

Diffusion in a Cellular Medium: A (1+1)-Dimensional Model

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Abstract

We consider the diffusion of a material in a one-dimensional medium consisting of a large number of cells separated from the extracellular space by permeable membranes. The extracellular space is completely connected and allows unrestricted diffusion of the material. Furthermore, the material can diffuse within a given cell, i.e., the intracellular space; however, direct diffusion from one cell to another cell cannot occur. There is a movement of material across the permeable membranes between the intra- and extracellular spaces. Material from one cell can cross the permeable membrane into the extracellular space, diffuse through the extracellular space, and eventually enter the intracellular space of a second cell. Here we develop a simple set of model equations to describe this phenomenon and obtain the solutions using an eigenfunction expansion. We show that the solutions obtained using this method are particularly convenient for interpreting data from experiments that use techniques from Nuclear Magnetic Resonance Imaging.

1 Introduction

In this paper, we present a model for restricted diffusion in a medium with permeable interfaces. An example in a biological setting is the diffusion of oxygen and water molecules in living tissue [3]. In this case, the cell boundaries can be treated as interfaces permeable to these molecules. Similar systems arise under a variety of circumstances, e.g., in thermal contact problems [6].

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Imaging techniques based on nuclear magnetic resonance (NMR) are useful tools for obtaining structural information about the medium. In this case, it is essential to have a detailed understanding of the diffusive characteristics through the medium. An important characteristic of diffusion in living tissue is the proximity of the intra- and extracellular spaces. Determining the bulk diffusive properties of a cellular medium requires an understanding of how material diffuses through the intra- and extracellular spaces coupled with how material pass through the cell membranes that separate the intra- and extracellular spaces.

Tanner [9] considered a simple one-dimensional model that neglected the extracellular space and contained only the intracellular space. All cells had equal length and were separated by an array of permeable barriers that allowed material to pass from one cell to its neighbor. He used an eigenfunction expansion method and derived the general solution for diffusion in this system. He then used the solution to understand how ‘spin-echo attenuation’ measurements in NMR experiments were related to the spacing and permeability of the barriers. The solution method that he derived is highly efficient in determining the suitably averaged spin-echo attenuation data that are pertinent for NMR. The approach used by Tanner provides a simple model for diffusion in a cellular system. By simplifying the highly complicated geometry in a natural way, the model allows significant analytic progress to be made for the problem of diffusion restricted by barriers. It has therefore proven to be highly influential and has been studied and used by a number of authors.

An approximate expression for the spin-echo attenuation was obtained by von Meerwall & Ferguson [12]. This expression is sufficiently simple to be used by nonlinear curve fitting programs. Rather than using the eigenfunction expansion adopted by Tanner, Powles *et al.* [8] used a Green’s function approach. They showed how their method could be modified to deal with situations in which the lengths of all the cells are not equal. Dudko *et al.* [2] determined an exact expression for the Laplace transform of a suitably defined time-dependent diffusion coefficient. Kuchel & Durrant [4] also considered a generalization of Tanner’s problem with uneven cell lengths. They considered the ‘inverse problem’ in which one must estimate the permeability of the membrane given the spin-echo attenuation measurements. Kuchel *et al.* [5] determined a postprocessing technique for the inverse problem that is highly robust. The problem of diffusion between concentric cylindrical compartments separated by permeable barriers was considered by van der Weerd *et al.* [11].

A feature of cellular systems that is neglected in Tanner’s model is that a cellular medium generally contains a significant fraction of extracellular space. For material to diffuse from a given location in one cell to a given location in another cell, it first must diffuse to the cell membrane, pass through this membrane, diffuse through the extracellular space, pass through the membrane of the second cell, and finally diffuse within the second cell. Of course, the material could enter and leave several cells before finally ending up in the specific second cell. Unlike the intracellular space, the extracellular space is connected and particles can diffuse between points in the extracellular space without having

to pass through any cell membranes. This can clearly have important consequences for diffusive transport. Furthermore, we assume that material mass is conserved.

In this paper, we consider a model that includes the effects of the extracellular space, but still takes advantage of a geometric simplification similar to that used by Tanner. By using an eigenfunction expansion, we derive the solutions for diffusive spreading in a medium with intra- and extracellular compartments. We also show that spin-echo attenuation data can be computed in a highly efficient manner and show how the presence of extracellular space affects the data.

2 Model

We consider diffusion of a substance in a composite medium with two distinct phases. Linear diffusion occurs in each phase with (possibly) different diffusion coefficients. One of the phases is completely connected and the other is composed of a large number of disconnected regions. We will refer to the disconnected regions as the intracellular space and the connected region as the extracellular space. The boundaries between the intra- and extracellular spaces are permeable and admit a flux that depends on the difference between the concentrations on the two sides of the boundary.

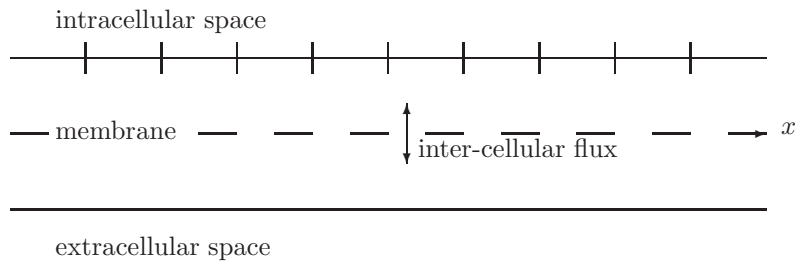


Figure 1: Schematic of the (1+1)-dimensional model. The intra- and extracellular regions are modelled as overlapping one-dimensional regions embedded in the same space. Fluxes across the cell membranes are modelled as locally conservative transfers of material between the intra- and extracellular regions. The intracellular space is partitioned into a linear array of adjacent cells separated by impermeable barriers that do not allow direct cell-to-cell diffusion.

The two main characteristics of this system are: (i) since the intracellular space is not connected, material cannot directly diffuse from one cell to another. In order for material to move between two cells, it must diffuse through the extracellular space; and (ii) since the extracellular space is connected, material can diffuse from one point in the extracellular to another point either by directly

diffusing through the extracellular space or by making excursions into the intracellular space along the way. When material passes through the interface between the intracellular space and extracellular space, the mass of material is conserved. That is, there are no sources or sinks of mass associated with the interface.

Since the number of cells one needs to consider is enormous, it is computationally intensive to solve the diffusion problem. In fact, we are only interested in averaged quantities instead of any detailed knowledge of geometry of the cells. Therefore, we consider a simplified two-compartment model that retains the two main characteristics described above, but neglects the details of the geometry (see Figure 1). The intracellular space is represented by a one-dimensional array of uniformly spaced cells separated by impermeable barriers. The extracellular space contains no barriers and fills the entire space. We assume that the intracellular space occupies a fraction ν of the total volume and the extracellular space occupies the remaining $1 - \nu$ fraction. There is a local mass flux through the membrane separating the two compartments that is a function of the two concentrations.

The dimensionless equations are given by

$$u_t = u_{xx} + \frac{f(u, v)}{\nu}, \quad x \in (2j - 1, 2j + 1), \quad j = 0, \pm 1, \dots, \quad (1)$$

$$v_t = Dv_{xx} - \frac{f(u, v)}{1 - \nu}, \quad x \in \mathfrak{R}, \quad (2)$$

where t is the time, x is the spatial variable, u and v are the dimensionless intra- and extracellular concentrations, respectively, and D is the ratio of the diffusion coefficients. The function $f(u, v)$ represents the dimensionless flux between the intra- and extracellular spaces. These terms are normalized by the factors ν and $1 - \nu$ to ensure that the total mass of material is conserved. Here we have non-dimensionalized the spatial variable by the half-length of the periodic cells, time by the diffusive time scale for the intracellular space, and u and v by the initial concentrations. Similar equations have been derived for ionic diffusion in the context of cortical spreading depression (CSD) [7, 10] and for other applications [13, 14]. The above model can be considered as a simplified or idealized version of the equations that model CSD. At the locations $x = 2j + 1$, there is no flux of material from one cell to another and so u satisfies

$$\frac{\partial u}{\partial x} = 0. \quad (3)$$

We will consider a local mass flux term $f(u, v)$ with the property that the flux is zero when the concentrations are equal. We will further simplify the problem by assuming that f is a linear function of u and v . In this case, we obtain

$$u_t = u_{xx} + \frac{p}{\nu}(v - u), \quad x \in (2j - 1, 2j + 1), \quad j = 0, \pm 1, \dots, \quad (4)$$

$$v_t = Dv_{xx} - \frac{p}{1 - \nu}(v - u), \quad x \in \mathfrak{R}, \quad (5)$$

where p can be considered as the dimensionless permeability of the cell boundary. For the initial conditions, we will assume that the initial mass is highly localized. The problem can be solved by taking a linear combination of the solutions for the following two initial conditions:

$$u(x, 0) = \delta(x - x_0), \quad v(x, 0) = 0, \quad (6)$$

and

$$u(x, 0) = 0, \quad v(x, 0) = \delta(x - x_0) \quad (7)$$

where $\delta(x - x_0)$ is the Dirac delta function centered at $x = x_0$. We assume that the delta functions are applied at the same point, x_0 .

3 Solution

The system is invariant under translations in x of length 2 and therefore, without loss of generality, we need only solve the problem for x_0 in the range $[-1, 1]$. Following the approach of Tanner [9], we can approximate the infinite domain problem by solving the problem on a large finite domain $[-N, N]$. Here N must be chosen to be sufficiently large so that for the longest times under consideration, there is negligible diffusion into the outermost cells.

We perform a straightforward eigenfunction expansion of the form

$$\begin{pmatrix} u(x, t; x_0) \\ v(x, t; x_0) \end{pmatrix} = \sum_{k=1}^{\infty} \alpha_k(x_0) \begin{pmatrix} u_k(x) \\ v_k(x) \end{pmatrix} e^{-\beta_k^2 t} \quad (8)$$

where β_k and $(u_k(x), v_k(x))^T$ are the eigenvalues and associated eigenvectors, respectively. It can be shown that the resulting differential operator for $(u_k(x), v_k(x))^T$ is self-adjoint. As a result, the eigenvalues are real and the eigenvectors are orthogonal in the following sense

$$\int_{-2N-1}^{2N+1} [u_k(x)u_j(x) + v_k(x)v_j(x)] dx = \delta_{kj} \int_{-2N-1}^{2N+1} [u_k^2(x) + v_k^2(x)] dx. \quad (9)$$

Therefore, the coefficients $\alpha_k(x_0)$ can be determined by using the initial conditions. For the initial condition $u(x, 0) = \delta(x - x_0)$ and $v(x, 0) = 0$, we obtain

$$\alpha_k(x_0) = \frac{u_k(x_0)}{\int_{-2N-1}^{2N+1} [u_k^2(x) + v_k^2(x)] dx}. \quad (10)$$

Whereas, for the initial condition $u(x, 0) = 0$ and $v(x, 0) = \delta(x - x_0)$, we obtain

$$\alpha_k(x_0) = \frac{v_k(x_0)}{\int_{-2N-1}^{2N+1} [u_k^2(x) + v_k^2(x)] dx}. \quad (11)$$

The eigenvectors can be determined by first solving the differential equations,

$$0 = u_k'' + \frac{p}{\nu}(v_k - u_k) + \beta_k^2 u_k, \quad (12)$$

$$0 = Dv_k'' - \frac{p}{1-\nu}(v_k - u_k) + \beta_k^2 v_k, \quad (13)$$

on each block $[2j - 1, 2j + 1]$. The eigenfunctions u_k must satisfy zero flux at the edges of each block, that is, $u'_k = 0$ at $x = 2j \pm 1$. Therefore, on each block $[2j - 1, 2j + 1]$, we obtain

$$u_k = a_{k,j}\psi_{k,j}(x) + b_{k,j}\phi_{k,j}(x) \quad (14)$$

where $a_{k,j}$ and $b_{k,j}$ are constants,

$$\begin{aligned} \psi_{k,j} &= [\lambda_k^{-1} \cosh(\mu_k) \sinh(\lambda_k(x - 2j)) \\ &\quad - \mu_k^{-1} \cosh(\lambda_k) \sinh(\mu_k(x - 2j))] I_{x \in [-2j-1, 2j+1]}, \end{aligned} \quad (15)$$

$$\begin{aligned} \phi_{k,j} &= [\mu_k \sinh(\mu_k) \cosh(\lambda_k(x - 2j)) \\ &\quad - \lambda_k \sinh(\lambda_k) \cosh(\mu_k(x - 2j))] I_{x \in [-2j-1, 2j+1]}, \end{aligned} \quad (16)$$

and

$$\lambda_k = \sqrt{\frac{1}{2D} \left[\frac{Dp}{\nu} + \frac{p}{1-\nu} - \beta_k^2(1+D) \right] + \frac{1}{2D} \sqrt{\Delta}}, \quad (17)$$

$$\mu_k = \sqrt{\frac{1}{2D} \left[\frac{Dp}{\nu} + \frac{p}{1-\nu} - \beta_k^2(1+D) \right] - \frac{1}{2D} \sqrt{\Delta}}, \quad (18)$$

$$\Delta = \left[\frac{Dp}{\nu} + \frac{p}{1-\nu} - \beta_k^2(1+D) \right]^2 + 4D\beta_k^2 \left[\frac{p}{\nu} + \frac{p}{1-\nu} - \beta_k^2 \right] \quad (19)$$

for $k = 1, \dots, \infty$ and $j = -N, \dots, N$.

The eigenfunctions also must have the property that v_k and its derivative are continuous at $x = 2j \pm 1$. We first assemble the solution for the entire domain by combining the solutions on each block to give

$$u_k(x) = \vec{w}_k \cdot \vec{U}_k(x), \quad v_k(x) = \left(1 - \frac{\nu}{p}(\beta_k^2 + \partial_x^2) \right) u_k(x) \quad (20)$$

where

$$\vec{U}_k(x) = \begin{pmatrix} \psi_{k,-N}(x) \\ \phi_{k,-N}(x) \\ \psi_{k,-N+1}(x) \\ \phi_{k,-N+1}(x) \\ \vdots \\ \psi_{k,N}(x) \\ \phi_{k,N}(x) \end{pmatrix}, \quad \vec{w}_k = \begin{pmatrix} a_{k,-N} \\ b_{k,-N} \\ a_{k,-N+1} \\ b_{k,-N+1} \\ \vdots \\ a_{k,N} \\ b_{k,N} \end{pmatrix}. \quad (21)$$

We now use the fact that v_k and its derivative are continuous at $x = 2j \pm 1$ to obtain a set of linear equations relating the components of w_k . In addition, following Tanner [9], we assume that there is a sink for v at the outermost faces of the domain $x = \pm(2N + 1)$. This results in a linear system for \vec{w}_k that we denote as

$$M(\beta_k)\vec{w}_k = 0 \quad (22)$$

where $M(\beta_k)$ is a $(2N + 2) \times (2N + 2)$ matrix. The eigenvalues β_k are given by solving $\det(M) = 0$ and the corresponding eigenvectors \vec{w}_k are given by the basis of the corresponding null space.

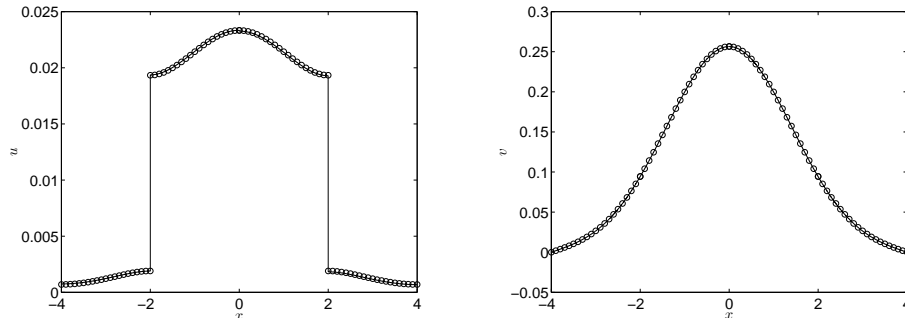


Figure 2: Solutions at $t = 1$ for $D = 0.5$ and $p = 0.05$ with $u(x, 0) = 0$ and $v(x, 0) = \delta(x)$. The solid lines represent analytical solutions while the numerical solutions are indicated by the circles. The cell boundaries are located at $x = 0, \pm 2, \pm 4, \dots$.

4 Numerical Comparisons

In this section, we compare the analytical solution obtained in the previous section with numerical solutions of the system using a finite-difference method.

In Figure 2, we have plotted the solutions at $t = 1$ for $p = 0.05$ and $D = 0.5$ with the initial conditions, $u(x, 0) = 0$ and $v(x, 0) = \delta(x)$. In Figure 3, we have plotted the solutions with the same parameters, but with the initial conditions, $u(x, 0) = \delta(x)$ and $v(x, 0) = 0$. It can be seen that the agreement between the analytical solution and the numerical solution is excellent. In Figure 4, we have plotted the solutions for $p = 1$ with an initial condition $v(x, 0) = \delta(x)$ at $t = 1, 2,$ and 5 . The results demonstrate the different characteristics of diffusive processes in the intra- and extracellular spaces.

5 Discussion

In spin-echo NMR experiments, the echo is attenuated by the application of pairs of external field gradient pulses [1]. It can be shown that the relevant quantity arising from such experiments is the relative echo height given in dimensionless form by the real component of

$$R(t) = \frac{1}{2} \int_{-1}^1 \int_{-\infty}^{\infty} \rho(x, t; x_0) e^{i\omega(x-x_0)} dx dx_0 \quad (23)$$

where ρ is the transitional probability density function for a particle initially at x_0 to arrive at location x at time t . Here $\omega = \gamma\delta GL$ where γ is the nuclear gyromagnetic ratio, δ is the duration between pulses, G is the magnitude of the gradient of the applied pulses, and L is the half-length of the cells. In the context of our model, we need to solve the equations (4)-(5) with initial

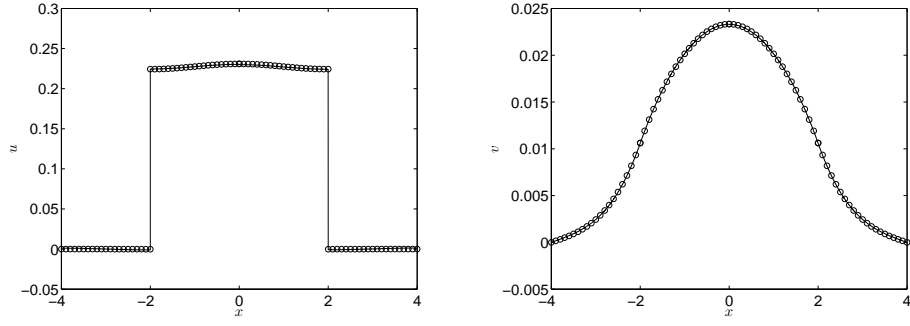


Figure 3: Solutions at $t = 1$ for $D = 0.5$ and $p = 0.05$ with $u(x, 0) = \delta(x)$ and $v(x, 0) = 0$. The solid lines represent analytical solutions while the numerical solutions are indicated by the circles. The cell boundaries are located at $x = 0, \pm 2, \pm 4, \dots$.

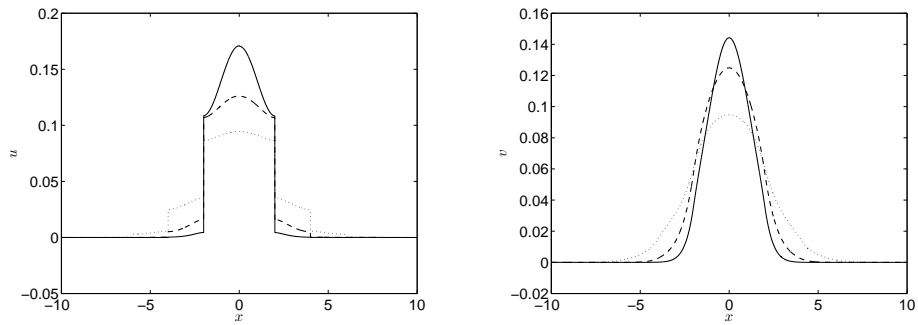


Figure 4: Solutions for $D = 0.5$ and $p = 1$ with $u(x, 0) = \delta(x)$ at $t = 1$ (solid), 2 (dashed) and 5 (dotted). Here the cell boundaries are located at $x = 0, \pm 2, \pm 4, \dots$.

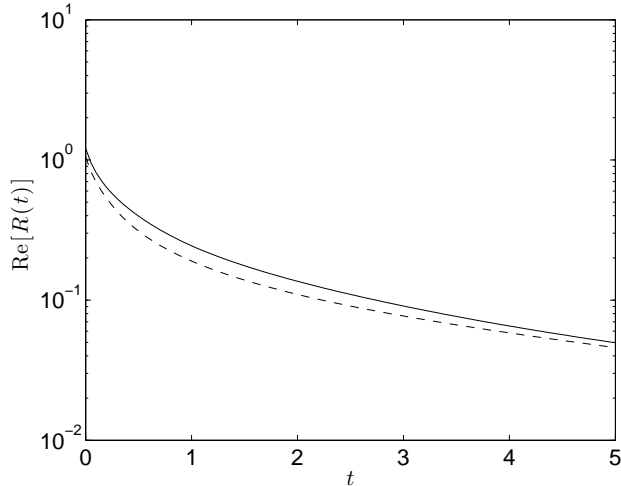


Figure 5: The real component of the relative spin echo height $R(t)$ as a function of time for parameter values $p = 1$ (solid) and $p = 5$ (dashed). The other parameter values are $D = 2$, $\nu = 0.5$, and $\omega = 1$.

conditions $u(x, 0; x_0) = \nu\delta(x - x_0)$ and $v(x, 0; x_0) = (1 - \nu)\delta(x - x_0)$. The transitional probability density ρ is then given by $\rho = u(x, t; x_0) + v(x, t; x_0)$. If the solution for ρ had been obtained by traditional numerical methods, such as finite differences, the evaluation of $R(t)$ would be computationally intensive since it would require solving for ρ for a large number of values of x_0 . However, using the solution obtained earlier, we can readily obtain the following expression

$$R(t) = \sum_{k=1}^{\infty} \frac{e^{-\beta_k^2 t}}{2I_k} \left(a_{k0} \hat{P}_k + b_{k0} \hat{Q}_k \right) \sum_{j=-N}^N (a_{kj} P_k + b_{kj} Q_k) e^{2ij\omega}, \quad (24)$$

$$I_k = E_k \sum_{j=-N}^N a_{kj}^2 + F_k \sum_{j=-N}^N b_{kj}^2. \quad (25)$$

Here the coefficients β_k , a_{kj} , and b_{kj} are obtained using the method described in Section 3. Other coefficients E_k , F_k , \hat{P}_k , \hat{Q}_k , P_k , and Q_k are integrals of exponential functions, given in the Appendix.

In Figure 5, we plot the real component of the relative spin echo height against time for two different values of the permeability p . The larger value of p allows material to move more easily between the intra- and extracellular spaces. The larger value of p , therefore, has a higher effective diffusivity. This is reflected by the smaller values of $R(t)$, as seen in the figure.

In summary, we have introduced a new model for diffusion in a space composed of a large number of disconnected cells surrounded by a completely connected extracellular space. We have determined an efficient method that uses

eigenfunction expansions to solve the diffusion problem. We have presented the solution method for the problem in which all cells have the same length, but our methodology can be generalized to arbitrary cell lengths in a straightforward way. We have compared the results from our method with those obtained by traditional finite difference methods and found good agreement. Finally, we have shown how the results of the method can be used to efficiently obtain values of the relative spin echo height that are appropriate for Nuclear Magnetic Resonance Imaging.

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6 Appendix

Coefficients for $R(t)$

$$\begin{aligned}
P_k &= \left(2 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p}\right) \lambda_k^{-1} \cosh(\mu_k) S(\lambda_k, \omega) \\
&\quad - \left(2 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p}\right) \mu_k^{-1} \cosh(\lambda_k) S(\mu_k, \omega),
\end{aligned} \tag{26}$$

$$\begin{aligned}
Q_k &= \left(2 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p}\right) \mu_k \sinh(\mu_k) C(\lambda_k, \omega) \\
&\quad - \left(2 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p}\right) \lambda_k \sinh(\lambda_k) C(\mu_k, \omega),
\end{aligned} \tag{27}$$

$$\begin{aligned}
\hat{P}_k &= - \left(1 - \frac{\nu(1-\nu)(\beta_k^2 + \lambda_k^2)}{p}\right) \lambda_k^{-1} \cosh(\mu_k) S(\lambda_k, \omega) \\
&\quad + \left(1 - \frac{\nu(1-\nu)(\beta_k^2 + \mu_k^2)}{p}\right) \mu_k^{-1} \cosh(\lambda_k) S(\mu_k, \omega),
\end{aligned} \tag{28}$$

$$\begin{aligned}
\hat{Q}_k &= \left(1 - \frac{\nu(1-\nu)(\beta_k^2 + \lambda_k^2)}{p}\right) \mu_k \sinh(\mu_k) C(\lambda_k, \omega) \\
&\quad - \left(1 - \frac{\nu(1-\nu)(\beta_k^2 + \mu_k^2)}{p}\right) \lambda_k \sinh(\lambda_k) C(\mu_k, \omega),
\end{aligned} \tag{29}$$

$$\begin{aligned}
E_k &= \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p} \right)^2 \right] \lambda_k^{-2} \cosh^2(\mu_k) \left[\frac{\sinh(2\lambda_k)}{2\lambda_k} - 1 \right] \\
&+ \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p} \right)^2 \right] \mu_k^{-2} \cosh^2(\lambda_k) \left[\frac{\sinh(2\mu_k)}{2\mu_k} - 1 \right] \\
&- 2 \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p} \right) \left(1 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p} \right) \right] \lambda_k^{-1} \mu_k^{-1} \cosh(\lambda_k) \\
&\times \cosh(\mu_k) \left[\frac{\sinh(\lambda_k + \mu_k)}{\lambda_k + \mu_k} - \frac{\sinh(\lambda_k - \mu_k)}{\lambda_k - \mu_k} \right], \tag{30}
\end{aligned}$$

$$\begin{aligned}
F_k &= \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p} \right)^2 \right] \mu_k^2 \sinh^2(\mu_k) \left[\frac{\sinh(2\lambda_k)}{2\lambda_k} + 1 \right] \\
&+ \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p} \right)^2 \right] \lambda_k^2 \sinh^2(\lambda_k) \left[\frac{\sinh(2\mu_k)}{2\mu_k} + 1 \right] \\
&- 2 \left[1 + \left(1 - \frac{\nu(\beta_k^2 + \lambda_k^2)}{p} \right) \left(1 - \frac{\nu(\beta_k^2 + \mu_k^2)}{p} \right) \right] \lambda_k \mu_k \sinh(\lambda_k) \\
&\times \sinh(\mu_k) \left[\frac{\sinh(\lambda_k + \mu_k)}{\lambda_k + \mu_k} + \frac{\sinh(\lambda_k - \mu_k)}{\lambda_k - \mu_k} \right], \tag{31}
\end{aligned}$$

where

$$\begin{aligned}
S(\ell, \omega) &= \frac{\sinh(i\omega + \ell)}{i\omega + \ell} - \frac{\sinh(i\omega - \ell)}{i\omega - \ell}, \\
C(\ell, \omega) &= \frac{\sinh(i\omega + \ell)}{i\omega + \ell} + \frac{\sinh(i\omega - \ell)}{i\omega - \ell}.
\end{aligned}$$