_2)+\tau_1^{(c)}\tau_3^{(c)}(a_1+a_3)+\tau_2^{(c)}\tau_3^{(c)}(a_2+a_3)\right]\\+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}(h_1a_1+h_2a_2+h_3a_3)\end{array}\right\}\frac{\partial^2 C_{EC}}{\partial t^2}\\
&\quad+\left[\left(\tau_1^{(c)}\tau_2^{(c)}+\tau_1^{(c)}\tau_3^{(c)}+\tau_2^{(c)}\tau_3^{(c)}\right)+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}(a_1+a_2+a_3)\right]\frac{\partial^3 C_{EC}}{\partial t^3}+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}\frac{\partial^4 C_{EC}}{\partial t^4}\\
&\quad+\sum_{k=4}^{N}\left[\left(1+\tau_1^{(c)}h_k+\tau_2^{(c)}h_k\right)+h_k\tau_3^{(c)}\right]\frac{\partial C_k}{\partial t}+\sum_{k=4}^{N}h_kC_k\\
&\quad+\sum_{k=4}^{N}\left[\left(\tau_1^{(c)}+\tau_2^{(c)}\right)+\tau_3^{(c)}\left(1+\tau_1^{(c)}h_k+\tau_2^{(c)}h_k\right)+\left(\tau_1^{(c)}\tau_2^{(c)}h_k\right)\right]\frac{\partial^2 C_k}{\partial t^2}\\
&\quad+\sum_{k=4}^{N}\left[\left(\tau_1^{(c)}+\tau_2^{(c)}\right)\tau_3^{(c)}+\left(\tau_1^{(c)}\tau_2^{(c)}\right)+\left(\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}h_k\right)\right]\frac{\partial^3 C_k}{\partial t^3}+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}\sum_{k=4}^{N}\frac{\partial^4 C_k}{\partial t^4}\\
&=D_{eff}\left[\nabla^2C_{EC}+\left(\tau_1^{(c)}+\tau_2^{(c)}+\tau_3^{(c)}\right)\frac{\partial}{\partial t}\nabla^2C_{EC}+\left(\tau_1^{(c)}\tau_2^{(c)}+\tau_1^{(c)}\tau_3^{(c)}+\tau_2^{(c)}\tau_3^{(c)}\right)\frac{\partial^2}{\partial t^2}\nabla^2C_{EC}\right.\\
&\quad\left.+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}\frac{\partial^3}{\partial t^3}\nabla^2C_{EC}\right]
\end{aligned}
\tag{5.42}
$$

Eq. (5.42) is a PDE of the fifth order in $N-2$ unknowns, namely, C_4, …, C_N and C_{EC}. It is similar to Eq. (5.40) and its additional terms are multiplied by a factor of $\tau_3^{(c)}$. Also, if three different types of cells exchange drug with the EC space, that is, $N=3$, Eq. (5.42) reduces to

$$
\begin{aligned}
&\left\{\left(1+\tau_1^{(c)}a_1+\tau_2^{(c)}a_2+\tau_3^{(c)}a_3\right)+\tau_1^{(c)}\tau_2^{(c)}(h_1a_1+h_2a_2)+\left[\begin{array}{l}\tau_1^{(c)}\tau_3^{(c)}(h_1a_1+h_3a_3)\\+\tau_2^{(c)}\tau_3^{(c)}(h_2a_2+h_3a_3)\end{array}\right]\right\}\frac{\partial C_{EC}}{\partial t}\\
&\quad+\left(\tau_1^{(c)}h_1a_1+\tau_2^{(c)}h_2a_2+\tau_3^{(c)}h_3a_3\right)C_{EC}\\
&\quad+\left\{\left(\tau_1^{(c)}+\tau_2^{(c)}+\tau_3^{(c)}\right)+\tau_1^{(c)}\tau_2^{(c)}(a_1+a_2)+\left[\begin{array}{l}\tau_1^{(c)}\tau_3^{(c)}(a_1+a_3)+\tau_2^{(c)}\tau_3^{(c)}(a_2+a_3)\\+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}(h_1a_1+h_2a_2+h_3a_3)\end{array}\right]\right\}\frac{\partial^2 C_{EC}}{\partial t^2}\\
&\quad+\left\{\tau_1^{(c)}\tau_2^{(c)}+\left[\tau_1^{(c)}\tau_3^{(c)}+\tau_2^{(c)}\tau_3^{(c)}+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}(a_1+a_2+a_3)\right]\right\}\frac{\partial^3 C_{EC}}{\partial t^3}+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}\frac{\partial^4 C_{EC}}{\partial t^4}\\
&=D_{eff}\left[\nabla^2C_{EC}+\left(\tau_1^{(c)}+\tau_2^{(c)}+\tau_3^{(c)}\right)\frac{\partial}{\partial t}\nabla^2C_{EC}+\left(\tau_1^{(c)}\tau_2^{(c)}+\tau_1^{(c)}\tau_3^{(c)}+\tau_2^{(c)}\tau_3^{(c)}\right)\frac{\partial^2}{\partial t^2}\nabla^2C_{EC}\right.\\
&\quad\left.+\tau_1^{(c)}\tau_2^{(c)}\tau_3^{(c)}\frac{\partial^3}{\partial t^3}\nabla^2C_{EC}\right]
\end{aligned}
\tag{5.43}
$$

that is a PDE of fifth order in the only unknown C_{EC}.

5.3.2 Transformed mass balance equation for the extracellular space

The treatment is here limited to $N=1$, 2, or 3. Eqs. (5.36), (5.41) and (5.43) represent the transformed drug mass balance equation for the EC space valid for $N=1$, 2, and 3, respectively. They can be unified by only one single equation as

$$\begin{aligned}&\frac{\partial C_{EC}}{\partial t}+\frac{A_N^{(2)}}{A_N^{(1)}}\frac{\partial^2 C_{EC}}{\partial t^2}+\frac{A_N^{(3)}}{A_N^{(1)}}\frac{\partial^3 C_{EC}}{\partial t^3}+\frac{A_N^{(4)}}{A_N^{(1)}}\frac{\partial^4 C_{EC}}{\partial t^4}+\frac{A_N^{(0)}}{A_N^{(1)}}C_{EC}\\&=\frac{D_{eff}}{A_N^{(1)}}\left(\nabla^2 C_{EC}+B_N^{(1)}\frac{\partial}{\partial t}\nabla^2 C_{EC}+B_N^{(2)}\frac{\partial^2}{\partial t^2}\nabla^2 C_{EC}+B_N^{(3)}\frac{\partial^3}{\partial t^3}\nabla^2 C_{EC}\right)\end{aligned}\tag{5.44}$$

where N can be equal to 1, 2, or 3. The coefficients listed in the above equation are given in Section 5.A (Appendix A).

When the reaction terms are negligible, i.e., $h_k=0$, Eq. (5.44) simplifies to

$$\begin{aligned}&\frac{\partial C_{EC}}{\partial t}+R_N^{(2)}\frac{\partial^2 C_{EC}}{\partial t^2}+R_N^{(3)}\frac{\partial^3 C_{EC}}{\partial t^3}+\varepsilon A_N^{(4)}\frac{\partial^4 C_{EC}}{\partial t^4}\\&=\varepsilon D_{eff}\left(\nabla^2 C_{EC}+B_N^{(1)}\frac{\partial}{\partial t}\nabla^2 C_{EC}+B_N^{(2)}\frac{\partial^2}{\partial t^2}\nabla^2 C_{EC}+B_N^{(3)}\frac{\partial^3}{\partial t^3}\nabla^2 C_{EC}\right)\end{aligned}\tag{5.45}$$

where the coefficients $R_N^{(2)}$ and $R_N^{(3)}$ are also given in Section 5.A (Appendix A).

5.3.3 Physical interpretation: The dual-phase-lag model

Eq. (5.45) does not obey the classical theory of transient mass diffusion based on Fick's law, where the mass flux vector ($\mathbf{j}$) and the concentration (∇C_{EC}) are assumed to occur at the same instant of time. In fact, the Fick constitutive equation $\mathbf{j}=-(D_{eff}/A_N^{(1)})\nabla C_{EC}$ would lead (when combined with the mass balance diffusion–reaction equation) to the classical PDE

$$\frac{\partial C_{EC}}{\partial t}+\frac{A_N^{(0)}}{A_N^{(1)}}C_{EC}=-\nabla\cdot\mathbf{j}=\left(\frac{D_{eff}}{A_N^{(1)}}\right)\nabla^2 C_{EC}\tag{5.46}$$

where $\nabla\cdot\mathbf{j}$ is the divergence of the mass flux vector.

Eq. (5.45) seems to obey the dual-phase-lag (DPL) nonconventional theory of transient mass diffusion that is based on the following constitutive equation:

$$\mathbf{j}\left(\mathbf{r},t+\tau_{EC}^{(j)}\right)=-\left(\frac{D_{eff}}{A_N^{(1)}}\right)\nabla C_{EC}\left(\mathbf{r},t+\tau_{EC}^{(c)}\right)\tag{5.47}$$

where $\tau_{EC}^{(c)}$ is the phase lag of the concentration gradient while $\tau_{EC}^{(j)}$ is the phase lag of the mass flux. If $\tau_{EC}^{(c)}>\tau_{EC}^{(j)}$, the mass flux is the cause, and the concentration gradient is the effect. On the other hand, if $\tau_{EC}^{(c)}<\tau_{EC}^{(j)}$, the concentration gradient is the cause, while the mass flux is the effect.

Now, the first-order approximation of Eq. (5.47) by using Taylor series reads

$$\mathbf{j}(\mathbf{r},t)+\tau_{EC}^{(j)}\frac{\partial\mathbf{j}}{\partial t}(\mathbf{r},t)\approx-\left(\frac{D_{eff}}{A_N^{(1)}}\right)\left[\nabla C_{EC}(\mathbf{r},t)+\tau_{EC}^{(c)}\frac{\partial}{\partial t}\nabla C_{EC}(\mathbf{r},t)\right]\tag{5.48}$$

Combining this equation with the mass balance yields

$$\frac{\partial C_{EC}}{\partial t} + \tau_{EC}^{(j)} \frac{\partial^2 C_{EC}}{\partial t^2} + \frac{A_N^{(0)}}{A_N^{(1)}} C_{EC} = \left(\frac{D_{eff}}{A_N^{(1)}}\right)\left(\nabla^2 C_{EC} + \tau_{EC}^{(c)} \frac{\partial}{\partial t} \nabla^2 C_{EC}\right) \tag{5.49}$$

If now the third- and fourth-order time partial derivatives are neglected on the LHS of Eq. (5.44) and the fourth- and fifth-order mixed partial derivatives are neglected on its RHS as well, this equation reduces to Eq. (5.49) where the time phase lags may be taken as

$$\tau_{EC}^{(j)} = \frac{A_N^{(2)}}{A_N^{(1)}}, \quad \tau_{EC}^{(c)} = B_N^{(1)} \tag{5.50}$$

The above coefficients are given in Table 5.A1 of Section 5.A (Appendix A). If the reaction terms are negligible, $A_N^{(0)} = 0$ and $A_N^{(1)} = 1/\varepsilon$ in Eq. (5.49), and the former of the above two time phase lags modifies as

$$\tau_{EC}^{(j)} = R_N^{(2)} \tag{5.51}$$

where $R_N^{(2)}$ is shown in Table 5.A2 of Section 5.A (Appendix A).

By applying again Taylor series to Eq. (5.47) but performing a third-order approximation to both mass flux and concentration gradient, it results in

$$\begin{aligned} &\mathbf{j}(\mathbf{r},t) + \tau_{EC}^{(j)} \frac{\partial \mathbf{j}}{\partial t}(\mathbf{r},t) + \frac{1}{2}\left(\tau_{EC}^{(j)}\right)^2 \frac{\partial^2 \mathbf{j}}{\partial t^2}(\mathbf{r},t) + \frac{1}{6}\left(\tau_{EC}^{(j)}\right)^3 \frac{\partial^3 \mathbf{j}}{\partial t^3}(\mathbf{r},t) \\ &\approx -\left(\frac{D_{eff}}{A_N^{(1)}}\right)\left[\begin{array}{l} \nabla C_{EC}(\mathbf{r},t) + \tau_{EC}^{(c)} \dfrac{\partial}{\partial t} \nabla C_{EC}(\mathbf{r},t) \\ \quad + \dfrac{1}{2}\left(\tau_{EC}^{(c)}\right)^2 \dfrac{\partial^2}{\partial t^2} \nabla C_{EC}(\mathbf{r},t) + \dfrac{1}{6}\left(\tau_{EC}^{(c)}\right)^3 \dfrac{\partial^3}{\partial t^3} \nabla C_{EC}(\mathbf{r},t) \end{array}\right] \end{aligned} \tag{5.52}$$

where the quadratic and cubic nonlinear terms of $\tau_{EC}^{(c)}$ and $\tau_{EC}^{(j)}$ have been considered.

Combining this equation with the mass balance yields

$$\begin{aligned} &\frac{\partial C_{EC}}{\partial t} + \tau_{EC}^{(j)} \frac{\partial^2 C_{EC}}{\partial t^2} + \frac{1}{2}\left(\tau_{EC}^{(j)}\right)^2 \frac{\partial^3 C_{EC}}{\partial t^3} + \frac{1}{6}\left(\tau_{EC}^{(j)}\right)^3 \frac{\partial^4 C_{EC}}{\partial t^4} + \frac{A_N^{(0)}}{A_N^{(1)}} C_{EC} \\ &= \left(\frac{D_{eff}}{A_N^{(1)}}\right)\left[\nabla^2 C_{EC} + \tau_{EC}^{(c)} \frac{\partial}{\partial t} \nabla^2 C_{EC} + \frac{1}{2}\left(\tau_{EC}^{(c)}\right)^2 \frac{\partial^2}{\partial t^2} \nabla^2 C_{EC} + \frac{1}{6}\left(\tau_{EC}^{(c)}\right)^3 \frac{\partial^3}{\partial t^3} \nabla^2 C_{EC}\right] \end{aligned} \tag{5.53}$$

Comparing Eqs. (5.44) and (5.53) gives

$$\frac{A_N^{(3)}}{A_N^{(1)}} < \frac{1}{2}\left(\tau_{EC}^{(j)}\right)^2 = \frac{1}{2}\left(\frac{A_N^{(2)}}{A_N^{(1)}}\right)^2 \tag{5.54a}$$

$$\frac{A_N^{(4)}}{A_N^{(1)}} < \frac{1}{6}\left(\tau_{EC}^{(j)}\right)^3 = \frac{1}{6}\left(\frac{A_N^{(2)}}{A_N^{(1)}}\right)^3 \tag{5.54b}$$

$$B_N^{(2)} < \frac{1}{2}\left(\tau_{EC}^{(c)}\right)^2 = \frac{1}{2}\left(B_N^{(1)}\right)^2 \tag{5.54c}$$

$$B_N^{(3)} < \frac{1}{6}\left(\tau_{EC}^{(c)}\right)^3 = \frac{1}{6}\left(B_N^{(1)}\right)^3 \tag{5.54d}$$

The equations listed above state that the third and fourth terms appearing on both sides of Eq. (5.44) are smaller than the corresponding terms appearing on both sides of Eq. (5.53) and coming from the third-order approximation of Taylor series Eq. (5.52). In other words, Eq. (5.44) does not represent rigorously the dual-phase-lag model when the quadratic and cubic nonlinear terms of $\tau_{EC}^{(c)}$ and $\tau_{EC}^{(j)}$ are considered for the constitutive Eq. (5.47). As they are smaller and, in addition, the linear terms are greater than the quadratic and cubic nonlinear terms of $\tau_{EC}^{(c)}$ and $\tau_{EC}^{(j)}$, Eq. (5.45) can reasonably be rewritten as Eq. (5.49), where both the time phase lags are defined through Eq. (5.50).

Similarly, when the reaction terms are negligible. In such a case, in fact, by comparing Eqs. (5.45) and (5.53), it results in

$$R_N^{(3)} < \frac{1}{2}\left(\tau_{EC}^{(j)}\right)^2 = \frac{1}{2}\left(R_N^{(2)}\right)^2 \tag{5.55a}$$

$$R_N^{(4)} < \frac{1}{6}\left(\tau_{EC}^{(j)}\right)^3 = \frac{1}{6}\left(R_N^{(2)}\right)^3 \tag{5.55b}$$

As the third and fourth terms appearing on both sides of Eq. (5.45) are smaller than the corresponding terms appearing on both sides of Eq. (5.53) and, also, the linear terms are greater than the quadratic and cubic nonlinear terms of $\tau_{EC}^{(c)}$ and $\tau_{EC}^{(j)}$, Eq. (5.45) can reasonably be rewritten as Eq. (5.49) where $\tau_{EC}^{(c)}$ is defined by the second of the two Eqs. (5.50) and $\tau_{EC}^{(j)}$ by Eq. (5.51).

5.3.4 Concentration distribution of the *k*-th type of cell

Once Eq. (5.49) is solved and the concentration distribution $C_{EC}(\mathbf{r},t)$ is calculated, the concentration $C_k(\mathbf{r},t)$ of the k-th type of cell, with $k = 1, 2, \ldots, N$ and $N = 1, 2$, or 3, may be obtained by solving Eq. (5.31) that is a well-established first-order and linear ODE. Following a standard integration procedure (Gradshteyn and Ryzhik, 2007; see p. 1096, No. 16.316), the result is

$$\begin{aligned} C_k(\mathbf{r},t) &= C_k(\mathbf{r},0)\exp\left(-\frac{t}{\tau_k^{(c)}}\right) + a_k\int_0^t C_{EC}(\mathbf{r},\tau)\exp\left(\frac{\tau-t}{\tau_k^{(c)}}\right)d\tau \\ &= a_k\int_0^t C_{EC}(\mathbf{r},\tau)\exp\left(\frac{\tau-t}{\tau_k^{(c)}}\right)d\tau \end{aligned} \tag{5.56}$$

where $C_k(\mathbf{r},0) = 0$ according to the first of the two Eq. (5.26b); while a_k and $\tau_k^{(c)}$ are defined by Eqs. (5.25) and (5.30a), respectively.

5.4 Case study: A 3D rectangular biological tissue

The case study considered here is a three-dimensional rectangular tissue that can exchange drug with three different types of cells ($N = 3$), as depicted in Fig. 5.4A. The reaction terms within the cells are assumed to be negligible ($h_k \approx 0$) and the EC space is impermeable at all boundaries with the exception

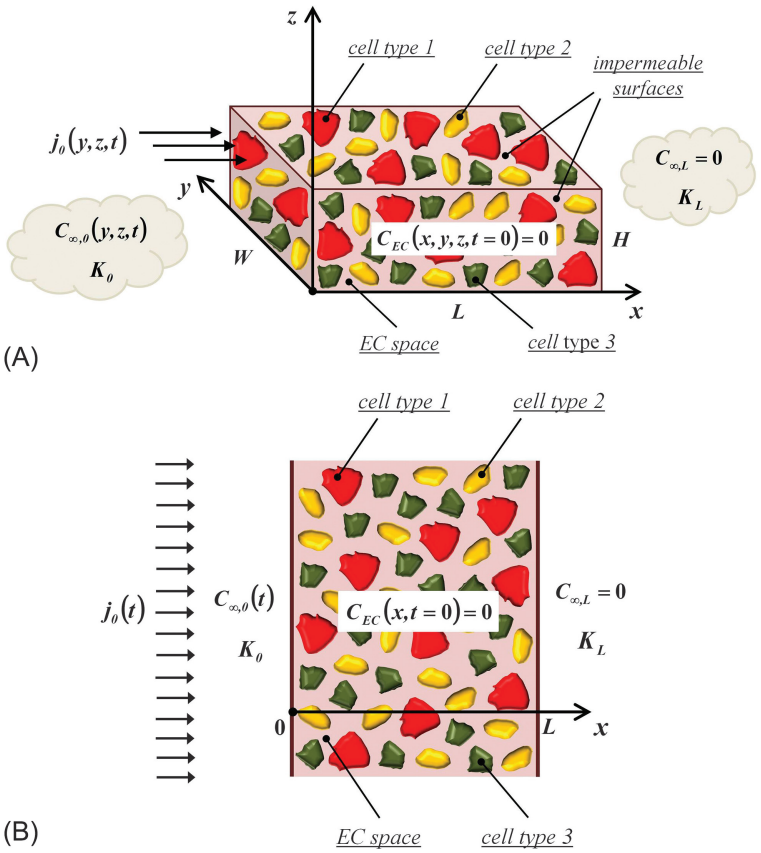

FIG. 5.4

Schematic of the case study with three different types of cells: (A) parallelepiped-shaped biological tissue; (B) reduced slab-shaped tissue.

of the ones along x. At the $x=0$ surface, in fact, the EC space can receive drug due to both an applied surface mass flux $j_0(y,z,t)$ and advection with a reservoir at $C_{\infty,0}(y,z,t)$ concentration by a mass transfer coefficient, say K_0. At the $x=L$ surface, however, the EC space can release drug by advection with a reservoir at concentration $C_{\infty,L}=0$ by a mass transfer coefficient, say K_L. Also, the parallelepiped-shaped biological tissue is initially at zero concentration of drug as well as the three different types of cells. The symbols L, W, and H are the overall dimensions of the parallelepiped in the x, y, and z directions, respectively.

5.4.1 One-dimensional governing equations

If $j_0(y,z,t)$ and $C_{\infty,0}(y,z,t)$ are space-independent, that is $j_0(y,z,t)=j_0(t)$ and $C_0(y,z,t)=C_0(t)$, then the 3D transient, rectangular problem described above reduces to a 1D case due to the homogeneous

boundary conditions of the second kind applied along y and z, as shown in Fig. 5.4B. The governing equations of this problem are

$$\frac{\partial C_{EC}}{\partial t} + \tau_{EC}^{(j)} \frac{\partial^2 C_{EC}}{\partial t^2} = (\varepsilon D_{eff}) \left[\frac{\partial^2 C_{EC}}{\partial x^2} + \tau_{EC}^{(c)} \frac{\partial}{\partial t} \frac{\partial^2 C_{EC}}{\partial x^2} \right] \qquad 0 < x < L; \quad t > 0 \tag{5.57a}$$

$$-D_{eff} \left(\frac{\partial C_{EC}}{\partial x} \right)_{x=0} = K_0 [C_{\infty,0}(t) - C_{EC}(0,t)] + j_0(t) \qquad t > 0 \tag{5.57b}$$

$$-D_{eff} \left(\frac{\partial C_{EC}}{\partial x} \right)_{x=L} = K_L C_{EC}(L,t) \qquad t > 0 \tag{5.57c}$$

$$C_{EC}(x,0) = 0 \qquad 0 < x < L \tag{5.57d}$$

$$\left(\frac{\partial C_{EC}}{\partial t} \right)_{t=0} = 0 \qquad 0 < x < L \tag{5.57e}$$

where Eq. (5.57a) comes from Eq. (5.49) (where $A_N^{(0)} = 0$ and $A_N^{(1)} = 1/\varepsilon$) readapted for the current 1D rectangular problem. Also, a second initial condition, namely, Eq. (5.57e), has been added according to the DPL model. It is zero as the initial drug concentration within the EC space is zero. Also, the phase lag times are

$$\begin{aligned} \tau_{EC}^{(j)} = R_3^{(2)} = {} & \tau_1^{(c)} [\varepsilon + f_2(1-\varepsilon) + f_3(1-\varepsilon)] + \tau_2^{(c)} [\varepsilon + f_1(1-\varepsilon) + f_3(1-\varepsilon)] \\ & + \tau_3^{(c)} [\varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon)] \end{aligned} \tag{5.58a}$$

$$\tau_{EC}^{(c)} = B_3^{(1)} = \tau_1^{(c)} + \tau_2^{(c)} + \tau_3^{(c)} \tag{5.58b}$$

Once the above equations are solved and the concentration distribution $C_{EC}(x,t)$ obtained, the concentration $C_k(x,t)$ is (see Section 5.3.4)

$$C_k(x,t) = a_k \int_0^t C_{EC}(x,\tau) \exp\left(\frac{\tau - t}{\tau_k^{(c)}} \right) d\tau \qquad 0 \le x \le L; \quad t \ge 0 \tag{5.59}$$

where

$$a_k = \frac{1-\varepsilon}{\varepsilon} \left(\frac{f_k}{\tau_k^{(c)}} \right) \qquad k = 1, 2, N = 3 \tag{5.60a}$$

$$\tau_k^{(c)} = \frac{1}{\mu_k} \qquad k = 1, 2, N = 3 \tag{5.60b}$$

As far as $j_0(t)$ and $C_{\infty,0}(t)$ are concerned, it is assumed that the drug delivery occurs for a finite duration, say $0 \le t \le t_d$, where t_d denotes the delivery time. Thus, $j_0(t)$ and $C_{\infty,0}(t)$ may be taken as

$$j_0(t) = j_0[1 - H(t - t_d)] \tag{5.61a}$$

$$C_0(t) = C_{\infty,0}[1 - H(t - t_d)] \tag{5.61b}$$

where $H(.)$ is the unit step or Heaviside function, while j_0 and $C_{\infty,0}$ are time-independent functions in the range $0 \le t \le t_d$.

5.4.2 Exact analytical solution

5.4.2.1 Extracellular space solution

The EC concentration distribution has to be calculated both when the drug delivery is "on" ($0 \le t \le t_d$) and when it is "off" ($t > t_d$). By using the principle of superposition, it may be given in a general form as

$$C_{EC} = \begin{cases} C_{EC}(x,t) & 0 \le t \le t_d \\ C_{EC}(x,t) - C_{EC}(x,t-t_d) & t > t_d \end{cases} \tag{5.62}$$

where $C_{EC}(x,t)$ is the EC concentration distribution when $j_0(t) = j_0$ and $C_{\infty,0}(t) = C_{\infty,0}$ in Eq. (5.57b); while $C_{EC}(x,t-t_d)$ is the EC concentration solution when $j_0(t) = j_0 H(t-t_d)$ and $C_{\infty,0}(t) = C_{\infty,0} H(t-t_d)$ in the nonhomogeneous boundary condition Eq. (5.57b). Once $C_{EC}(x,t)$ is computed, $C_{EC}(x,t-t_d)$ may be derived from the former by simply replacing t with $t-t_d$.

The starting point to calculate $C_{EC}(x,t)$ when $j_0(t) = j_0$ and $C_{\infty,0}(t) = C_{\infty,0}$ is to apply again the principle of superposition for linear problems according to the fact that the boundary condition Eq. (5.57b) is nonhomogeneous. In addition, as this boundary condition is time-independent, the function $C_{EC}(x,t)$ may be split into two parts: a steady-state solution and a 'complementary' transient solution, that is,

$$C_{EC}(x,t) = C_{EC,ss}(x) + C_{EC,ct}(x,t) \quad 0 \le t \le t_d \tag{5.63}$$

The steady-state solution keeps the nonhomogeneous boundary condition; it is very simple as is linear in space. For an analogous heat diffusive problem, see the one given by Cole et al. (2016). Readapting it to the current mass diffusive problem yields

$$C_{EC,ss}(x) = P_1 - P_2 \frac{x}{L} \tag{5.64a}$$

where

$$P_1 = \left(\mathrm{Bi}_0 C_{\infty,0} + \frac{j_0 L}{D_{eff}} \right) \frac{1 + \mathrm{Bi}_L}{\mathrm{Bi}_0 + \mathrm{Bi}_0 \mathrm{Bi}_L + \mathrm{Bi}_L} \tag{5.64b}$$

$$P_2 = \left(\mathrm{Bi}_0 C_{\infty,0} + \frac{j_0 L}{D_{eff}} \right) \frac{\mathrm{Bi}_L}{\mathrm{Bi}_0 + \mathrm{Bi}_0 \mathrm{Bi}_L + \mathrm{Bi}_L} \tag{5.64c}$$

$$\mathrm{Bi}_0 = \frac{K_0 L}{D_{eff}}, \quad \mathrm{Bi}_L = \frac{K_L L}{D_{eff}} \tag{5.64d}$$

The complementary transient part is much more complicated. In fact, it is the solution of the following governing equations:

$$\frac{\partial C_{EC,ct}}{\partial t} + \tau_{EC}^{(j)} \frac{\partial^2 C_{EC,ct}}{\partial t^2} = \left(\varepsilon D_{eff}\right) \left[\frac{\partial^2 C_{EC,ct}}{\partial x^2} + \tau_{EC}^{(c)} \frac{\partial}{\partial t} \frac{\partial^2 C_{EC,ct}}{\partial x^2} \right] \qquad 0 < x < L;\ t > 0 \tag{5.65a}$$

$$-D_{eff} \left(\frac{\partial C_{EC,ct}}{\partial x} \right)_{x=0} = -K_0 C_{EC,ct}(0,t) \qquad t > 0 \tag{5.65b}$$

$$-D_{eff}\left(\frac{\partial C_{EC,ct}}{\partial x}\right)_{x=L} = K_L C_{EC,ct}(L,t) \qquad t>0 \tag{5.65c}$$

$$C_{EC,ct}(x,0) = -C_{EC,ss}(x) \qquad 0<x<L \tag{5.65d}$$

$$\left(\frac{\partial C_{EC,ct}}{\partial t}\right)_{t=0} = 0 \qquad 0<x<L \tag{5.65e}$$

where the two boundary conditions are both homogeneous and the first initial condition is the negative part of the steady-state solution defined by Eqs. (5.64a)–(5.64d).

The solution to Eqs. (5.65a)–(5.65e) is presented in the next section using a classical Fourier series technique, as proposed by de Monte and Haji-Sheikh (2017b) for an analogous heat diffusive problem. Concerning this, it is important to recall the fundamental solution of the classical Fick-type mass diffusion equation.

5.4.2.2 Solution of the Fick-type diffusive equation

The fundamental solution of the classical 1D Fick-type mass diffusion equation

$$\frac{\partial C_{EC,ct}}{\partial t} = \left(\varepsilon D_{eff}\right)\frac{\partial^2 C_{EC,ct}}{\partial x^2} \tag{5.66}$$

in a finite 1D rectangular body subject to homogeneous boundary conditions, using the classical separation of variables technique, is

$$C_{EC,ct}(x,t) = \sum_{n=1}^{\infty} b_n X_n(x) e^{-\gamma_n t} \tag{5.67}$$

The space-variable function $X_n(x)$ is the n-th eigenfunction (corresponding to the n-th eigenvalue γ_n and accounting for the diffusivity, εD_{eff}) that satisfies the following equations:

$$\frac{d^2 X_n}{dx^2} + \left(\frac{\gamma_n}{\varepsilon D_{eff}}\right)X_n(x) = 0 \tag{5.68a}$$

$$-\left(\frac{dX_n}{dx}\right)_{x=0} + \frac{K_0}{D_{eff}}X_n(0) = 0 \tag{5.68b}$$

$$\left(\frac{dX_n}{dx}\right)_{x=L} + \frac{K_L}{D_{eff}}X_n(L) = 0 \tag{5.68c}$$

The function $X_n(x)$ satisfying the above equations may be taken as

$$X_n(x) = \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}\cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x\right) + \frac{K_0}{D_{eff}}\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x\right); \tag{5.69}$$

while the eigencondition for computing the eigenvalues is

$$\tan\left(\tilde{\gamma}_n\right) = \frac{\tilde{\gamma}_n\left(\mathrm{Bi}_0 + \mathrm{Bi}_L\right)}{\tilde{\gamma}_n^2 - \mathrm{Bi}_0\mathrm{Bi}_L} \qquad \tilde{\gamma}_n = \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L \tag{5.70}$$

where $\tilde{\gamma}_n$ is the dimensionless eigenvalue. In accordance with the Sturm-Liouville problem, the function $X_n(x)$ defined by Eq. (5.69) also satisfies the orthogonality property

$$\int_0^L X_n(x')X_m(x')dx' = \begin{cases} 0 & \text{when} \quad n = m \\ N_n & \text{when} \quad n \neq m \end{cases} \tag{5.71}$$

where N_n is the so-called norm that may be taken as

$$N_n = \frac{1}{2L}\left[\left(\tilde{\gamma}_n^2 + \mathrm{Bi}_0^2\right) \cdot \left(1 + \frac{\mathrm{Bi}_L}{\tilde{\gamma}_n^2 + \mathrm{Bi}_L^2}\right) + \mathrm{Bi}_0\right] \tag{5.72}$$

Also, b_n in Eq. (5.67) is a coefficient depending on the first initial condition Eq. (5.65d):

$$b_n = -\frac{1}{N_n}\int_0^L C_{EC,ss}(x')X_n(x')dx'. \tag{5.73}$$

Substituting Eqs. (5.64a) and Eq. (5.69) into Eq. (5.73) yields (see Section 5.B—Appendix B)

$$b_n = -\frac{P_1}{N_n}I_{1n} + \frac{P_2}{N_nL}\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}I_{2n,c} + \frac{K_{EC,0}}{D_{eff}}I_{2n,s}\right) \tag{5.74}$$

where I_{1n}, $I_{2n,\,c}$, and $I_{2n,\,s}$ are given in Section 5.B (Appendix B) by Eqs. (5.B2), (5.B4a), and (5.B4b), respectively.

5.4.2.3 Fourier series-based solution

The exact analytical solution of Eqs. (5.65a)–(5.65e) having the initial condition as only driving term can be obtained by modifying Eq. (5.67) as

$$C_{EC,ct}(x,t) = \sum_{n=1}^{\infty}\varphi_n(t)X_n(x)e^{-\gamma_n t} \tag{5.75}$$

where $\varphi_n(t)$ is an unknown function of time that accounts for the phase lags appearing in Eq. (5.65a).

The computation of the function $\varphi_n(t)$ may be obtained by substituting $C_{EC,ct}(x,t)$ defined by Eq. (5.75) into Eq. (5.65a) and using first Eq. (5.68a) and then Eq. (5.71). It produces a linear, homogeneous, ODE of second order for the determination of the time function $\varphi_n(t)$ as

$$\frac{d^2\varphi_n(t)}{dt^2} - 2\beta_n\frac{d\varphi_n(t)}{dt} + \lambda_n^2\varphi_n(t) = 0 \tag{5.76}$$

where

$$\beta_n = \gamma_n\left(1 - \frac{\tau_{EC}^{(c)}}{2\tau_{EC}^{(j)}} - \frac{1}{2\gamma_n\tau_{EC}^{(j)}}\right) \tag{5.77a}$$

$$\lambda_n = \gamma_n\left(1 - \frac{\tau_{EC}^{(c)}}{\tau_{EC}^{(j)}}\right)^{1/2} \tag{5.77b}$$

The solution of this ODE with constant coefficients provides the function $\varphi_n(t)$ to be inserted into Eq. (5.75) as

$$\begin{aligned}\varphi_n(t) &= B_{1n}\exp\left(\beta_n t+\sqrt{\beta_n^2-\lambda_n^2}t\right)+B_{2n}\exp\left(\beta_n t-\sqrt{\beta_n^2-\lambda_n^2}t\right)\\ &= e^{\beta_n t}\left[U_{1n}\sinh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)+U_{2n}\cosh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)\right]\end{aligned} \tag{5.78}$$

where $U_{1n}=B_{1n}-B_{2n}$ and $U_{2n}=B_{1n}+B_{2n}$.

The two initial conditions to be used for the determination of coefficients U_{1n} and U_{2n} are defined by Eqs. (5.65d) and (5.65e). Thus, by imposing that Eq. (5.75) (with the function $\varphi_n(t)$ defined through Eq. (5.78)) satisfy the two initial conditions and bearing in mind the orthogonality property of Eq. (5.71), results in

$$U_{1n}=\frac{\gamma_n-\beta_n}{\sqrt{\beta_n^2-\lambda_n^2}}U_{2n} \tag{5.79a}$$

$$U_{2n}=-\frac{1}{N_n}\int_0^L C_{EC,ss}(x')X_n(x')dx'=b_n \tag{5.79b}$$

where b_n may be calculated through Eq. (5.74). After determination of these constants, the function $\varphi_n(t)$ defined by Eq. (5.78) becomes

$$\varphi_n(t)=b_n e^{\beta_n t}\left[(\gamma_n-\beta_n)\frac{\sinh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)}{\sqrt{\beta_n^2-\lambda_n^2}}+\cosh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)\right] \tag{5.80}$$

Now, substituting Eq. (5.80) into Eq. (5.75) yields the complementary part $C_{EC,ct}(x,t)$ of the concentration solution. Then, the complete solution is

$$\begin{aligned}C_{EC}(x,t)=C_{EC,ss}(x)+\sum_{n=1}^{\infty}b_n&\left[(\gamma_n-\beta_n)\frac{\sinh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)}{\sqrt{\beta_n^2-\lambda_n^2}}+\cosh\left(\sqrt{\beta_n^2-\lambda_n^2}t\right)\right]\\ &\times X_n(x)e^{-(\gamma_n-\beta_n)t}\end{aligned} \tag{5.81}$$

The relative magnitude of β_n and λ_n defined by Eqs. (5.77a) and (5.77b), respectively, affects the quantity $\sqrt{\beta_n^2-\lambda_n^2}$ appearing in Eq. (5.80) and, hence, in Eq. (5.81). This quantity can in general be real or imaginary, while the function $\varphi_n(t)$ is always real. Whenever $\beta_n^2-\lambda_n^2<0$, the $C_{EC}(x,t)$ solution can exhibit a wave-like behavior and the convergence of Eq. (5.81) is fast (exponential convergence). However, it is proven in Section 5.4.4 that this case cannot be verified as the difference $\beta_n^2-\lambda_n^2$ is always positive. Consequently, the series convergence is complex and demanding and will be analyzed in Section 5.4.4.

5.4.2.4 Special case: Boundary condition of the first kind

If $K_0 \to \infty$, the generalized boundary condition of the third kind defined by Eq. (5.57b) reduces to a nonhomogeneous boundary condition of the first kind, namely, $C_{EC}(0,t) = C_{\infty,0}(t)$, where $C_{\infty,0}(t)$ is defined through Eq. (5.61b). In such a case, Eqs. (5.64b), (5.64c), (5.69), (5.70), (5.72), and (5.74) reduce, respectively, to

$$\begin{aligned} &P_1 = C_{\infty,0}; && P_2 = C_{\infty,0}\frac{\mathrm{Bi}_L}{1+\mathrm{Bi}_L}; && X_n(x) = \sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x\right); \\ &\tilde{\gamma}_n \cot(\tilde{\gamma}_n) = -\mathrm{Bi}_L; && N_n = \frac{L}{2}\left(1+\frac{\mathrm{Bi}_L}{\tilde{\gamma}_n^2+\mathrm{Bi}_L^2}\right); && b_n = -\frac{P_1}{N_n}I_{1n} + \frac{P_2}{N_n L}I_{2n} \end{aligned} \tag{5.82}$$

where I_{1n} and I_{2n} are given in Section 5.B (Appendix B) by Eqs. (5.B5) and (5.B6), respectively.

5.4.2.5 Cell concentration solution

As the drug delivery occurs for a while according to the two relationships in Eq. (5.61), the concentration $C_k(x,t)$ defined by Eq. (5.59) for $k = 1, 2$, $N = 3$ has to be calculated both when it is "on" ($0 \le t \le t_d$) and when is "off" ($t > t_d$). By using the principle of superposition, it may be given in a general form as

$$C_k(x,t) = \begin{cases} C_k(x,t) & 0 \le t \le t_d \\ C_k(x,t) - C_k(x,t-t_d) & t > t_d \end{cases} \tag{5.83}$$

where $C_k(x,t-t_d)$ may be obtained from $C_k(x,t)$ simply replacing t by $t-t_d$.

Substitution of Eq. (5.81) into Eq. (5.59) yields

$$\begin{aligned} C_k(x,t) = a_k e^{-\frac{t}{\tau_k^{(c)}}} \Bigg\{ & C_{EC,ss}(x) \int_0^t e^{\frac{\tau}{\tau_k^{(c)}}} d\tau \\ & + \sum_{n=1}^{\infty} b_n \frac{(\gamma_n - \beta_n)}{\sqrt{\beta_n^2 - \lambda_n^2}} X_n(x) \int_0^t \sinh\left(\sqrt{\beta_n^2 - \lambda_n^2}\,\tau\right) e^{-\left(\gamma_n - \beta_n - \frac{1}{\tau_k^{(c)}}\right)\tau} d\tau \\ & + \sum_{n=1}^{\infty} b_n X_n(x) \int_0^t \cosh\left(\sqrt{\beta_n^2 - \lambda_n^2}\,\tau\right) e^{-\left(\gamma_n - \beta_n - \frac{1}{\tau_k^{(c)}}\right)\tau} d\tau \Bigg\} \end{aligned} \tag{5.84}$$

where b_n may be calculated through Eq. (5.74).

Then, by performing the last two integrals by parts (Gradshteyn and Ryzhik, 2007; see p. 148) and after some algebra, the concentration $C_k(x,t)$ results in

$$
\begin{aligned}
C_k(x,t) = a_k \Bigg\{ & C_{EC,ss}(x)\,\tau_k^{(c)}\left(1 - e^{-\frac{t}{\tau_k^{(c)}}}\right) \\
& - \sum_{n=1}^{\infty} b_n \frac{\dfrac{(\gamma_n - \beta_n)}{\sqrt{\beta_n^2 - \lambda_n^2}}\left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right) + \sqrt{\beta_n^2 - \lambda_n^2}}{\left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right)^2 - \left(\beta_n^2 - \lambda_n^2\right)} \sinh\left(\sqrt{\beta_n^2 - \lambda_n^2}\,t\right) X_n(x)\, e^{-(\gamma_n - \beta_n)t} \\
& - \sum_{n=1}^{\infty} b_n \frac{(\gamma_n - \beta_n) + \left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right)}{\left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right)^2 - \left(\beta_n^2 - \lambda_n^2\right)} \cosh\left(\sqrt{\beta_n^2 - \lambda_n^2}\,t\right) X_n(x)\, e^{-(\gamma_n - \beta_n)t} \\
& + e^{-\frac{t}{\tau_k^{(c)}}} \sum_{n=1}^{\infty} b_n \frac{(\gamma_n - \beta_n) + \left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right)}{\left(\gamma_n - \beta_n - \dfrac{1}{\tau_k^{(c)}}\right)^2 - \left(\beta_n^2 - \lambda_n^2\right)} X_n(x) \Bigg\}
\end{aligned}
\tag{5.85}
$$

5.4.3 Concentration solution in dimensionless form

By defining the following dimensionless groups:

$$
\begin{aligned}
&\tilde{x} = \frac{x}{L}; \qquad \tilde{t} = \frac{\varepsilon D_{eff}}{L^2} t; \qquad \tilde{C}_{EC} = \frac{C_{EC}}{C_{\infty,0}}; \qquad \tilde{C}_k = \frac{C_k}{C_{\infty,0}}; \qquad \tilde{j}_0 = \frac{j_0 L}{C_{\infty,0} D_{eff}}; \\
&\tilde{\tau}_{EC}^{(c)} = \frac{\varepsilon D_{eff}}{L^2}\tau_{EC}^{(c)}; \qquad \tilde{\tau}_{EC}^{(j)} = \frac{\varepsilon D_{eff}}{L^2}\tau_{EC}^{(j)}; \qquad \tilde{\tau}_k^{(c)} = \frac{\varepsilon D_{eff}}{L^2}\tau_k^{(c)}; \qquad \tilde{a}_k = \frac{a_k}{\varepsilon D_{eff}/L^2},
\end{aligned}
\tag{5.86}
$$

the concentration solution C_{EC}, Eq. (5.81), can be rewritten in dimensionless form as

$$
\tilde{C}_{EC}(\tilde{x},\tilde{t}\,) = \tilde{C}_{EC,ss}(\tilde{x}) + \sum_{n=1}^{\infty} B_n \left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) \frac{\sinh\left(\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\,\tilde{t}\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} + \cosh\left(\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\,\tilde{t}\right) \right] \tilde{X}_n(\tilde{x})\; e^{-\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)\tilde{t}} \tag{5.87a}
$$

where

$$\tilde{C}_{EC,ss}(\tilde{x}) = \tilde{P}_1 - \tilde{P}_2\tilde{x} \tag{5.87b}$$

$$\tilde{P}_1 = \frac{P_1}{C_{\infty,0}} = \left(\mathrm{Bi}_0 + \tilde{j}_0\right)\frac{1+\mathrm{Bi}_L}{\mathrm{Bi}_0 + \mathrm{Bi}_0\mathrm{Bi}_L + \mathrm{Bi}_L}; \quad \tilde{P}_2 = \frac{P_2}{C_{\infty,0}} = \left(\mathrm{Bi}_0 + \tilde{j}_0\right)\frac{\mathrm{Bi}_L}{\mathrm{Bi}_0 + \mathrm{Bi}_0\mathrm{Bi}_L + \mathrm{Bi}_L} \tag{5.87c}$$

$$\tilde{X}_n(\tilde{x}) = X_n L = \tilde{\gamma}_n \cos\left(\tilde{\gamma}_n\tilde{x}\right) + \mathrm{Bi}_0 \sin\left(\tilde{\gamma}_n\tilde{x}\right) \tag{5.87d}$$

$$\tilde{\beta}_n = \frac{\beta_n}{\varepsilon D_{eff}/L^2} = \tilde{\gamma}_n^2\left(1 - \frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} - \frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}\right); \quad \tilde{\lambda}_n = \frac{\lambda_n}{\varepsilon D_{eff}/L^2} = \tilde{\gamma}_n^2\sqrt{1 - \frac{\tilde{\tau}_{EC}^{(c)}}{\tilde{\tau}_{EC}^{(j)}}} \tag{5.87e}$$

Also, the dimensionless constant B_n results in

$$B_n = \frac{b_n}{C_{\infty,0}L} = -\frac{\tilde{P}_1}{\tilde{N}_n}I_{1n} + \frac{\tilde{P}_2}{\tilde{N}_n}\tilde{I}_{2n} \tag{5.87f}$$

where

$$\tilde{N}_n = N_n L = \frac{1}{2}\left[\left(\tilde{\gamma}_n^2 + \mathrm{Bi}_0{}^2\right)\left(1 + \frac{\mathrm{Bi}_L}{\tilde{\gamma}_n^2 + \mathrm{Bi}_L^2}\right) + \mathrm{Bi}_0\right] \tag{5.87g}$$

$$I_{1n} = \sin\left(\tilde{\gamma}_n\right) + \frac{\mathrm{Bi}_0}{\tilde{\gamma}_n}\left[1 - \cos\left(\tilde{\gamma}_n\right)\right]; \quad \tilde{I}_{2n} = \frac{I_{2n}}{L} = \tilde{\gamma}_n\tilde{I}_{2n,c} + \mathrm{Bi}_0\tilde{I}_{2n,s} \tag{5.87h}$$

$$\tilde{I}_{2n,c} = \frac{I_{2n,c}}{L^2} = \frac{\tilde{\gamma}_n \sin\left(\tilde{\gamma}_n\right) + \cos\left(\tilde{\gamma}_n\right) - 1}{\tilde{\gamma}_n^2} \tag{5.87i}$$

$$\tilde{I}_{2n,s} = \frac{I_{2n,s}}{L^2} = \frac{\sin\left(\tilde{\gamma}_n\right) - \tilde{\gamma}_n\cos\left(\tilde{\gamma}_n\right)}{\tilde{\gamma}_n^2} \tag{5.87j}$$

Once $\tilde{C}_{EC}(\tilde{x},\tilde{t})$ is known through Eqs. (5.87a)–(5.87j), the concentration $\tilde{C}_{EC}(\tilde{x},\tilde{t}-\tilde{t}_d)$ may be derived from the former by simply replacing $\tilde{t}$ with $\tilde{t}-\tilde{t}_d$, where $\tilde{t}_d = \frac{\varepsilon D_{eff}}{L^2}t_d$.

By using the dimensionless groups defined by Eq. (5.87), the concentration solution $C_k(x,t)$, Eq. (5.85), can be rewritten in a dimensionless form as

$$
\begin{aligned}
\tilde{C}_k(\tilde{x},\tilde{t}) = \tilde{a}_k \Bigg\{ & \tilde{C}_{EC,ss}(\tilde{x})\,\tilde{\tau}_k^{(c)}\left(1-e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}\right) \\
& -\sum_{n=1}^{\infty} B_n \frac{\dfrac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)^2-\left(\tilde{\beta}_n^2-\tilde{\lambda}_n^2\right)} \sinh\left(\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\,\tilde{t}\right)\tilde{X}_n(\tilde{x})\,e^{-\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)\tilde{t}} \\
& -\sum_{n=1}^{\infty} B_n \frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)^2-\left(\tilde{\beta}_n^2-\tilde{\lambda}_n^2\right)} \cosh\left(\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\,\tilde{t}\right)\tilde{X}_n(\tilde{x})\,e^{-\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)\tilde{t}} \\
& +e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}\sum_{n=1}^{\infty} B_n \frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n-\dfrac{1}{\tilde{\tau}_k^{(c)}}\right)^2-\left(\tilde{\beta}_n^2-\tilde{\lambda}_n^2\right)} \tilde{X}_n(\tilde{x}) \Bigg\}
\end{aligned}
\tag{5.88}
$$

Before proceeding to calculate the concentration solution of the EC space as well as of the k-th cell, the convergence of both the series-solutions Eqs. (5.87) and (5.88) has to be analyzed and discussed. Similarly, the computation of the eigenvalues.

5.4.4 Convergence of the series-solution

Computational difficulties might arise during the evaluation of the single summation appearing in Eq. (5.87a) due to the argument $\sqrt{\beta_n^2-\lambda_n^2}\,\tilde{t}$ of the hyperbolic functions that is always real. In fact, by using Eq. (5.84e), the term $\tilde{\beta}_n^2-\tilde{\lambda}_n^2$ results in

$$
\tilde{\beta}_n^2-\tilde{\lambda}_n^2 = \tilde{\gamma}_n^4\left(1-\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}-\frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}\right)^2-\tilde{\gamma}_n^4\left(1-\frac{\tilde{\tau}_{EC}^{(c)}}{\tilde{\tau}_{EC}^{(j)}}\right), \tag{5.89}
$$

that is always positive as, in the current case, the ratio $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}$ is always greater than 1, as shown in Section 5.C (Appendix C).

Therefore, when n and the dimensionless time $\tilde{t}$ increase, the argument $\sqrt{\beta_n^2-\lambda_n^2}\,\tilde{t}$ can be very large, and the hyperbolic sine and cosine can become extremely large leading to a possible overflow error. For this reason, it is convenient to write out these two hyperbolic functions and to combine their argument, $\sqrt{\beta_n^2-\lambda_n^2}\,\tilde{t}$, with the one, $-\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)\tilde{t}$, of the exponential appearing in Eq. (5.87a). After some algebra, an alternative form of the concentration series-solution is as

$$\tilde{C}_{EC}(\tilde{x},\tilde{t}) = \tilde{P}_1 - \tilde{P}_2\tilde{x} + \underbrace{\frac{1}{2}\sum_{n=1}^{\infty} B_n \left[\frac{(\tilde{\gamma}_n^2 - \tilde{\beta}_n)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} + 1\right] \tilde{X}_n(\tilde{x})\ e^{-\left[(\tilde{\gamma}_n^2 - \tilde{\beta}_n) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}}}_{S_{EC}^{(1)}} - \underbrace{\frac{1}{2}\sum_{n=1}^{\infty} B_n \left[\frac{(\tilde{\gamma}_n^2 - \tilde{\beta}_n)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} - 1\right] \tilde{X}_n(\tilde{x})\ e^{-\left[(\tilde{\gamma}_n^2 - \tilde{\beta}_n) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}}}_{S_{EC}^{(2)}} \tag{5.90}$$

In the above equation both the summations seem to exhibit an exponential convergence and, hence, very fast. However, some attention should be paid on the quantity $(\tilde{\gamma}_n^2 - \tilde{\beta}_n) \mp \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}$ of the argument of the exponential terms. In fact, bearing in mind Eq. (5.87e), it is found that

$$\tilde{\gamma}_n^2 - \tilde{\beta}_n \mp \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} = \tilde{\gamma}_n^2 \left[\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} + \frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}} \mp \sqrt{\left(\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} + \frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}\right)^2 - \frac{1}{\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}}\right], \tag{5.91a}$$

whose limit, when $n \to \infty$, is

$$\lim_{n\to\infty}\left[(\tilde{\gamma}_n^2 - \tilde{\beta}_n) \mp \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right] = \begin{cases} \dfrac{1}{\tilde{\tau}_{EC}^{(c)}} & \text{for } "-" \text{ sign} \\ \infty & \text{for } "+" \text{ sign} \end{cases} \tag{5.91b}$$

Therefore, the first summation of Eq. (5.90) only apparently exhibits an exponential convergence; it actually exhibits an algebraic convergence (very slow). Conversely, the second summation is a "true" exponentially convergent series. The former of the two limits in Eq. (5.91b) has been proven numerically in Section 5.D (Appendix D). Both of them requires an infinite number of terms.

However, as an infinite number of terms cannot be considered, a convergence criterion for the two series appearing in Eq. (5.90) has been defined in Section 5.D (Appendix D). It gives the maximum number of terms, $N_{S_{EC}^{(1)}}$ and $N_{S_{EC}^{(2)}}$, for truncation errors less than 10^{-A} (with $A = 2, 3, \ldots$) through Eqs. (5.D6) and (5.D10), respectively.

To appreciate the difference in magnitude between $N_{S_{EC}^{(1)}}$ and $N_{S_{EC}^{(2)}}$, they have been computed in Section 5.D (Appendix D) for different numerical accuracies and the results given by Table 5.D1.

The same computational difficulties might arise during the evaluation of the first two single summations appearing in Eq. (5.88). Then, an alternative form of the concentration $C_k(x,t)$ can be obtained writing conveniently out the hyperbolic functions as exponentials. In addition, the third summation of Eq. (5.88) exhibits an algebraic convergence. By some algebra, this summation can be split into two parts as

$$\sum_{n=1}^{\infty} B_n \frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \left(\tilde{\gamma}_n^2 - \tilde{\beta}_n - \dfrac{1}{\tilde{\tau}_k^{(c)}}\right)}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n - \dfrac{1}{\tilde{\tau}_k^{(c)}}\right)^2 - \left(\tilde{\beta}_n^2 - \tilde{\lambda}_n^2\right)} \tilde{X}_n(\tilde{x})$$

$$= \frac{1}{2} \sum_{n=1}^{\infty} B_n \left\{ \frac{\left[\dfrac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} + 1\right]}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n - \dfrac{1}{\tilde{\tau}_k^{(c)}}\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} - \frac{\left[\dfrac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} - 1\right]}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n - \dfrac{1}{\tilde{\tau}_k^{(c)}}\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} \right\} \tilde{X}_n(\tilde{x}) \tag{5.92}$$

Therefore, Eq. (5.88) becomes

$$\begin{aligned}
\tilde{C}_k(\tilde{x},\tilde{t}) = \tilde{a}_k \Bigg\{ & \tilde{C}_{EC,ss}(\tilde{x}) \tilde{\tau}_k^{(c)} \left(1 - e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}\right) \\
& + \frac{1}{2} e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}} \underbrace{\sum_{n=1}^{\infty} B_n \left[\frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} + 1\right] \frac{\tilde{X}_n(\tilde{x})}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \dfrac{1}{\tilde{\tau}_k^{(c)}}}}_{S_k^{(1)}} \\
& \underbrace{- \frac{1}{2} \sum_{n=1}^{\infty} B_n \left[\frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} + 1\right] \frac{\tilde{X}_n(\tilde{x})}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \dfrac{1}{\tilde{\tau}_k^{(c)}}} e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right] \tilde{t}}}_{S_k^{(2)}} \\
& - \frac{1}{2} e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}} \underbrace{\sum_{n=1}^{\infty} B_n \left[\frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} - 1\right] \frac{\tilde{X}_n(\tilde{x})}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \dfrac{1}{\tilde{\tau}_k^{(c)}}}}_{S_k^{(3)}} \\
& \underbrace{+ \frac{1}{2} \sum_{n=1}^{\infty} B_n \left[\frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} - 1\right] \frac{\tilde{X}_n(\tilde{x})}{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \dfrac{1}{\tilde{\tau}_k^{(c)}}} e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right] \tilde{t}}}_{S_k^{(4)}} \Bigg\}
\end{aligned} \tag{5.93}$$

where, bearing in mind Eq. (5.91), the second summation exhibits an algebraic convergence too. Only the fourth one is a "true" exponentially convergent series.

All the series stated before require an infinite number of terms. As this cannot be performed, an appropriate convergence criterion is discussed in Section 5.E (Appendix E). The maximum number of terms to ensure a truncation error less than 10^{-A} (with $A=2,\ 3,\ \ldots$) for either series of Eq. (5.93) is given by Eqs. (5.E5), (5.E9), and (5.E13). Furthermore, the maximum number of terms is computed for different accuracies and the results given by Table 5.E1.

5.4.5 Computation of the eigenvalues

The eigencondition defined by Eq. (5.70) is the same as the corresponding equation of the 1D linear transient heat conduction problem involving a slab with boundary conditions of the third kind on both sides (assuming Bi_0 at $x=0$ and Bi_L at $x=L$). This problem is denoted by X33 and treated by Haji-Sheikh and Beck (2000). Therefore, its roots (eigenvalues) may be computed by using the same explicit approximate relations based on the third-order modified Newton method (Haji-Sheikh and Beck, 2000). In particular, the n-th approximate eigenvalue ζ_n is obtained by means of the following formula:

$$\beta_n \approx \zeta_n = z_n + \varepsilon_n(z_n) \tag{5.94}$$

where β_n is the exact eigenvalue, z_n is the initial guess value used in the first iteration and ε_n is the deviation which yields the update value for ζ_n.

These relations provide approximate values of the exact eigenvalues with high accuracy for Bi_0, $\mathrm{Bi}_L \in [0, \infty)$. In particular, after one iteration they yield an accuracy with at least seven decimal places for the first eigenvalue ($n=1$), and even higher for $n>1$. To obtain eigenvalues with an accuracy of 10^{-15}, two more iterations may be required.

The first 10 eigenvalues computed for $\mathrm{Bi}_0=\mathrm{Bi}_\mathrm{L}=1$ through the method mentioned above are shown in Table 5.1, where the exact eigenvalues β_n listed in the last column are obtained by using the internal Matlab function "fsolve" setting the tolerance parameter equal to 10^{-15}.

Note that, after two iterations, ζ_n is exactly the same as β_n.

Table 5.1 Calculated eigenvalue, ζ_n, using explicit approximate formulation and comparison with results after three iterations and exact eigenvalues β_n.

n	z_n	ζ_n (after 1 iteration)	ζ_n (after 2 iterations)	β_n (exact)
1	1.30592200212618	1.30654237415872	1.30654237418881	1.30654237418881
2	3.69018331600398	3.67319480171322	3.67319440630425	3.67319440630425
3	6.60338479754574	6.58462058161976	6.58462004256417	6.58462004256417
4	9.64809957042428	9.63168500010130	9.63168463569187	9.63168463569187
5	12.7376635033563	12.7232410324830	12.7232407841313	12.7232407841313
6	15.8470284168283	15.8341055484253	15.8341053693324	15.8341053693324
7	18.9667292229825	18.9549715459113	18.9549714108416	18.9549714108416
8	22.0924755521163	22.0816597411699	22.0816596359426	22.0816596359426
9	25.2220576131836	25.2120269725290	25.2120268885508	25.2120268885508
10	28.3542254064965	28.3448642178852	28.3448641495999	28.3448641495999

5.5 Results and discussion

As an example, the concentration of the parallelepiped-shaped EC space of Section 5.4 is now computed for a 10-mm-thick biological tissue subject to an applied mass flux of $\tilde{j}_0 = 1$ for the finite-time duration of $\tilde{t}_d = 10$. Also, it can exchange mass at the boundaries through the Biot numbers of $\mathrm{Bi}_0 = \mathrm{Bi}_\mathrm{L} = 1$ and the dimensionless phase lags of concentration and mass flux are $\tilde{\tau}_{EC}^{(c)} = 4.5135$ and $\tilde{\tau}_{EC}^{(j)} = 4.4905$, respectively. These values come from the mass transfer coefficients of $\mu_1 = 10^{-4}\mathrm{s}^{-1}$, $\mu_2 = 5 \times 10^{-5}\mathrm{s}^{-1}$, and $\mu_3 = 10^{-7}\mathrm{s}^{-1}$ at the EC/cell interface and volume fractions of $f_1 = 0.75$, $f_2 = 0.245$ and $f_3 = 0.005$ for the three types of cells, respectively. A porosity of $\varepsilon = 0.18$ is assumed for the EC porous medium as well as an effective diffusivity of $D_{eff} = 2.5 \times 10^{-10}\,\mathrm{m}^2\mathrm{s}^{-1}$. These numerical values are typical of electroporated tissues (Argus et al., 2017). Similarly, the dimensionless phase lags of concentration for the three types of cell result in $\tilde{\tau}_1{}^{(c)} = 4.5 \cdot 10^{-3}$, $\tilde{\tau}_2{}^{(c)} = 9 \cdot 10^{-3}$, and $\tilde{\tau}_3{}^{(c)} = 4.50$, respectively.

The dimensionless EC intrinsic concentration, $\tilde{c}_{EC}(\tilde{x}, \tilde{t}) = \tilde{C}_{EC}(\tilde{x}, \tilde{t})/\varepsilon$, as well as the dimensionless intrinsic concentrations $\tilde{c}_k(\tilde{x}, \tilde{t}) = \tilde{C}_k(\tilde{x}, \tilde{t})/[\, f_k(1-\varepsilon)]\,(k = 1, 2, 3)$ of the three types of cell are plotted in Fig. 5.5 as a function of the dimensionless time for different values of the dimensionless space coordinate.

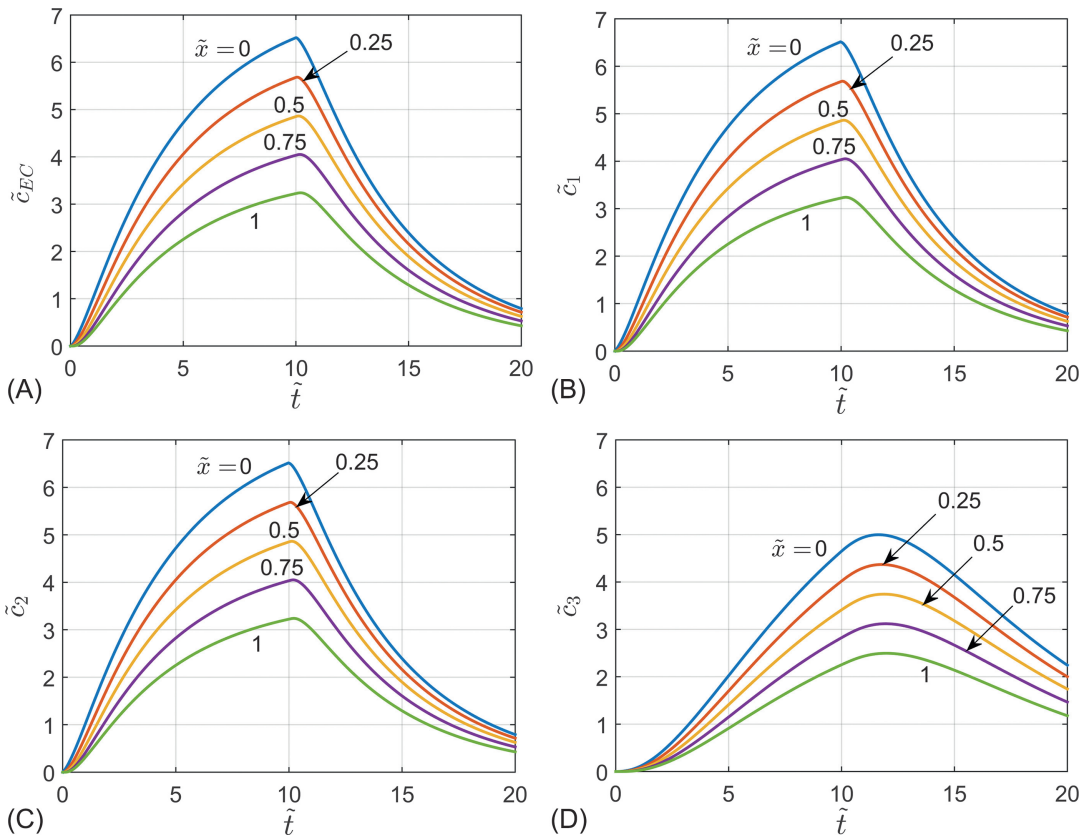

FIG. 5.5

Dimensionless intrinsic concentrations (when $\tilde{t}_d = 10$) as a function of the dimensionless time with the space coordinate $\tilde{x}$ as a parameter: (A) EC space; (B) cell of type "1"; (C) cell of type "2"; and (D) cell of type "3."

The concentration profiles of Fig. 5.5 are in agreement with Eq. (5.29) concerning volume-averaged concentrations. In fact, as $\tau_k^{(c)}$ is always positive, it states that the concentration C_k is delayed with respect to the concentration C_{EC}. This is also seen in the intrinsic volume-averaged concentrations c_k and c_{EC} that are plotted in Fig. 5.5. In the current case, as $\tilde{\tau}_1^{(c)} = 4.5 \cdot 10^{-3}$ and $\tilde{\tau}_2^{(c)} = 9 \cdot 10^{-3}$, this delay is practically zero. However, as $\tilde{\tau}_3^{(c)} = 4.50$ for the third type of cell, its concentration is delayed with respect to the EC concentration. Fig. 5.5D in fact indicates that there exists a delay for this cell concentration but it is nearly 2 vs 4.5 due to the fact the second part of Eq. (5.29) is an approximate expression of the mass balance for the k-th type of cell. In addition, the cell concentration is damped as its peak value is lower. A comparison among the dimensionless intrinsic concentration of the EC space and the three types of cell is also shown by means of a contour plot in Fig. 5.6.

Lastly, Fig. 5.7 shows a comparison of small and large values of the dimensionless time. The concentration $\tilde{c}_3$ is always less than the others with the exception of very large values of the time (larger than $\tilde{t}_d = 10$) according to its large phase lag of $\tilde{\tau}_3^{(c)} = 4.50$.

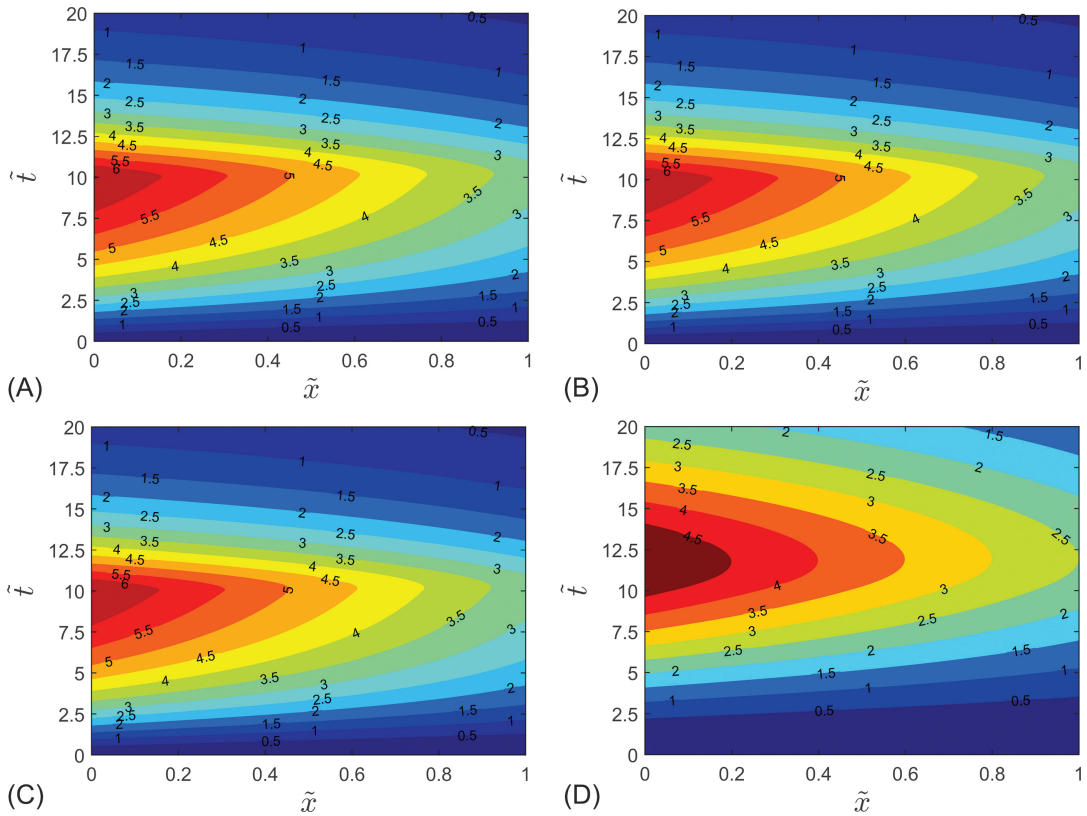

FIG. 5.6

Contour plot for the dimensionless intrinsic concentrations when $\tilde{t}_d = 10$ in the: (A) EC space; (B) cell of type "1"; (C) cell of type "2"; and (D) cell of type "3."

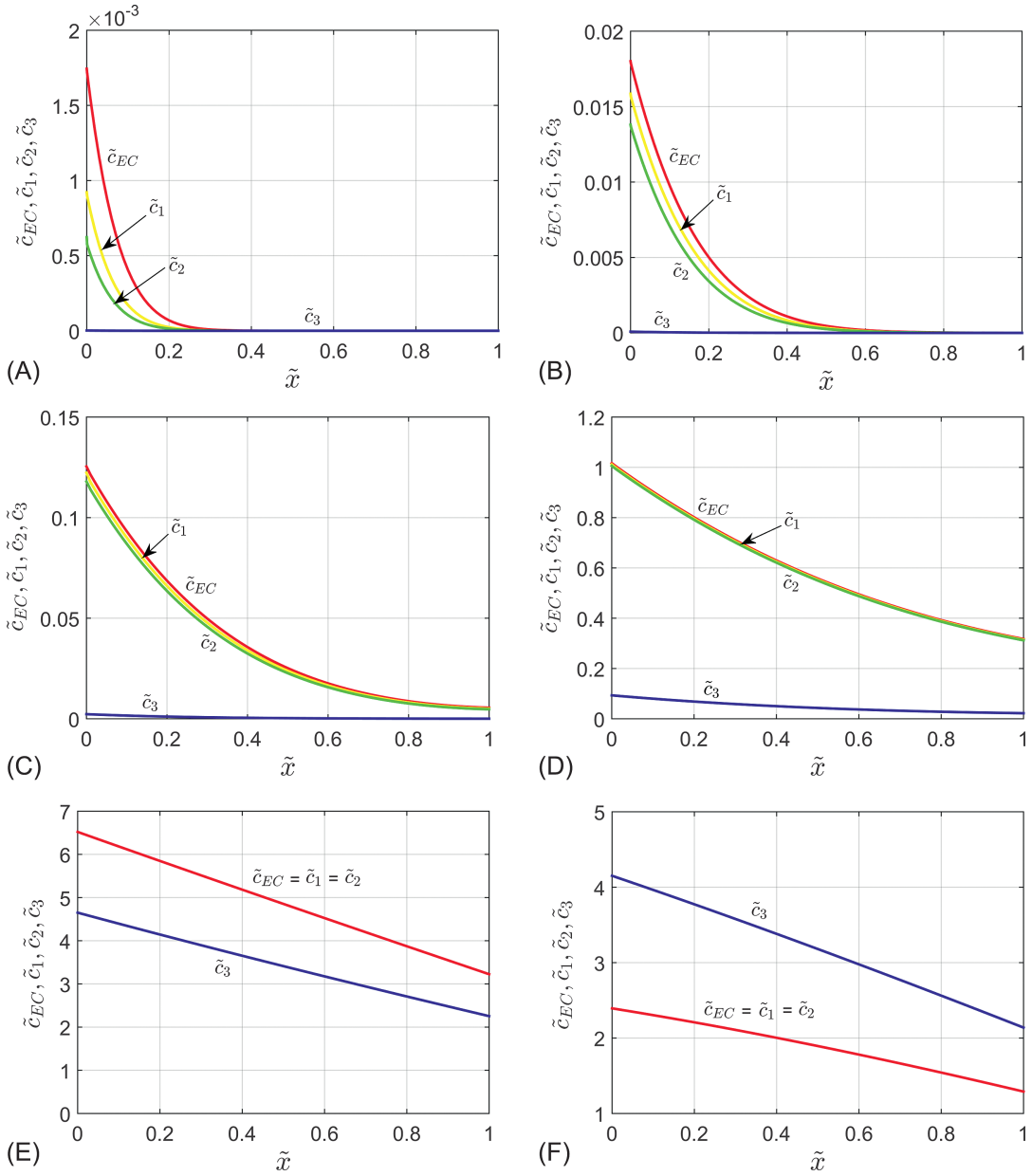

FIG. 5.7

Comparison among the intrinsic concentration of the EC space and the intrinsic concentrations of the three different types of cell immersed in it for $\tilde{t}_d = 10$ and different times: (A) $\tilde{t} = 0.01$; (B) $\tilde{t} = 0.05$; (C) $\tilde{t} = 0.2$; (D) $\tilde{t} = 1$; (E) $\tilde{t} = 10$; and (F) $\tilde{t} = 15$.

5.6 Conclusions

A mathematical model concerning the mass transport between an extracellular and an intracellular space consisting of N different types of cell was presented. Mass transfer coefficients as well as reaction coefficients were assumed to be space- and time-independent. The solution to the system of coupled partial/ordinary differential equations was performed by using an uncoupling procedure that has allowed these equations to be adequately decoupled. This procedure led a governing partial equation of high order for the extracellular space in the form of the well-established dual-phase-lag equation. Then, its exact solution was derived analytically for a parallelepiped-shaped biological tissue, exchanging drug with three different types of cell, using a modified separation-of-variable method. The concentration profile of the extracellular domain was presented in a graphical form and compared with the profiles of the three different cells considered.

5.A Appendix A

The coefficients appearing in Eq. (5.44) are

$$A_N^{(0)} = \sum_{k=1}^{N} \tau_k^{(c)} h_k a_k \tag{5.A1}$$

$$\begin{aligned} A_N^{(1)} = {} & \left(1 + \sum_{k=1}^{N} \tau_k^{(c)} a_k\right) + \operatorname{sign}(N-1)\left(\prod_{k=1}^{2} \tau_k^{(c)}\right)\left(\sum_{k=1}^{2} h_k a_k\right) \\ & + \frac{(N-1)(N-2)}{2}\left[\left(\prod_{k=1}^{2} \tau_{2k-1}^{(c)}\right)\left(\sum_{k=1}^{2} h_{2k-1} a_{2k-1}\right) + \left(\prod_{k=2}^{3} \tau_k^{(c)}\right)\left(\sum_{k=2}^{3} h_k a_k\right)\right] \end{aligned} \tag{5.A2}$$

$$\begin{aligned} A_N^{(2)} = {} & \sum_{k=1}^{N} \tau_k^{(c)} + \operatorname{sign}(N-1)\left(\prod_{k=1}^{2} \tau_k^{(c)}\right)\left(\sum_{k=1}^{2} a_k\right) \\ & + \frac{(N-1)(N-2)}{2}\left[\left(\prod_{k=1}^{2} \tau_{2k-1}^{(c)}\right)\left(\sum_{k=1}^{2} a_{2k-1}\right) + \left(\prod_{k=2}^{3} \tau_k^{(c)}\right)\left(\sum_{k=2}^{3} a_k\right) + \left(\prod_{k=1}^{3} \tau_k^{(c)}\right)\left(\sum_{k=1}^{3} h_k a_k\right)\right] \end{aligned} \tag{5.A3}$$

$$A_N^{(3)} = \operatorname{sign}(N-1)\prod_{k=1}^{2} \tau_k^{(c)} + \frac{(N-1)(N-2)}{2}\left[\prod_{k=1}^{2} \tau_{2k-1}^{(c)} + \prod_{k=2}^{3} \tau_k^{(c)} + \left(\prod_{k=1}^{3} \tau_k^{(c)}\right)\left(\sum_{k=1}^{3} a_k\right)\right] \tag{5.A4}$$

$$A_N^{(4)} = \frac{(N-1)(N-2)}{2}\prod_{k=1}^{3} \tau_k^{(c)} \tag{5.A5}$$

$$B_N^{(1)} = \sum_{k=1}^{N} \tau_k^{(c)} \tag{5.A6}$$

$$B_N^{(2)} = \text{sign}(N-1) \prod_{k=1}^{2} \tau_k^{(c)} + \frac{(N-1)(N-2)}{2} \left(\prod_{k=1}^{2} \tau_{2k-1}^{(c)} + \prod_{k=2}^{3} \tau_k^{(c)} \right) \tag{5.A7}$$

$$B_N^{(3)} = A_N^{(4)} \tag{5.A8}$$

Note that, for $z > 0$, $\text{sign}(z) = 1$ and $\text{sign}(-z) = -1$. Also, $\text{sign}(0) = 0$ as introduced by Oldham et al. (2010). The coefficients listed before are given in Table 5.A1 for $N = 1$, 2 and 3.

When the reaction terms are negligible ($h_k \to 0$), the coefficients listed before by Eqs. (5.A1)–(5.A8) simplify. In fact, bearing in mind Eqs. (5.25) and (5.30a), the product $\tau_k^{(c)} a_k$ reduces to

$$\tau_k^{(c)} a_k = \frac{V_k}{V_{EC}} = \frac{V_k}{V_C} \frac{V_C}{V_{EC}} = f_k \left(\frac{1-\varepsilon}{\varepsilon} \right) \tag{5.A9}$$

Therefore, the coefficients $A_N^{(0)}$, $A_N^{(1)}$, $A_N^{(2)}$, and $A_N^{(3)}$ listed before through Eqs. (5.A1)–(5.A4) become, respectively,

$$A_N^{(0)} = 0 \tag{5.A10}$$

$$A_N^{(1)} = 1 + \sum_{k=1}^{N} \tau_k^{(c)} a_k = 1 + \left(\frac{1-\varepsilon}{\varepsilon} \right) \underbrace{\sum_{k=1}^{N} f_k}_{=1} = \frac{1}{\varepsilon} \tag{5.A11}$$

$$\begin{aligned} A_N^{(2)} = {} & \tau_1^{(c)} \frac{1}{\varepsilon} \left[\varepsilon + \text{sign}(N-1) f_2 (1-\varepsilon) + \frac{(N-1)(N-2)}{2} f_3 (1-\varepsilon) \right] \\ & + \text{sign}(N-1) \tau_2^{(c)} \frac{1}{\varepsilon} \left[\varepsilon + f_1 (1-\varepsilon) + \frac{(N-1)(N-2)}{2} f_3 (1-\varepsilon) \right] \\ & + \frac{(N-1)(N-2)}{2} \tau_3^{(c)} \frac{1}{\varepsilon} [\varepsilon + f_1 (1-\varepsilon) + f_2 (1-\varepsilon)] = \frac{1}{\varepsilon} R_N^{(2)} \end{aligned} \tag{5.A12}$$

$$\begin{aligned} A_N^{(3)} = {} & \text{sign}(N-1) \tau_1^{(c)} \tau_2^{(c)} \frac{1}{\varepsilon} \left[\varepsilon + \frac{(N-1)(N-2)}{2} f_3 (1-\varepsilon) \right] \\ & + \frac{(N-1)(N-2)}{2} \tau_1^{(c)} \tau_3^{(c)} \frac{1}{\varepsilon} [\varepsilon + f_2 (1-\varepsilon)] \\ & + \frac{(N-1)(N-2)}{2} \tau_2^{(c)} \tau_3^{(c)} \frac{1}{\varepsilon} [\varepsilon + f_1 (1-\varepsilon)] = \frac{1}{\varepsilon} R_N^{(3)} \end{aligned} \tag{5.A13}$$

where the coefficients $R_N^{(2)}$ and $R_N^{(3)}$ are shown in Table 5.A2 for $N = 1$, 2, and 3.

The coefficients $A_N^{(4)}$, $B_N^{(1)}$, $B_N^{(2)}$, and $B_N^{(3)}$ given by Eqs. (5.A5)–(5.A8) do however not modify and, hence, are still defined by these equations.

Table 5.A1 Coefficients appearing in Eq. (5.44) for $N = 1$, 2 and 3.

	$N=1$	$N=2$	$N=3$
$A_N^{(0)}$	$\tau_1^{(c)} h_1 a_1$	$\tau_1^{(c)} h_1 a_1 + \tau_2^{(c)} h_2 a_2$	$\tau_1^{(c)} h_1 a_1 + \tau_2^{(c)} h_2 a_2 + \tau_3^{(c)} h_3 a_3$
$A_N^{(1)}$	$1 + \tau_1^{(c)} a_1$	$\left(1 + \tau_1^{(c)} a_1 + \tau_2^{(c)} a_2\right)$ $+ \tau_1^{(c)} \tau_2^{(c)} (h_1 a_1 + h_2 a_2)$	$\left(1 + \tau_1^{(c)} a_1 + \tau_2^{(c)} a_2 + \tau_3^{(c)} a_3\right)$ $+ \tau_1^{(c)} \tau_2^{(c)} (h_1 a_1 + h_2 a_2)$ $+ \begin{bmatrix} \tau_1^{(c)} \tau_3^{(c)} (h_1 a_1 + h_3 a_3) \\ + \tau_2^{(c)} \tau_3^{(c)} (h_2 a_2 + h_3 a_3) \end{bmatrix}$
$A_N^{(2)}$	$\tau_1^{(c)}$	$\left(\tau_1^{(c)} + \tau_2^{(c)}\right) + \tau_1^{(c)} \tau_2^{(c)} (a_1 + a_2)$ $= \tau_1^{(c)} \left(1 + \tau_2^{(c)} a_2\right) + \tau_2^{(c)} \left(1 + \tau_1^{(c)} a_1\right)$	$\left(\tau_1^{(c)} + \tau_2^{(c)} + \tau_3^{(c)}\right) + \tau_1^{(c)} \tau_2^{(c)} (a_1 + a_2)$ $+ \begin{bmatrix} \tau_1^{(c)} \tau_3^{(c)} (a_1 + a_3) + \tau_2^{(c)} \tau_3^{(c)} (a_2 + a_3) \\ + \tau_1^{(c)} \tau_2^{(c)} \tau_3^{(c)} (h_1 a_1 + h_2 a_2 + h_3 a_3) \end{bmatrix}$ $= \tau_1^{(c)} \left(1 + \tau_2^{(c)} a_2 + \tau_3^{(c)} a_3\right)$ $+ \tau_2^{(c)} \left(1 + \tau_1^{(c)} a_1 + \tau_3^{(c)} a_3\right)$ $+ \tau_3^{(c)} \left(1 + \tau_1^{(c)} a_1 + \tau_2^{(c)} a_2\right)$ $+ \tau_1^{(c)} \tau_2^{(c)} \tau_3^{(c)} (h_1 a_1 + h_2 a_2 + h_3 a_3)$
$A_N^{(3)}$	0	$\tau_1^{(c)} \tau_2^{(c)}$	$\tau_1^{(c)} \tau_2^{(c)} + \begin{bmatrix} \tau_1^{(c)} \tau_3^{(c)} + \tau_2^{(c)} \tau_3^{(c)} \\ + \tau_1^{(c)} \tau_2^{(c)} \tau_3^{(c)} (a_1 + a_2 + a_3) \end{bmatrix}$ $= \tau_1^{(c)} \tau_2^{(c)} \left(1 + \tau_3^{(c)} a_3\right)$ $+ \tau_1^{(c)} \tau_3^{(c)} \left(1 + \tau_2^{(c)} a_2\right)$ $+ \tau_2^{(c)} \tau_3^{(c)} \left(1 + \tau_1^{(c)} a_1\right)$
$A_N^{(4)}$	0	0	$\tau_1^{(c)} \tau_2^{(c)} \tau_3^{(c)}$
$B_N^{(1)}$	$\tau_1^{(c)}$	$\tau_1^{(c)} + \tau_2^{(c)}$	$\tau_1^{(c)} + \tau_2^{(c)} + \tau_3^{(c)}$
$B_N^{(2)}$	0	$\tau_1^{(c)} \tau_2^{(c)}$	$\tau_1^{(c)} \tau_2^{(c)} + \tau_1^{(c)} \tau_3^{(c)} + \tau_2^{(c)} \tau_3^{(c)}$
$B_N^{(3)}$	0	0	$\tau_1^{(c)} \tau_2^{(c)} \tau_3^{(c)}$

Table 5.A2 Coefficients $R_N^{(2)}$ and $R_N^{(3)}$ appearing in Eq. (5.45) for $N = 1$, 2 and 3.

	$N=1$	$N=2$	$N=3$
$R_N^{(2)}$	$\tau_1^{(c)}$	$\tau_1^{(c)}[\varepsilon + f_2(1-\varepsilon)]$ $+ \tau_2^{(c)}[\varepsilon + f_1(1-\varepsilon)]$	$\tau_1^{(c)}[\varepsilon + f_2(1-\varepsilon) + f_3(1-\varepsilon)]$ $+ \tau_2^{(c)}[\varepsilon + f_1(1-\varepsilon) + f_3(1-\varepsilon)]$ $+ \tau_3^{(c)}[\varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon)]$
$R_N^{(3)}$	0	$\tau_1^{(c)}\tau_2^{(c)}$	$\tau_1^{(c)}\tau_2^{(c)}[\varepsilon + f_3(1-\varepsilon)]$ $+ \tau_1^{(c)}\tau_3^{(c)}[\varepsilon + f_2(1-\varepsilon)]$ $+ \tau_2^{(c)}\tau_3^{(c)}[\varepsilon + f_1(1-\varepsilon)]$

5.B Appendix B

Substitution of Eq. (5.64a) in Eq. (5.73) yields

$$b_n = -\frac{P_1}{N_n}\underbrace{\int_0^L X_n(x')dx'}_{I_{1n}} + \frac{P_2}{N_nL}\underbrace{\int_0^L x'X_n(x')dx'}_{I_{2n}} = -\frac{P_1}{N_n}I_{1n} + \frac{P_2}{N_nL}I_{2n} \tag{5.B1}$$

Now, by substituting Eq. (5.69) in the above two integrals, it results in

$$\begin{aligned} I_{1n} &= \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}\int_0^L \cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' + \frac{K_0}{D_{eff}}\int_0^L \sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' \\ &= \sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right) + K_0\sqrt{\frac{\varepsilon}{\gamma_n D_{eff}}}\cdot\left[1 - \cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right)\right] \end{aligned} \tag{5.B2}$$

$$\begin{aligned} I_{2n} &= \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}\underbrace{\int_0^L x'\cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx'}_{I_{2n,c}} + \frac{K_0}{D_{eff}}\underbrace{\int_0^L x'\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx'}_{I_{2n,s}} \\ &= \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}I_{2n,c} + \frac{K_0}{D_{eff}}I_{2n,s} \end{aligned} \tag{5.B3}$$

where

$$I_{2n,c} = \int_0^L x'\cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' = \frac{\varepsilon D_{eff}}{\gamma_n}\left[\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right) + \cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right) - 1\right] \tag{5.B4a}$$

$$I_{2n,s} = \int_0^L x'\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' = \frac{\varepsilon D_{eff}}{\gamma_n}\left[\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right) - \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right)\right] \tag{5.B4b}$$

If $K_0 \to \infty$, Eqs. (5.B2) and (5.B3) reduce, respectively, to

$$I_{1n} = \int_0^L \sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' = \sqrt{\frac{\varepsilon D_{eff}}{\gamma_n}}\left[1 - \cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right)\right] \tag{5.B5}$$

$$I_{2n} = \int_0^L x' \sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}x'\right)dx' = \frac{\varepsilon D_{eff}}{\gamma_n}\left[\sin\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right) - \sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\cos\left(\sqrt{\frac{\gamma_n}{\varepsilon D_{eff}}}L\right)\right] \tag{5.B6}$$

5.C Appendix C

Eqs (5.58a) and (5.58b) are here rewritten for convenience as

$$\begin{aligned}\tau_{EC}^{(j)} = R_3^{(2)} = \tau_1^{(c)}\underbrace{[\varepsilon + f_2(1-\varepsilon) + f_3(1-\varepsilon)]}_{=\alpha_1} + \tau_2^{(c)}\underbrace{[\varepsilon + f_1(1-\varepsilon) + f_3(1-\varepsilon)]}_{=\alpha_2} \\ + \tau_3^{(c)}\underbrace{[\varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon)]}_{=\alpha_3}\end{aligned} \tag{5.C1}$$

$$\tau_{EC}^{(c)} = B_3^{(1)} = \tau_1^{(c)} + \tau_2^{(c)} + \tau_3^{(c)} \tag{5.C2}$$

where the quantities α_1, α_2, and α_3 are less than one as shown below

$$\begin{aligned}\alpha_1 &= \varepsilon + f_2(1-\varepsilon) + f_3(1-\varepsilon) < \varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon) + f_3(1-\varepsilon) \\ &= \varepsilon + (1-\varepsilon)\underbrace{(f_1 + f_2 + f_3)}_{=1} = \varepsilon + (1-\varepsilon) = 1\end{aligned} \tag{5.C3a}$$

$$\begin{aligned}\alpha_2 &= \varepsilon + f_1(1-\varepsilon) + f_3(1-\varepsilon) < \varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon) + f_3(1-\varepsilon) \\ &= \varepsilon + (1-\varepsilon)\underbrace{(f_1 + f_2 + f_3)}_{=1} = \varepsilon + (1-\varepsilon) = 1\end{aligned} \tag{5.C3b}$$

$$\begin{aligned}\alpha_3 &= \varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon) < \varepsilon + f_1(1-\varepsilon) + f_2(1-\varepsilon) + f_3(1-\varepsilon) \\ &= \varepsilon + (1-\varepsilon)\underbrace{(f_1 + f_2 + f_3)}_{=1} = \varepsilon + (1-\varepsilon) = 1\end{aligned} \tag{5.C3c}$$

Therefore, the ratio $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}$ results in

$$\frac{\tilde{\tau}_{EC}^{(c)}}{\tilde{\tau}_{EC}^{(j)}} = \frac{\tau_1^{(c)} + \tau_2^{(c)} + \tau_3^{(c)}}{\alpha_1\tau_1^{(c)} + \alpha_2\tau_2^{(c)} + \alpha_3\tau_3^{(c)}}, \tag{5.C4}$$

that is always greater than 1, as α_1, α_2, $\alpha_3 < 1$.

5.D Appendix D

The most critical exponential appearing in Eq. (5.90) is the one having the following quantity within its argument

$$\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)-\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}=\tilde{\gamma}_n^2\left[\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}+\frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}-\sqrt{\left(\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}+\frac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}\right)^2-\frac{1}{\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}}\right] \tag{5.D1}$$

It depends on four parameters, namely $\tilde{\tau}_{EC}^{(c)}$, $\tilde{\tau}_{EC}^{(j)}$, Bi_0 and Bi_L, as $\tilde{\gamma}_n=\tilde{\gamma}_n(\mathrm{Bi}_0,\mathrm{Bi}_\mathrm{L})$. Then, valuable insight of Eq. (5.D1) when $n\to\infty$ can be obtained through a numerical investigation. For this purpose, Eq. (5.D1) has been plotted as a function of the eigenvalue $\tilde{\gamma}_n$ with $\tilde{\tau}_{EC}^{(c)}$ as a parameter and for different values of the ratio $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}$. In particular, Fig. 5.D1 shows the results obtained for $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}=1.5$. But similar curves can be obtained for any value of the ratio $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}>1$.

Fig. 5.D1 proves that $\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)-\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\right]\to 1/\tilde{\tau}_{EC}^{(c)}$ for $n\to\infty$. Therefore, the first series appearing on the RHS of Eq. (5.90) exhibits an algebraic convergence. A convergence criterion for it can be defined, in a conservative way, by considering the following companion summation:

$$\sum_{n=1}^{\infty}\frac{\tilde{\gamma}_n^2-\tilde{\beta}_n}{\tilde{\gamma}_n\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}e^{-\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)-\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\right]\tilde{t}} \tag{5.D2}$$

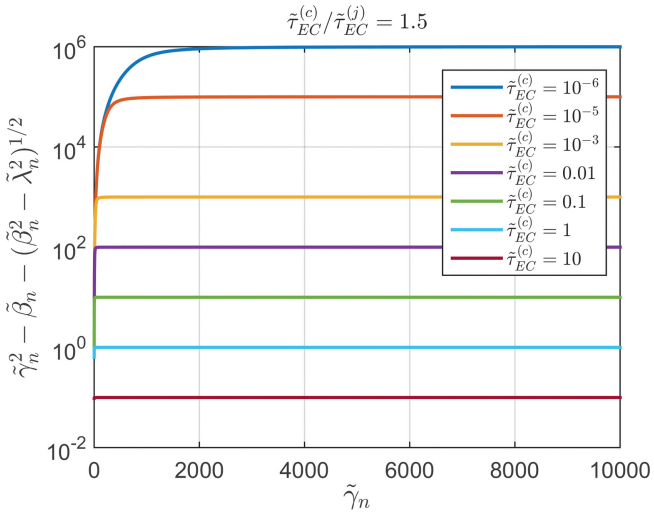

FIG. 5.D1

Exponential argument vs. the dimensionless eigenvalue for $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}=1.5$.

The above summation has been obtained by splitting up the first series of Eq. (5.90) into simpler series and by finding among them the one exhibiting the slowest convergence. Also, in Eq. (5.D2) the trigonometric functions have been dropped, as they are always (in absolute value) less than or equal to 1.

Then, bearing in mind Eq. (5.87e), the constant $\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)/\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}$ appearing in Eq. (5.D2) can be rewritten, after some algebra, as

$$\frac{\tilde{\gamma}_n^2 - \tilde{\beta}_n}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} = \frac{\dfrac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} + \dfrac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}}{\sqrt{\left(\dfrac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} + \dfrac{1}{2\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}\right)^2 - \dfrac{1}{\tilde{\gamma}_n^2\tilde{\tau}_{EC}^{(j)}}}} \tag{5.D3}$$

As $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)} > 1$, the ratio given by Eq. (5.D3) is in general greater than 1. In fact, the denominator of Eq. (5.D3) is less than the numerator. By a numerical investigation, it has been proven that it has a maximum when $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}$ is close to 1, that is in the neighborhood of the zero of $\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}$ that occurs for $\tilde{\gamma}_n = \left(1/\tilde{\tau}_{EC}^{(c)}\right)^{1/2}$. Also, after this maximum it approaches the unit when n increases.

In detail, the constant $\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)/\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}$ is less than 50 when $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)} = 1.001$ and $n \geq 2$. As this value would lead to a very conservative criterion, it is convenient to consider more terms in order to reduce such a constant. In particular, for $n \geq 131$ and $\tilde{\tau}_{EC}^{(c)} \geq 10^{-5}$ it is always less than 5. In addition, by means of numerical investigation, it has been proven that the argument $\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}$ is less than or equal to $\frac{1}{\tilde{\tau}_{EC}^{(c)}}$ when $\tilde{\tau}_{EC}^{(c)} \geq 10^{-3}$; and it is greater than 1000 when $\tilde{\tau}_{EC}^{(c)} < 10^{-3}$. In other words,

$$e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}} \leq \begin{cases} \exp\left(-10^3\tilde{t}\right) & \text{for} \quad \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \exp\left(-\dfrac{1}{\tilde{\tau}_{EC}^{(c)}}\tilde{t}\right) & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-3} \end{cases} \tag{5.D4}$$

Then, by using these findings, for $n \geq 131$ it results in

$$\frac{1}{\tilde{\gamma}_n}\frac{\tilde{\gamma}_n^2 - \tilde{\beta}_n}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}} \leq \begin{cases} \dfrac{5\,e^{-1000\tilde{t}}}{(n-1)\pi} & \text{for} \quad 10^{-5} \leq \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \dfrac{5\,e^{-\frac{1}{\tilde{\tau}_{EC}^{(c)}}\tilde{t}}}{(n-1)\pi} & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-3} \end{cases} \tag{5.D5}$$

where $(n-1)\pi$ has been used as a very conservative estimate of the n-th eigenvalue $\tilde{\gamma}_n$.

5.D.1 Convergence criteria

Then, a convergence criterion can be derived by setting the arguments appearing on the RHS of Eq. (5.D5) equal to 10^{-A} (with $A = 2,3, \ldots 15$). Behaving like this, the maximum number of required

terms to obtain a truncation error less than 10^{-A} for the series of Eq. (5.D2) may be taken in a conservative way as

$$N_{S_{EC}^{(1)}} = \begin{cases} \max\left[131;\, 1 + \text{ceil}\left(\dfrac{5\,e^{-1000\,\tilde{t}}}{10^{-A}\pi}\right)\right] & \text{for} \quad 10^{-5} \le \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \max\left[131;\, 1 + \text{ceil}\left(\dfrac{5\,e^{-\frac{1}{\tilde{\tau}_{EC}^{(c)}}\tilde{t}}}{10^{-A}\pi}\right)\right] & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \ge 10^{-3} \end{cases} \tag{5.D6}$$

As regards the second summation on the RHS of Eq. (5.90), that exhibits a "true" exponential convergence, the maximum number of required terms can be defined using the following companion and conservative series:

$$\sum_{n=1}^{\infty} \frac{\tilde{\gamma}_n^2 - \tilde{\beta}_n}{\tilde{\gamma}_n \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}} \tag{5.D7}$$

To define a convergence criterion for the above series, some attention should be paid on the exponential term. In fact, in the exponential argument the eigenvalue $\tilde{\gamma}_n$ appears both outside and inside a square root, as shown by Eq. (5.91a) (for the plus sign). For this reason, it is convenient to use a conservative value for this argument. It can be obtained by noting that the term $\sqrt{\beta_n^2 - \lambda_n^2}$ appearing in Eq. (5.87a) is always real. Therefore,

$$\tilde{\gamma}_n^2 - \tilde{\beta}_n + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} \;>\; \tilde{\gamma}_n^2 \frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}} \tag{5.D8}$$

Using this upper limit and the considerations discussed above, in a conservative way (for $n \ge 2$) it follows

$$\frac{1}{\tilde{\gamma}_n} \frac{\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right]\tilde{t}} < \frac{50}{\pi} \exp\left[-\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}(n-1)^2\pi^2\tilde{t}\right] \tag{5.D9}$$

where $(n-1)\pi$ has been used as a conservative estimate of the n-th eigenvalue.

Then, by setting the RHS of Eq. (5.D9) equal to 10^{-A}, the maximum number of required terms for the exponentially-convergent series may be taken as

$$N_{S_{EC}^{(2)}} = 1 + \text{ceil}\left[\frac{1}{\pi}\sqrt{\frac{A\ln(10) + \ln\left(\frac{50}{\pi}\right)}{\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}\tilde{t}}}\right], \tag{5.D10}$$

and depends on the ratio $\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)}$.

The maximum number of required terms defined through Eqs. (5.D6) and (5.D10) are now computed for different A and $\tilde{\tau}_{EC}^{(c)}$ values and shown in Table 5.D1.

As shown in Table 5.D1, when accurate numerical values are desired, the number of required terms for computing the first series of Eq. (5.90) can be extremely large.

Table 5.D1 Maximum number of required terms to compute the two series of Eq. (5.90) for different accuracies 10^{-A} and $\tilde{\tau}_{EC}^{(c)}$ values ($\tilde{t}$=0.1).

	$N_{S_{EC}^{(1)}}$—Eq. (5.D6)			$N_{S_{EC}^{(2)}}$—Eq. (5.D10) $(\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)} = 2)$		
$\tilde{\tau}_{EC}^{(c)}$	$A=2$	$A=4$	$A=6$	$A=2$	$A=4$	$A=6$
10^{-4}	131	131	131	4	5	6
10^{-3}	131	131	131	4	5	6
0.01	131	131	131	4	5	6
0.1	131	5856	585500	4	5	6
0.5	132	13032	1303052	4	5	6
1	146	14402	1440095	4	5	6
1.5	150	14891	1488907	4	5	6
2	153	15141	1513930	4	5	6
5	158	15602	1560036	4	5	6
10	159	15759	1575715	4	5	6
100	160	15901	1589960	4	5	6
1000	161	15915	1591392	4	5	6

5.E Appendix E

Consider the first two series of Eq. (5.93) exhibiting an algebraic convergence. A convergence criterion can be fixed by analyzing the following associate conservative summation

$$\sum_{n=1}^{\infty} \frac{1}{\tilde{\gamma}_n} \frac{\tilde{\gamma}_n^2 - \tilde{\beta}_n}{\sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}} \frac{e^{-\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2}\right] \tilde{t}}}{\left[\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \frac{1}{\tilde{\tau}_k^{(c)}}\right]} \tag{5.E1}$$

By using the results of Section 5.D (Appendix D), it is found that

$$\lim_{n\to\infty} \left(\tilde{\gamma}_n^2 - \tilde{\beta}_n - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \frac{1}{\tilde{\tau}_k^{(c)}} \right) = \frac{1}{\tilde{\tau}_{EC}^{(c)}} - \frac{1}{\tilde{\tau}_k^{(c)}} \tag{5.E2}$$

where $\tilde{\tau}_{EC}^{(c)} > \tilde{\tau}_k^{(c)}$ (with $k = 1, 2, N = 3$) due to Eq. (5.58b). Also, a lower limit for this quantity can be defined as

$$\tilde{\gamma}_n^2 - \tilde{\beta}_n - \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - \frac{1}{\tilde{\tau}_k^{(c)}} \geq \begin{cases} 10^3 - \dfrac{1}{\tilde{\tau}_k^{(c)}} & \text{for} \quad \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \dfrac{\left|\tilde{\tau}_k^{(c)} - \tilde{\tau}_{EC}^{(c)}\right|}{\tilde{\tau}_{EC}^{(c)} \tilde{\tau}_k^{(c)}} & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-3} \end{cases} \tag{5.E3}$$

By following the same procedure used in Section 5.D (Appendix D), for $n \geq 131$ it results in

$$\frac{1}{\tilde{\gamma}_n}\frac{\tilde{\gamma}_n^2-\tilde{\beta}_n}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\frac{e^{-\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)-\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\right]\tilde{t}}}{\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)-\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}\right]} \leq \begin{cases} \dfrac{\tilde{\tau}_k^{(c)}}{\left|10^3\,\tilde{\tau}_k^{(c)}-1\right|}\dfrac{5\,e^{-1000\,\tilde{t}}}{(n-1)\pi} & \text{for} \quad 10^{-5} \leq \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \dfrac{\tilde{\tau}_{EC}^{(c)}\tilde{\tau}_k^{(c)}}{\left|\tilde{\tau}_k^{(c)}-\tilde{\tau}_{EC}^{(c)}\right|}\dfrac{5\,e^{-\frac{1}{\tilde{\tau}_{EC}^{(c)}}\tilde{t}}}{(n-1)\pi} & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-3} \end{cases} \tag{5.E4}$$

where $(n-1)\pi$ has been used as conservative estimate of the n-th eigenvalue.

5.E.1 Convergence criteria

By setting the arguments appearing on the RHS of Eq. (5.E4) equal to 10^{-A} (with $A = 2,3,\ldots 15$), the maximum number of required terms to obtain a truncation error less than 10^{-A} for the first two series of Eq. (5.93) may be taken in a conservative way as

$$N_{S_k^{(1)}} = N_{S_k^{(2)}} = \begin{cases} \max\left[131;\ 1+\text{ceil}\left(\dfrac{\tilde{\tau}_k^{(c)}}{\left|10^3\,\tilde{\tau}_k^{(c)}-1\right|}\dfrac{5\,e^{-1000\,\tilde{t}}}{10^{-A}\pi}\right)\right] & \text{for} \quad 10^{-5} \leq \tilde{\tau}_{EC}^{(c)} < 10^{-3} \\ \max\left[131;\ 1+\text{ceil}\left(\dfrac{\tilde{\tau}_{EC}^{(c)}\tilde{\tau}_k^{(c)}}{\left|\tilde{\tau}_k^{(c)}-\tilde{\tau}_{EC}^{(c)}\right|}\dfrac{5\,e^{-\frac{1}{\tilde{\tau}_{EC}^{(c)}}\tilde{t}}}{10^{-A}\pi}\right)\right] & \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-3} \end{cases} \tag{5.E5}$$

Consider now the third summation appearing in Eq. (5.93) exhibiting an algebraic convergence as well. A convergence criterion can be obtained through the following companion conservative series:

$$\sum_{n=1}^{\infty}\frac{1}{\tilde{\gamma}_n}\frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\frac{1}{\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}\right]} \tag{5.E6a}$$

where the quantity $\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}\right]$ appearing in the denominator of the above equation vanishes for $\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}=\frac{1}{\tilde{\tau}_k^{(c)}}$ and then, it increases monotonically with n. By means of a numerical investigation, it has been shown that, for any $\tilde{\tau}_k^{(c)} \leq \tilde{\tau}_{EC}^{(c)}$, the above quantity is greater than 2 when the following constraint is verified

$$n \geq 1+\text{ceil}\left[\frac{2}{\pi}\sqrt{\frac{\left(1+\tilde{\tau}_k^{(c)}\right)\tilde{\tau}_{EC}^{(j)}}{\tilde{\tau}_k^{(c)}\tilde{\tau}_{EC}^{(c)}}}\right]. \tag{5.E6b}$$

Then, similarly to what was done for the previous case, it is found that

$$\frac{1}{\tilde{\gamma}_n}\frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\frac{e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}} \leq \frac{5e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}}{2(n-1)\pi} \quad \text{for} \quad n \geq n_1^{(k)} \quad \text{and} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-5} \tag{5.E7}$$

where $(n-1)\pi$ has been used as conservative estimate of the n-th eigenvalue, and

$$n_1^{(k)} = \max\left\{130; 1+\text{ceil}\left[\frac{2}{\pi}\sqrt{\frac{\left(1+\tilde{\tau}_k^{(c)}\right)\tilde{\tau}_{EC}^{(j)}}{\tilde{\tau}_k^{(c)}\tilde{\tau}_{EC}^{(c)}}}\right]\right\} \tag{5.E8}$$

Therefore, by setting the RHS of Eq. (5.E7) equal to 10^{-A}, the maximum number of required terms for the third series appearing in Eq. (5.93) may be taken as

$$N_{S_k^{(3)}} = \max\left\{1+n_1^{(k)}; 1+\text{ceil}\left[\frac{5e^{-\frac{\tilde{t}}{\tilde{\tau}_k^{(c)}}}}{10^{-A}2\pi}\right]\right\} \quad \text{for} \quad \tilde{\tau}_{EC}^{(c)} \geq 10^{-5} \tag{5.E9}$$

A convergence criterion for the last series of Eq. (5.93) which exhibits a "true" exponential convergence can be defined through the following related conservative summation

$$\sum_{n=1}^{\infty}\frac{1}{\tilde{\gamma}_n}\frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\frac{e^{-\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\right]\tilde{t}}}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}} \tag{5.E10}$$

By the same argumentations used above and bearing in mind Eq. (5.D8), it follows in a conservative way

$$\frac{1}{\tilde{\gamma}_n}\frac{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)}{\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}}\frac{e^{-\left[\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}\right]\tilde{t}}}{\left(\tilde{\gamma}_n^2-\tilde{\beta}_n\right)+\sqrt{\tilde{\beta}_n^2-\tilde{\lambda}_n^2}-\frac{1}{\tilde{\tau}_k^{(c)}}} < \frac{50}{2\pi}e^{-\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}(n-1)^2\pi^2\tilde{t}} \quad \text{for } n \geq n_2^{(k)} \tag{5.E11}$$

where $(n-1)\pi$ has again been used as a conservative estimate of the n-th eigenvalue, and

$$n_2^{(k)} = 1+\text{ceil}\left[\frac{2}{\pi}\sqrt{\frac{\left(1+\tilde{\tau}_k^{(c)}\right)\tilde{\tau}_{EC}^{(j)}}{\tilde{\tau}_k^{(c)}\tilde{\tau}_{EC}^{(c)}}}\right] \tag{5.E12}$$

Then, by setting the RHS of Eq. (5.E11) equal to 10^{-A}, the maximum number of required terms may be taken as

Table 5.E1 Maximum number of required terms to compute the four series of Eq. (5.93) for different accuracies and $\tilde{\tau}_{EC}^{(c)}$ values (when $\tilde{t} = 0.1$ and $\tilde{\tau}_k^{(c)} = \tilde{\tau}_{EC}^{(c)}/100$).

	$N_{S_k^{(1)}} = N_{S_k^{(2)}}$—Eq. (5.E5)			$N_{S_k^{(3)}}$—Eq. (5.E9) $(\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)} = 2)$			$N_{S_k^{(4)}}$—Eq. (5.E13) $(\tilde{\tau}_{EC}^{(c)}/\tilde{\tau}_{EC}^{(j)} = 2)$		
$\tilde{\tau}_{EC}^{(c)}$	$A = 2$	$A = 4$	$A = 6$	$A = 2$	$A = 4$	$A = 6$	$A = 2$	$A = 4$	$A = 6$
10^{-4}	131	131	131	453	453	453	453	453	453
10^{-3}	131	131	131	145	145	145	145	145	145
0.01	131	131	131	131	131	131	48	48	48
0.1	131	131	593	131	131	131	17	17	17
0.5	131	131	6583	131	131	131	9	9	9
1	131	147	14548	131	131	131	7	7	7
1.5	131	227	22561	131	131	1014	6	6	6
2	131	307	30586	131	131	5363	6	6	6
5	131	789	78791	131	1078	107698	5	5	6
10	131	1593	159164	131	2929	292751	4	5	6
100	162	16062	1606020	131	7202	720048	4	5	6
1000	1609	160748	16074651	131	7880	787858	4	5	6

$$N_{S_k^{(4)}} = \max\left\{1 + n_2^{(k)}; 1 + \text{ceil}\left[\frac{1}{\pi}\sqrt{\frac{A\ln(10) + \ln\left(\frac{25}{\pi}\right)}{\frac{\tilde{\tau}_{EC}^{(c)}}{2\tilde{\tau}_{EC}^{(j)}}\tilde{t}}}\right]\right\} \tag{5.E13}$$

The maximum number of terms defined above are now computed for different A and $\tilde{\tau}_{EC}^{(c)}$ values at $\tilde{\tau} = 0.1$ and the results shown in Table 5.E1.

As shown in Table 5.E1, the first two series of Eq. (5.93) can require a number of terms extremely large when accurate numerical values are desired. Also, even if the fourth series of Eq. (5.93) exhibits an exponential convergence, its computation may require a large number of terms for small values of $\tilde{\tau}_{EC}^{(c)}$ (and $\tilde{\tau}_k^{(c)}$) as, in such a case, according to Eq. (5.E6b) the quantity $\left(\tilde{\gamma}_n^2 - \tilde{\beta}_n\right) + \sqrt{\tilde{\beta}_n^2 - \tilde{\lambda}_n^2} - 1/\tilde{\tau}_k^{(c)}$ requires many terms to be greater than 2.

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