TRANSPORT OF NUTRIENTS IN BONES*

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Abstract. Lacunar-canalicular systems are networks of pores (lacunae) interconnected by thin channels (canaliculi) that are embedded in bones. The efficient transport of nutrients within lacunar-canalicular systems is necessary to keep bones healthy. Several theories have been proposed to identify the physical phenomena responsible for this efficient transport. In this paper, we develop and study a mathematical model motivated by one of those theories.

1. Introduction. As illustrated in Figure 1.1, we consider long bones of our extremities such as the femur. Bones are porous media with complex microgeometry. The particular components of bones that we discuss here are osteons. These are cylindrical structures of about 120 μm radii that extend along the long axis of the bone (see Figure 1.1). An osteonal canal is located at the center of osteons. This canal contains blood vessels, a nerve, and bone fluid (see Figure 1.1). Pores, called lacunae, are distributed within the osteon. Thin channels, called canaliculi, and the lacunae form a connected system known as the lacunar-canalicular system, which is filled with fluid and is connected to the osteonal canal. A cartoon of the osteon microgeometry is given in Figure 1.1. More details on the structure of bones are given in [4, 12, 13, 2, 14] among numerous other articles.
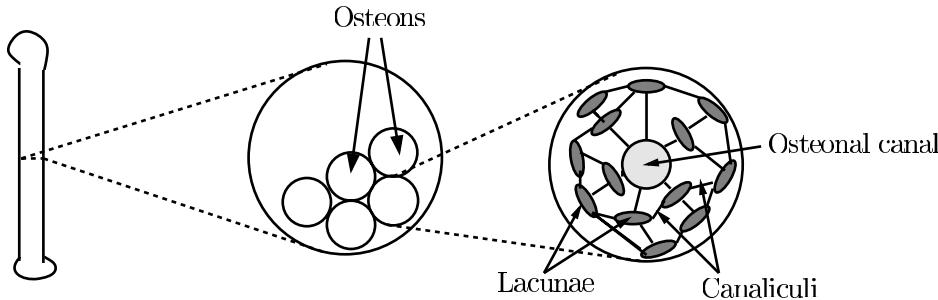
Fig. 1.1. *At left is the cartoon of a bone. A horizontal cross section (view from the top) is shown in the middle figure. The right-most image is a cartoon of the microgeometry of a section of an osteon (also viewed from the top); the white region is the solid part of the bone.*

Bones consume nutrients and produce waste products. It is believed that nutrients are transported from the osteonal canal into the rest of the osteon through the lacunar-canalicular system (see [17] and references therein). Waste products, on the other hand, are produced within the osteon and need to be transported to the osteonal

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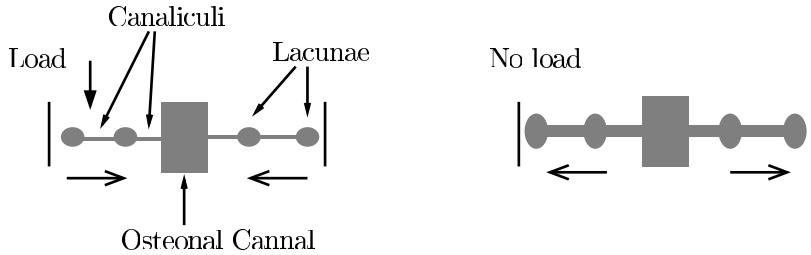
FIG. 1.2. *Cartoon of a vertical longitudinal section (parallel to the direction of the bone) of part of an osteon. The bone is supporting a load in the left-hand image. The load is removed in the right-hand image. The arrows at the bottom denote the direction of the flow.*
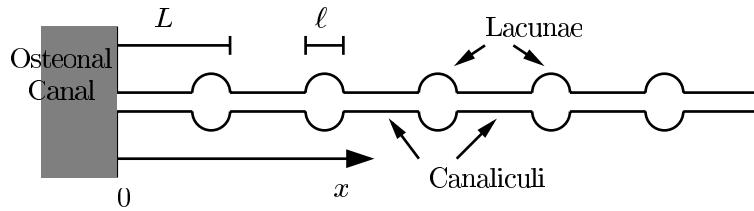
FIG. 1.3. *One-dimensional lacunar-canalicular system.*

canal so that they can be disposed of. Thus, efficient transport within the lacunar-canalicular system is necessary to maintain a healthy bone.

The solid part of the bone is an elastic material. Thus, activities that apply and remove loads to bones, such as walking, produce small deformations of the bone. As a consequence, the incompressible fluid that fills the lacunar-canalicular system is squeezed, producing fluid flow. This is illustrated in Figure 1.2. As shown in the left-hand image, when a bone is subjected to a load, fluid is squeezed out of the lacunar-canalicular system and into the osteonal canal. Once the load is removed, an equal volume of fluid flows back from the osteonal canal into the lacunar-canalicular system (see the right-hand image in Figure 1.2). After each cycle of a periodic load, there is no net volume of fluid transported from the osteonal canal into the lacunar-canalicular system simply because the volume of the bone does not change after each cycle.

In this paper we study the ideal one-dimensional lacunar-canalicular system illustrated in Figure 1.3. The length of each canaliculus is $L - \ell$, and the diameter of each lacuna is of the order ℓ (recall that the diameter of a set Ω is $\sup_{x,y \in \Omega} \|x - y\|$, where $\|x - y\|$ is the distance from x to y). As suggested by Figure 1.3, we assume that $L \gg \ell$.

We assume that there is a periodic exchange of fluid between the osteonal canal and the lacunar-canalicular system and denote that period by t_0. Motivated by the above discussion on flows in lacunar-canalicular systems induced by periodic applied loads, we assume that there is no net transport of any volume of fluid between the osteonal canal and the lacunar-canalicular system after each period. More precisely, we assume that there is $t^\star < t_0$ such that a volume V_F of fluid flows from the osteonal canal into the lacunar-canalicular system during the time interval $(0, t^\star)$ and the same volume of fluid flows back into the osteonal canal during the time interval $(t^\star, t_0)$.

We denote by V_ℓ the volume of each lacuna. Let D be the coefficient of diffusion of nutrients in the host liquid. Due to diffusion, the mixing of nutrients with the host

$$t = 0 \qquad t = t_1 \qquad t = t_2 \qquad t = t_0$$
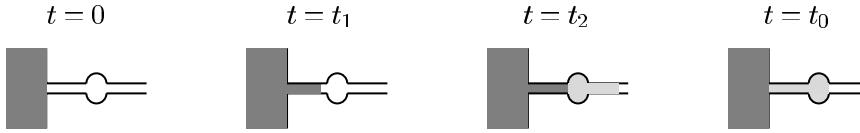
FIG. 1.4. *Nutrient concentration within the lacunar-canalicular system at four different times. The shades represent the concentration of nutrients. The darker the region, the higher the concentration of nutrients.*

fluid within each lacuna occurs in times of order ℓ^2/D. The time that an element of fluid stays in a lacuna is of the order $V_\ell t_0/V_F$. We restrict our attention to the parameter regime

$$(1.1) \qquad \ell^2/D \ll \min\left\{1, \frac{V_\ell}{V_F}\right\} t_0.$$

Thus, since we are interested in events that occur in the time scale of t_0, we can and do assume that mixing is instantaneous within each lacuna.

Within the canaliculi, nutrients are transported along the direction of the x-axis by convection and an effect known as Taylor dispersion (that is the result of fluid motion and diffusion); see [16, 1]. Note that velocities within the canaliculi are of the order $V_F/(at_0)$, where a is the cross-sectional area of each canaliculus. Thus, in a period of time of the order t_0, the distances traveled by nutrients due to Taylor dispersion are of the order $\sqrt{(D + V_F^2/(48at_0^2D))t_0}$; see [16, 1]. We will assume that

$$(1.2) \qquad \sqrt{Dt_0 + \frac{V_F^2}{48at_0D}} \ll L.$$

Since, as we will see later in the paper, we are interested in the parameter regime where fluid is convected from one end of a canaliculus to the other in times smaller than t_0, we can and do neglect diffusion and Taylor dispersion within the canaliculi in the direction of the x-axis.

The osteonal canal acts as a reservoir of nutrients, and thus the concentration of nutrients within the osteonal canal remains constant in time. Assume that the lacunar-canalicular system does not contain any nutrients initially. If $V_F < V_c$, where V_c is the volume of a canaliculus, the nutrients that enter the lacunar-canalicular system in the time interval $(0, t^\star)$ do not reach the first lacuna. Since there is no dispersion within the canaliculi and there is no net transport of volume of fluid between the osteonal canal and the lacunar-canalicular system after each period, all the nutrients that enter the system flow back to the osteonal canal during the time interval $(t^\star, t_0)$. Therefore, there is no transport of nutrients at the end of a cycle.

Assume now that $V_F > V_c$. In Figure 1.4 we show the osteonal canal and part of the lacunar-canalicular system (that includes only one lacuna) at four different times. The shades represent the concentration of nutrients: the darker the region, the higher the concentration of nutrients. At $t = 0$, the lacunar-canalicular system does not contain any nutrients. The times t_1 and t_2 satisfy $0 < t_1 < t_2 < t^\star$. The volume of fluid that enters the system in the time interval $(0, t_1)$ is smaller than V_c. As soon as some nutrient from the osteonal canal reaches the first lacuna, there is instantaneous mixing (of the nutrients with the host fluid) in that lacuna, and the fluid that flows from that lacuna into the second canaliculus carries nutrients (at some

lower concentration). This is illustrated in Figure 1.4; at $t = t_2$, the fluid that entered the system had reached the first lacuna. After a complete period, i.e., $t = t_0$, nutrient that was initially in the osteonal canal will be left in the lacunar-canalicular system (see Figure 1.4). In fact, if n is a positive integer such that $nV_c < V_F$, after a complete cycle there will be nutrients left in the first n lacunae and n canaliculi. Hence, there is a net transport of nutrients after each period. Moreover, in this paper we show that, in the parameter regime $V_c \ll V_F$, the system exhibits a diffusion-like macroscopic behavior with effective diffusion coefficient

$$(1.3) \qquad D_{\text{eff}} = \left(\frac{V_\ell}{V_c + V_\ell} \right)^2 \left(\frac{V_F}{V_c + V_\ell} \right) \left(\frac{L^2}{t_0} \right).$$

This paper is motivated by the work in [17], where the authors make the key assumptions of instantaneous mixing within lacunae and negligible Taylor dispersion within canaliculi. They argue that these assumption are valid by showing that (1.1) and (1.2) are satisfied for typical parameter values (see also [18]). They consider a one-dimensional lacunar-canalicular system with five lacunae, where neighboring lacunae are connected by ten canaliculi. They propose a numerical algorithm and explore the system numerically. Our work is based on the same key physical assumptions. Our new contribution is a detailed mathematical analysis, from which a more explicit description of the behavior of the system is achieved; in particular, we obtain (1.3).

Identifying the phenomena responsible for nutrient transport in bones has been a subject of study for several years. It was first proposed in [15] that convection in the lacunar-canalicular system induced by loading and unloading the bone increases the transport of nutrients (see also [11]). This phenomenon was studied experimentally in [5]. However, this is a partial picture of the relevant phenomena, and there is no agreement among the scientific community on the complete set of physical mechanisms responsible for the transport of nutrients in bones. See [17, 3, 6, 7, 8, 11, 9, 10, 18] for some of the proposed theories and related experiments.

The content of the rest of this paper is the following. In section 2 we derive the governing equations. In section 3 and the appendix we obtain the asymptotic approximation to the governing equations in the limit of a thin canaliculus. In section 4 we consider some examples. The paper ends with conclusions in section 5.

2. Governing equations. The lacunar-canalicular system we consider, displayed in Figure 1.3, extends to infinity in one direction. The right wall of the osteonal canal is the origin of the coordinate system, $x = 0$; the location of the ith canaliculus is the segment $[(i-1)L, iL - \ell]$; and the location of the ith lacuna is $[iL - \ell, iL]$. The cross-sectional area of a canaliculus is a. We denote by $V_c = (L - \ell)a$ and V_ℓ the volumes of the canaliculus and lacuna, respectively. We assume a, V_c, and V_ℓ to be constants. An incompressible fluid, of constant density both in space and time, fills the lacunar-canalicular system. The concentration of nutrients in the osteonal canal remains at the constant value c_0 at all times t.

We denote by $c_i(t)$ the concentration of nutrients at time t in the ith lacuna, and thus $\rho_f c_i(t)$ is the density of nutrients at time t in the ith lacuna, where ρ_f is the fluid density. For x in the canaliculi, we denote by $c(x, t)$ the concentration of nutrients at x and time t. Since Taylor dispersion is neglected within the canaliculi, nutrients flow with the same velocity as the fluid $v = v(x, t)$ within the canaliculi (more precisely, $v(x, t)$ is the average fluid velocity in the cross-section of the canaliculi at x). Fluid incompressibility and mass conservation imply that v is independent of x;

i.e., $v = v(t)$. Thus, conservation of nutrients within the canaliculi reduces to

$$(2.1) \qquad \frac{\partial c}{\partial t} + v \frac{\partial c}{\partial x} = 0$$

for all x in canaliculi.

Whenever the velocity is positive, nutrients flow from the ith canaliculus into the ith lacuna at a rate $a\rho_f v(t) c(iL - \ell, t)$. Nutrients also flow out of that same lacuna into the $(i+1)$th canaliculus at a rate $a\rho_f v(t) c_i(t)$. Analogously, when the velocity is negative, nutrients flow from the $(i+1)$th canaliculus into the ith lacuna at a rate $-a\rho_f v(t) c(iL, t)$ and flow out of that same lacuna into the ith canaliculus at a rate $-a\rho_f v(t) c_i(t)$. This implies

$$(2.2) \qquad V_\ell \frac{dc_i}{dt} = \begin{cases} av\left(c(iL - \ell, t) - c_i(t)\right) & \text{when } v(t) > 0, \\ av\left(c_i(t) - c(iL, t)\right) & \text{when } v(t) < 0 \end{cases}$$

for all positive integers i.

Whenever the velocity is positive, there is flow from each lacuna into the canaliculus located at its right, and thus the concentration of nutrients in the left end of a canaliculus is equal to the concentration of nutrients in the adjacent lacuna. Analogously, whenever the velocity is negative, the concentration of nutrients in the right end of a canaliculus is equal to the concentration of nutrients in the lacuna located at the right end of the canaliculus. Thus,

$$(2.3) \qquad \begin{array}{ll} c((i-1)L, t) = c_{i-1}(t) & \text{if } v(t) > 0, \\ c((i+1)L - \ell, t) = c_{i+1}(t) & \text{if } v(t) < 0, \end{array}$$

the first of the above equations being valid for all integers $i \geq 2$ and the second for all integers $i \geq 0$. Similarly, whenever the velocity is positive, there is flow from the osteonal canal into the first canaliculus, and thus the concentration of nutrients in the left end of the first canaliculus is equal to c_0, the concentration of nutrients in the osteonal canal,

$$(2.4) \qquad c(0, t) = c_0 \quad \text{if } v(t) > 0.$$

Consistent with our discussion in the introduction, we assume that the flow velocity in the canaliculi v is a known periodic function with period t_0 and zero time average

$$(2.5) \qquad \int_0^{t_0} v(t)\,dt = 0.$$

To simplify our analysis we assume that there exist $0 < t^\star < t_0$ such that $v(t) > 0$ if $t \in (0, t^\star)$ and $v(t) < 0$ if $t \in (t^\star, t_0)$. Thus, the volume of fluid that flows from the osteonal canal into the lacunar-canalicular system in the time interval $(0, t^\star)$ is

$$(2.6) \qquad V_F = a \int_0^{t^\star} v(t)dt.$$

Equations (2.1)–(2.4) can be solved once initial conditions and boundary conditions at ∞ are provided.

3. Solution to the governing equations in the thin canaliculus limit.
Assume that the initial conditions on the concentration of nutrients is regular enough that there exists a smooth function $\rho_{\text{in}} = \rho_{\text{in}}(z)$ (except probably in isolated points) defined for all $z \geq 0$ such that

$$(3.1) \qquad \rho_{\text{in}}(iL) = c_i(0) \quad \text{for all positive integers } i,$$

and the limit

$$(3.2) \qquad c_\infty = \lim_{i \to \infty} c_i(0)$$

exists. (More precisely, we need that $\rho'_{\text{in}} = O(V_c/(V_F L))$ except in isolated points.)
Let $\rho = \rho(z, t)$ be the solution

$$(3.3) \qquad \frac{\partial \rho}{\partial t} = D_{\text{eff}} \frac{\partial^2 \rho}{\partial z^2} \qquad \text{for } t > 0 \text{ and } z > 0,$$

where D_{eff} was defined in (1.3), subject to the initial conditions

$$(3.4) \qquad \rho(z, 0) = \rho_{\text{in}}(z) \quad \text{for } z > 0$$

and boundary conditions

$$(3.5) \qquad \rho(0, t) = c_0 \quad \text{and} \quad \lim_{z \to +\infty} \rho(z, t) = c_\infty \quad \text{for } t \geq 0.$$

We extend the definition of ρ to $z < 0$ as follows,

$$(3.6) \qquad \rho(z, t) = c_0 \quad \text{if } z \leq 0,$$

and let $z_i = z_i(t)$ be defined as

$$(3.7) \qquad z_i(t) = iL - \frac{aL}{V_\ell + V_c} \int_0^t v(s) \, ds.$$

In the appendix we show that ρ gives the asymptotic approximation of the concentrations; more precisely,

$$(3.8) \qquad c_i(t) \simeq \rho(z_i(t), t) \quad \text{if } V_F \gg V_c.$$

From (3.3) and (1.3) and the fact that distance between z_i and z_{i+1} remains equal to L for all i and all t, it follows that D_{eff} given in (1.3) is the effective diffusion coefficient of nutrients in the lacunar-canalicular system.

4. Examples. As an example, we now assume that there are no nutrients within the lacunar-canalicular system initially. This corresponds to the initial condition

$$(4.1) \qquad \rho(z, 0) = \rho_{\text{in}}(z) = 0 \quad \text{for all } z > 0,$$

and the condition at ∞

$$(4.2) \qquad \lim_{z \to +\infty} \rho(z, t) = 0 \quad \text{for } t \geq 0.$$

Given these conditions, ρ can be obtained explicitly; more precisely,

$$(4.3) \qquad \rho(z, t) = c_0 - c_0 \frac{2}{\sqrt{\pi}} \int_0^{z/(2\sqrt{D_{\text{eff}} t})} e^{-s^2} \, ds.$$
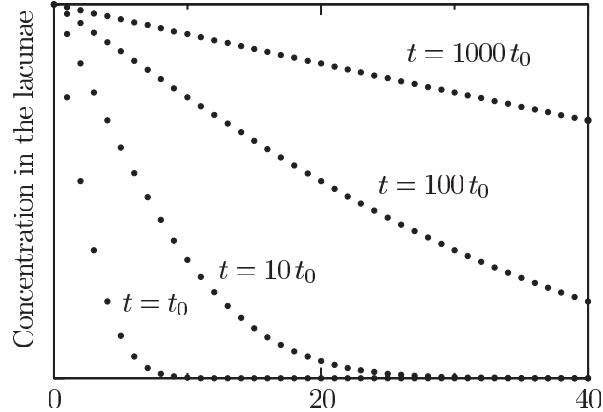
FIG. 4.1. *Plot of the concentration of nutrients in the lacunae $c_i(t) \simeq \rho(z_i(t), t)$ versus i for different fixed values of t.*
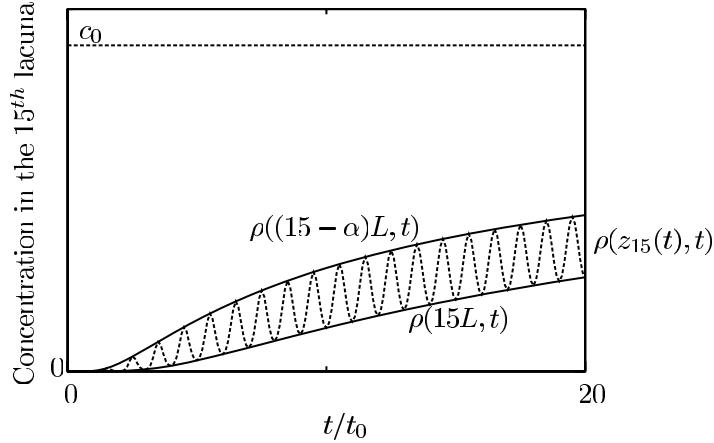
FIG. 4.2. *Plot of concentration of nutrients in the 15th lacuna, $c_{15}(t) \simeq \rho(z_{15}(t), t)$ (dashed line), and the envelopes $\rho(15L, t)$ (lower solid line) and $\rho((15 - \alpha)L, t)$ (upper solid line) versus normalized time t/t_0.*

In the example presented in this section, we select the velocity

$$(4.4) \qquad v(t) = \frac{\pi V_F}{a t_0} \sin\left(\frac{2\pi t}{t_0}\right),$$

and the parameters V_F, V_c, and V_ℓ satisfy $V_c = 0.01 V_\ell$ and $V_\ell = 0.2 V_F$.

In Figure 4.1, we show a plot of the concentration of nutrients in the lacunae, using the approximation $c_i(t) \simeq \rho(z_i(t), t)$, versus i for different fixed values of t.

We define the parameter α as follows:

$$(4.5) \qquad \alpha = \frac{V_F}{V_c + V_\ell}.$$

Figure 4.2 shows the evolution of concentration in the fifteenth lacuna $c_{15}(t) \simeq \rho(z_{15}(t), t)$ plotted against normalized time t/t_0. The oscillations in concentration reflect the evolution in concentration in each cycle of the periodic velocity field v. We
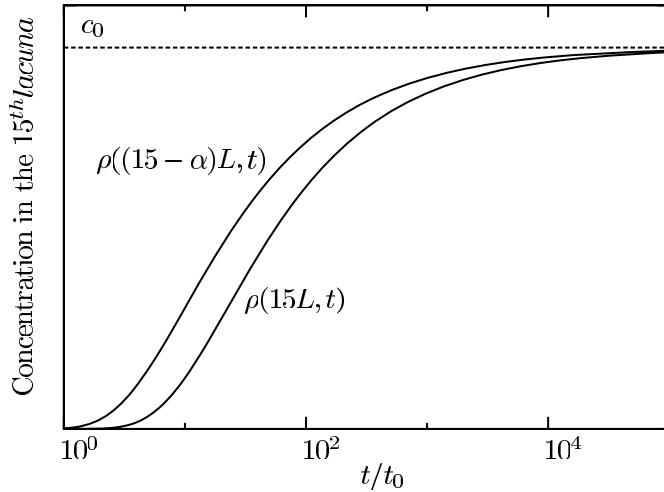
FIG. 4.3. *Plot of the envelopes of the concentration of nutrients in the 15th lacuna, $\rho(15L, t)$ and $\rho((15 - \alpha)L, t)$, versus normalized time t/t_0 in log scale.*

have also plotted the envelopes that are $\rho(15L, t)$ (lower envelope) and $\rho((15 - \alpha)L, t)$ (upper envelope) versus normalized time t/t_0. Figure 4.3 also shows the envelopes $\rho(15L, t)$ and $\rho((15 - \alpha)L, t)$ in a longer time scale to illustrate the convergence to c_0 of the concentration in the fifteenth lacuna after a large number of cycles.

5. Conclusions. In this paper we studied the transport of nutrients in a one-dimensional model lacunar-canalicular system. Our motivation was a recently proposed explanation of how nutrients are transported within bones [17]. We have shown that the system exhibits a diffusion-like macroscopic behavior with effective diffusion coefficient, given in (1.3). Note that the effective diffusion coefficient is explicitly given in terms of the geometry of the system and the applied velocity field. Our analysis is the simplest possible that keeps the relevant physics. Nevertheless, our analysis can be extended to include effects neglected here, such as considering a finite and elastic system instead of a rigid and infinite one (as we do in this work). More experimental and theoretical studies are required for a better and more clear understanding of the processes responsible for the transport of nutrients in bones. We hope our work will prove to be an important step toward that goal.

Appendix. Asymptotic analysis of the thin canaliculus limit. Our analysis is valid for thin canaliculus; more precisely, we assume that V_c, the volume of each canaliculus, is much smaller than V_F, the volume of fluid that enters the lacunar-canalicular system during the part of the period where $v > 0$; i.e.,

$$\text{(A.1)} \qquad\qquad \varepsilon = \frac{V_c}{V_F} \ll 1.$$

We first write the velocity v in the form

$$\text{(A.2)} \qquad\qquad v(t) = \frac{V_F}{a t_0} f\left(\frac{t}{t_0}\right).$$

Note that $f = f(s)$ is a periodic function of s with period 1 and that

$$(A.3) \qquad\qquad \int_0^1 |f(s)| \, ds = 2.$$

We define

$$(A.4) \qquad\qquad \beta = t_0 \varepsilon \left(\frac{1}{|f(t/t_0)|} + \varepsilon \frac{f'(t/t_0)}{2f^3(t/t_0)} + O(\varepsilon^2) \right).$$

In the subsection A.1 we show that

$$(A.5) \qquad\qquad \begin{array}{ll} c(iL - \ell, t) = c_{i-1}(t - \beta) & \text{if } v(t) > 0, \\ c(iL, t) = c_{i+1}(t - \beta) & \text{if } v(t) < 0. \end{array}$$

We use (A.5) to transform (2.2) into

$$(A.6) \qquad\qquad V_\ell \frac{dc_i}{dt} = \left\{ \begin{array}{ll} av \left(c_{i-1}(t - \beta) - c_i(t) \right) & \text{when } v(t) > 0, \\ av \left(c_i(t) - c_{i+1}(t - \beta) \right) & \text{when } v(t) < 0 \end{array} \right.$$

for all positive integers i, where β is again given by (A.4).

We now propose the ansatz

$$(A.7) \qquad\qquad c_i(t) \simeq \rho \left(y = \varepsilon i, \tau = \frac{t}{t_0} \right),$$

where $\rho(y, \tau)$ is a smooth function. We define the parameter

$$(A.8) \qquad\qquad \lambda = \frac{V_c}{V_\ell + V_c}.$$

In subsection A.2 we show that, given the ansatz (A.7), equations (A.6) reduce to the single PDE

$$(A.9) \qquad \frac{\partial \rho}{\partial \tau} + \lambda f \frac{\partial \rho}{\partial y} \simeq \varepsilon \frac{\lambda |f|}{2} \left(\frac{\partial^2 \rho}{\partial y^2} + \frac{2}{f} \frac{\partial^2 \rho}{\partial y \partial \tau} + \frac{1}{f^2} \frac{\partial^2 \rho}{\partial \tau^2} - \frac{f'}{f^3} \frac{\partial \rho}{\partial \tau} \right),$$

where ρ and its derivatives are evaluated in (y, τ) and f and f' are evaluated in τ (terms of higher order in ε are neglected).

Our next step, which we carry out in subsection A.3, is to show that, neglecting corrections of order ε^2, equation (A.9) reduces to

$$(A.10) \qquad\qquad \frac{\partial \rho}{\partial \tau} + \lambda f \frac{\partial \rho}{\partial y} \simeq \varepsilon \frac{\lambda |f|}{2} (1 - \lambda)^2 \frac{\partial^2 \rho}{\partial y^2}.$$

Finally, the asymptotic approximation of section 3 results from the two-time-scale analysis of subsection A.4.

A.1. Derivation of (A.4) and (A.5). Let $X(s)$ be the solution of

$$(A.11) \qquad\qquad X'(s) = v(s) \quad \text{and} \quad X(t) = iL - \ell,$$

where X' is the derivative of X. Fix t and let $\beta > 0$. If $(i - 1)L \leq X(s) \leq iL - \ell$ for all $s \in [t - \beta, t]$, then (2.1) implies that c is constant along the characteristic paths;

i.e., $c(X(s),s)$ is independent of s for $s \in [t-\beta, t]$. Assume that $v(s)$ is positive for all $s \in [t-\beta, t]$ and β is implicitly given by the equation

$$(A.12) \qquad X(t-\beta) = (i-1)L.$$

We have that $c(iL - \ell, t) = c(X(t), t) = c(X(t-\beta), t-\beta) = c((i-1)L, t-\beta)$. On the other hand, since $v(t-\beta) > 0$, equation (2.3) implies that $c((i-1)L, t-\beta) = c_{i-1}(t-\beta)$. Thus,

$$(A.13) \qquad c(iL - \ell, t) = c_{i-1}(t-\beta).$$

To compute β, we first use the expression for v given in (A.2) and expand v in powers of $(s-t)$ to get

$$(A.14) \qquad v(s) \simeq \frac{V_F}{at_0} f\left(\frac{t}{t_0}\right) + \frac{V_F}{at_0^2} f'\left(\frac{t}{t_0}\right)(s-t).$$

We then integrate this approximation of v and use the condition $X(t) = iL - \ell$ to get

$$(A.15) \qquad X(s) \simeq iL - \ell + \frac{V_F}{at_0} f\left(\frac{t}{t_0}\right)(s-t) + \frac{V_F}{2at_0^2} f'\left(\frac{t}{t_0}\right)(s-t)^2.$$

Next use this approximation of $X(s)$ in (A.12) to get

$$(A.16) \qquad (i-1)L \simeq iL - \ell - \frac{V_F}{at_0} f\left(\frac{t}{t_0}\right)\beta + \frac{V_F}{2at_0^2} f'\left(\frac{t}{t_0}\right)\beta^2.$$

We subtract $(i-1)L$ on both sides of the above equation, then multiply by a/V_F, note that $a(L - \ell) = V_c$, and recall that $\varepsilon = V_c/V_F$ to get

$$(A.17) \qquad 0 \simeq \varepsilon - f\left(\frac{t}{t_0}\right)\frac{\beta}{t_0} + \frac{1}{2}f'\left(\frac{t}{t_0}\right)\left(\frac{\beta}{t_0}\right)^2.$$

Once we note that we are considering the case $v(t) > 0$, and thus $f(t/t_0) > 0$, equation (A.17) and elementary calculations show the validity of (A.4) for t such that $v(t) > 0$. The case $v(t) < 0$ results from a similar analysis.

A.2. Derivation of (A.8). Use the ansatz (A.7) and the expression (A.2) for the velocity in (A.6), multiply that equation by t_0/V_F, recall that $\varepsilon = V_c/V_F$, make the change of variables $\tau = t/t_0$, and define $b = \beta/t_0$ to get

$$(A.18) \quad \frac{V_\ell}{V_F}\frac{\partial \rho}{\partial \tau}(i\varepsilon, \tau) = \begin{cases} f(\tau)\left(\rho((i-1)\varepsilon, \tau - b) - \rho(i\varepsilon, \tau)\right) & \text{if } f(\tau) > 0, \\ f(\tau)\left(\rho(i\varepsilon, \tau) - \rho((i+1)\varepsilon, \tau - b)\right) & \text{if } f(\tau) < 0, \end{cases}$$

where

$$(A.19) \qquad b = \varepsilon\frac{1}{|f(\tau)|} + \varepsilon^2\frac{f'(\tau)}{2f^3(\tau)} + O(\varepsilon^3).$$

Expanding in powers of ε, we have that, when $f(\tau) > 0$,

$$\rho((i-1)\varepsilon, \tau - b) \simeq \rho - \varepsilon\left(\frac{\partial \rho}{\partial y} + \frac{1}{f}\frac{\partial \rho}{\partial \tau}\right) + \frac{\varepsilon^2}{2}\left(\frac{\partial^2 \rho}{\partial y^2} + \frac{2}{f}\frac{\partial^2 \rho}{\partial y\partial \tau} + \frac{1}{f^2}\frac{\partial^2 \rho}{\partial \tau^2} - \frac{f'}{f^3}\frac{\partial \rho}{\partial \tau}\right).$$

Analogously, when $f(\tau) < 0$, we have

$$\rho((i+1)\varepsilon, \tau - b) \simeq \rho + \varepsilon\left(\frac{\partial \rho}{\partial y} + \frac{1}{f}\frac{\partial \rho}{\partial \tau}\right) + \frac{\varepsilon^2}{2}\left(\frac{\partial^2 \rho}{\partial y^2} + \frac{2}{f}\frac{\partial^2 \rho}{\partial y\partial \tau} + \frac{1}{f^2}\frac{\partial^2 \rho}{\partial \tau^2} - \frac{f'}{f^3}\frac{\partial \rho}{\partial \tau}\right).$$

In the last two equations ρ and its derivatives are evaluated in $(\varepsilon i, \tau)$, and f and f' are evaluated in τ. Once we plug these expressions into (A.18) and perform simple algebraic manipulations, we obtain (A.9).

A.3. Derivation of (A.10). From (A.9) we infer that

$$(A.20) \qquad \frac{\partial \rho}{\partial \tau} = -\lambda f \frac{\partial \rho}{\partial y} + O(\varepsilon).$$

Taking derivatives with respect to y in (A.20), we get

$$(A.21) \qquad \frac{\partial^2 \rho}{\partial y \partial \tau} = -\lambda f \frac{\partial^2 \rho}{\partial y^2} + O(\varepsilon).$$

On the other hand, taking derivatives with respect to τ in (A.20) and using (A.21), we have

$$(A.22) \qquad \frac{\partial^2 \rho}{\partial \tau^2} = -\lambda f \frac{\partial^2 \rho}{\partial y \partial \tau} - \lambda f' \frac{\partial \rho}{\partial y} + O(\varepsilon) = \lambda^2 f^2 \frac{\partial^2 \rho}{\partial y^2} - \lambda f' \frac{\partial \rho}{\partial y} + O(\varepsilon).$$

Once we replace $\partial \rho / \partial \tau$, $\partial^2 \rho / \partial y \partial \tau$, and $\partial^2 \rho / \partial \tau^2$ in the right-hand side of (A.9) by the expressions obtained in the last three equations and neglect terms of order ε^2, we obtain (A.10).

A.4. Two-time-scale analysis on (A.10). We now follow the standard procedures in two-time-scale asymptotics. We introduce a second time scale

$$(A.23) \qquad \theta = \varepsilon \lambda (1 - \lambda)^2 \tau.$$

We need to replace $\partial \rho / \partial \tau$ by $\varepsilon \lambda (1 - \lambda)^2 \partial \rho / \partial \theta + \partial \rho / \partial \tau$ in (A.10), treat τ and θ as independent variables, and assume that ρ depends on the three variables y, τ, and θ; i.e., $\rho = \rho(y, \tau, \theta)$. Equation (A.10) becomes

$$(A.24) \qquad \varepsilon \lambda (1 - \lambda)^2 \frac{\partial \rho}{\partial \theta} + \frac{\partial \rho}{\partial \tau} + \lambda f \frac{\partial \rho}{\partial y} = \varepsilon \frac{\lambda |f|}{2} (1 - \lambda)^2 \frac{\partial^2 \rho}{\partial y^2}.$$

Next we expand ρ in powers of ε,

$$(A.25) \qquad \rho = \rho_0 + \varepsilon \rho_1 + \varepsilon^2 \rho_2 + \cdots,$$

and require that $\rho_1 = \rho_1(y, \tau, \theta)$ be periodic (with period 1) in τ (this requirement makes the asymptotic approximation valid for long values of τ). We then plug this ansatz into (A.24) and collect powers of ε. At order 1 we get

$$(A.26) \qquad \frac{\partial \rho_0}{\partial \tau} + \lambda f \frac{\partial \rho_0}{\partial y} = 0,$$

and at order ε

$$(A.27) \qquad \lambda (1 - \lambda)^2 \frac{\partial \rho_0}{\partial \theta} + \frac{\partial \rho_1}{\partial \tau} + \lambda f \frac{\partial \rho_1}{\partial y} = \frac{\lambda |f|}{2} (1 - \lambda)^2 \frac{\partial^2 \rho_0}{\partial y^2}.$$

From (A.26), we obtain that the dependence of ρ_0 on y and τ is through the variable η defined as

$$(A.28) \qquad \eta = y - \lambda \int_0^\tau f(s) \, ds.$$

Thus, if we change independent variables from (y, τ, θ) to (η, τ, θ), we have

$$(A.29) \qquad \rho = \rho(\eta, \theta) \quad \text{and} \quad \rho_1 = \rho_1(\eta, \tau, \theta).$$

In the new independent variables, (A.27) becomes

$$\text{(A.30)} \qquad \lambda(1-\lambda)^2 \frac{\partial \rho_0}{\partial \theta} + \frac{\partial \rho_1}{\partial \tau} = \frac{\lambda |f|}{2}(1-\lambda)^2 \frac{\partial^2 \rho_0}{\partial \eta^2}.$$

Finally we take the average of the above equation with respect to τ, keeping η and θ fixed. Since ρ_1 is periodic in τ, we have

$$\text{(A.31)} \qquad \int_0^1 \frac{\partial \rho_1}{\partial \tau}\, \mathrm{d}\tau = 0.$$

Recalling the definition of f and its properties (see (A.2) and (A.3)), we have $\int_0^1 |f|\, \mathrm{d}\tau = 2$. Thus, given that ρ_0 is independent of τ, we have that, after averaging with respect to τ, (A.30) becomes

$$\text{(A.32)} \qquad \frac{\partial \rho_0}{\partial \theta} = \frac{\partial^2 \rho_0}{\partial \eta^2}.$$

We define the spatial variable

$$\text{(A.33)} \qquad z = \frac{L}{\varepsilon} y - \frac{aL}{V_\ell + V_c} \int_0^t v(s)\, \mathrm{d}s.$$

From the different changes of variables made, it follows that

$$\text{(A.34)} \qquad \eta = \frac{V_c}{V_F L} z \quad \text{and} \quad \theta = \frac{V_c^2 V_\ell^2}{V_F(V_\ell + V_c)^3} \frac{t}{t_0}.$$

The last three equations imply that ρ_0 satisfies (3.3). Thus, dropping the subindex 0 and observing the appropriate boundary and initial conditions, we obtain the asymptotic approximation of section 3.

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