Published in final edited form as:

J Eng Math. 2014 February 1; 84(1): 155–171. doi:10.1007/s10665-013-9665-2.

Singular perturbation theory for predicting extravasation of Brownian particles

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Abstract

Motivated by recent studies on tumor treatments using the drug delivery of nanoparticles, we provide a singular perturbation theory and perform Brownian dynamics simulations to quantify the extravasation rate of Brownian particles in a shear flow over a circular pore with a lumped mass transfer resistance. The analytic theory we present is an expansion in the limit of a vanishing Péclet number (P), which is the ratio of convective fluxes to diffusive fluxes on the length scale of the pore. We state the concentration of particles near the pore and the extravasation rate (Sherwood number) to $O(P^{1/2})$. This model improves upon previous studies because the results are valid for all values of the particle mass transfer coefficient across the pore, as modeled by the Damköhler number (κ), which is the ratio of the reaction rate to the diffusive mass transfer rate at the boundary. Previous studies focused on the adsorption-dominated regime (i.e., $\kappa \rightarrow \infty$). Specifically, our work provides a theoretical basis and an interpolation-based approximate method for calculating the Sherwood number (a measure of the extravasation rate) for the case of finite resistance [$\kappa \sim O(1)$] at small Péclet numbers, which are physiologically important in the extravasation of nanoparticles. We compare the predictions of our theory and an approximate method to Brownian dynamics simulations with reflection–reaction boundary conditions as modeled by κ . They are found to agree well at small P and for the $\kappa \ll 1$ and $\kappa \gg 1$ asymptotic limits representing the diffusion-dominated and adsorption-dominated regimes, respectively. Although this model neglects the finite size effects of the particles, it provides an important first step toward understanding the physics of extravasation in the tumor vasculature.

Keywords

Brownian dynamics; Extravasation; Law of additive resistances; Singular perturbation

1 Introduction

In many tumors, small pores (~100nm in size) develop through blood vessel walls as a result of abnormal endothelial cell growth near cancerous cells [1]. These pores provide an entry point to the tumor and thus are ideal targets for drug delivery nanoparticles. The efficacy of these treatments depend on the extravasation rate through these pores, which is in turn controlled by flow conditions, particle size, and particle shape (Smith et al. [1]). As a result, nanoparticles can be engineered with a particular geometry to preferentially target a tumor while reducing harmful side effects at other locations of the body.

In our study, we examine a simple model for the extravasation of nanoparticles in the tumor vasculature. We treat the pore as a circular pore, with Brownian point particles moving above the pore in a constant shear flow (Fig. 2). In actuality, pores take a wide variety of shapes, and tumors retain a finite concentration of nanoparticles. We incorporate these effects via a lumped mass transfer resistance coefficient, which in principle can be matched to experiments. This model neglects several aspects of microvascular drug delivery, including the finite size of particles, the velocity fluctuations created by red blood cells [2,3], pressure variation across the pore [4,5], and bifurcations in the channel geometry [4]. Nevertheless, this model provides a first step in understanding the basic physics of extravasation, as it captures the dependence on shear rate, pore size, and mass transfer resistance at the pore.

In the theory, we develop a perturbation expansion for the concentration distribution of particles in terms of a vanishing Péclet number, which is the ratio of convective to diffusive fluxes at the length scale of the pore. It is similar to analytical studies conducted by Phillips [6] and Ackerberg et al. [7] and numerical studies by Stone [8], although our model is valid for all values of the mass transfer coefficient, whereas the previous studies were restricted to $\kappa \rightarrow \infty$ (Fig. 1).

We then use what we will call the “law of additive resistances” in developing an approximate interpolation method to supplement the theory. In Sect. 2, we will estimate typical values of the Péclet number and mass transfer coefficients in the vasculature. We will then compare the theory and the approximation we develop in Sect. 3 to these previous studies as well as Brownian dynamics simulations, which we develop in Sect. 4. We discuss results in Sect. 5, with particular emphasis on the physiologically relevant regime of weak adsorption (i.e., diffusion-dominated mass transfer).

2 Estimates of parameters in tumor vasculature

The model we develop contains three important dimensionless parameters: Péclet number (P), Damköhler number (κ), and Sherwood number (S). The Péclet and Damköhler numbers are defined as

$$P = \frac{\dot{\gamma} B^2}{D}, \quad \kappa = \frac{kB}{D}, \quad (1)$$

where B is the radius of the pore, $\dot{\gamma}$ is the shear rate at the pore, D is the particle's diffusivity, and k is the reaction rate, which corresponds to an effective local mass transfer resistance at the pore mouth. The Péclet number indicates the relative strength of bulk convection to bulk diffusion, whereas the Damköhler number indicates the relative strength of the reaction rate (also known as extravasation) to the diffusion at the pore's boundary. A large value of κ indicates a rapid reaction and, hence, a small resistance to mass transfer at the pore, while a vanishingly small κ indicates a large resistance to mass transfer into the

pore. In this section, we provide estimates for the typical values of P and κ found in the vasculature.

In general, pore sizes in the vasculature are approximately 100–200nm in radius [1]. With microcirculatory shear rates on the order of $1,000 \text{ s}^{-1}$ and particle diffusivities on the order of $10^{-11} \text{ m}^2/\text{s}$, the Péclet number is $O(1)$. Thus, bulk diffusion and convection play an important role in the extravasation process. Although our theory assumes $P \ll 1$, we will show in Sect. 5 that it gives a reasonable approximation even at $P \sim O(1)$.

We estimate the physiological mass transfer coefficient at the pore by approximately solving a diffusion problem in a model pore. The pore is modeled as a cylindrical tube connecting two half-spaces corresponding to the blood vessel and the tumor interstitium. The flux at the pore from the blood vessel is calculated by our theory in Sect. 3 for stationary fluid, while the flux resulting from matter diffusing back from the cylindrical pore into the blood vessel is computed by solving the diffusion equation. When the tube height is approximately equal to the pore radius (which is found to be true experimentally [10–12]), the mass transfer resistance is similar in all three regions, indicating $\kappa \sim O(1)$. Previous analytical studies [6,8] of the same problem assumed $\kappa \gg 1$. We emphasize that the model developed in Sect. 3 lifts this restriction.

The Sherwood number, defined in Sect. 3, is a dimensionless measure of the extravasation rate through the pore. In this study, we quantify the dependence of the Sherwood number on the Péclet and Damköhler numbers using singular perturbation theory, an approximation method (Sect. 3), and Brownian dynamics simulations (Sect. 4). This dependence is studied for the entire range of Damköhler numbers and Péclet numbers ranging from 0 to 20 (Fig. 1).

3 Analytical theory for extravasation

3.1 Formulation

The geometry of the problem is shown in Fig. 2. A dilute bath of Brownian point particles with a far-field concentration of ϕ_0 moves in an external shear flow above a wall embedded with a circular pore of radius B . Without loss of generality, $\phi_0 = 1$ since this is a linear problem. The wall-normal coordinate is z and the flow direction x , so the far-field fluid velocity is given by $u_x^\infty = \dot{\gamma} z$. The diffusivity of the particles is D , and the lumped resistance to mass transfer across the pore is modeled by k .

When we scale all length scales by the pore radius B , all time scales by the inverse shear rate $\dot{\gamma}^{-1}$, and all concentrations by ϕ_0 , the concentration of Brownian particles obeys the following (nondimensional) advection–diffusion equation at steady state:

$$\nabla^2 \phi = Pz \frac{\partial \phi}{\partial x}; \quad (2a)$$

$$\frac{\partial \phi}{\partial z} = \kappa \phi \text{ at } z=0, \rho < 1; \quad (2b)$$

$$\frac{\partial \phi}{\partial z} = 0 \text{ at } z=0, \rho > 1; \quad (2c)$$

$$\phi \rightarrow 1 \text{ as } \rho, z \rightarrow \infty. \quad (2d)$$

In the preceding equations, ρ is the polar radial coordinate centered at the pore's center of mass ($\rho^2 = x^2 + y^2$), while P and κ are the Péclet and Damköhler numbers on the length scale of the pore ($P = \dot{\gamma} B^2/D$ and $\kappa = k B+/D$). We will perform a perturbation expansion in P for $P \ll 1$, which implies that bulk diffusion dominates shear convection at wall-normal distances on the order of the pore's radius. The boundary conditions (2b–d) are simply statements of the balance of diffusive and adsorption flux at the pore (2b), no flux at the channel wall (2c), and constant far-field concentration of the particle bath (2d).

The Sherwood number is a nondimensional number where mass transfer to the pore is scaled with the characteristic length scale, pore area, and diffusivity. It is a function of Péclet and Damköhler numbers and is simply the dimensionless diffusive flux through the pore:

$$S(P, \kappa) = \frac{1}{\pi_{\text{pore}}} \int \frac{\partial \phi}{\partial z} dA. \quad (3)$$

Note that Eqs. (2a–c) is a standard mathematical problem whose variants have been encountered in electrochemical flows and reaction engineering.

3.2 The principle of additive resistances

The problem of transport to a spherical surface with a first-order reaction embedded in a shear flow was studied previously by Batchelor [13], while the problem of heat transport to small particles suspended in linear shear flows was studied by Acrivos [14]. However, these problems are not completely representative of our physiological problem. Despite this, parallels can be drawn between our problem and the problem of reacting spherical surfaces in shear flow. Thus, before we formulate a strategy to solve the equations of transport (2a–d), we can compute S from the information we already have using an approximate method.

Consider the case of the reacting spherical surface embedded in shear flow. When $P = 0$, it is observed that the concentration is given by a field of the form $\phi = 1 - Ar^{-1}$ and the surface concentration is given by $\phi_s = 1 - \kappa\phi_s$. Thus, the area-averaged surface flux S_{sp} for the sphere is given by $\kappa\phi_s = \kappa/(\kappa + 1) = S_{\text{sp}}(0, \kappa)$. Noting that $S_{\text{sp}}(0, \infty) = 1$ when $\kappa = \infty$, the previous equation can be rewritten as

$$\frac{1}{S_{\text{sp}}(0, \kappa)} = \frac{1}{\kappa} + \frac{1}{S_{\text{sp}}(0, \infty)}.$$

Thus, at $P = 0$, the combined “resistance” to mass transfer by both diffusion and surface reaction equals the sum of the individual “resistances”. In the case of a flat reacting disk on a wall embedded in shear flow, a similar argument can be made regarding additive resistances, and the following approximate formula can be obtained:

$$\frac{1}{S(0, \kappa)} \approx \frac{1}{\kappa} + \frac{1}{S(0, \infty)}. \quad (4a)$$

It can be argued similarly that the same formula holds approximately for $P > 0$:

$$\frac{1}{S(P, \kappa)} \approx \frac{1}{\kappa} + \frac{1}{S(P, \infty)}. \quad (4b)$$

It is obvious that the overall rate of the dimensionless flux as given by $S(0, \kappa)$ approaches κ asymptotically from below when $\kappa \rightarrow 0$ irrespective of the shape of the reacting surface, which is consistent with Eq. (4a). Also, the value of S is always bounded above by $S(0, \infty)$, which is approached asymptotically in the limit of large κ . Thus the value $S(0, \kappa)$ is bounded above by $\min(\kappa, S(0, \infty))$, while in this case it is found to be closely approximated by the value of $S(0, \kappa)$ given by Eq. (4b). Similarly, in general, $S(P, \kappa)$ is bounded above by $\min(\kappa, S(P, \infty))$. As already mentioned (Fig. 1), Phillips [6] determined the following expression for $S(P, \infty)$, which is valid for $P \ll 1$, $\kappa \rightarrow \infty$:

$$S(P, \infty) = \frac{4}{\pi (1 - 0.20281 P^{1/2})}, \quad (5a)$$

$$S(0, \infty) = \frac{4}{\pi}. \quad (5b)$$

Knowing these asymptotic expressions, we use an interpolation technique described by Churchill and Usagi [15] to obtain the following general expression for $S(P, \kappa)$, which is valid for $P \ll 1$:

$$S(P, \kappa) \approx \left((\kappa)^{-n} + S(P, \infty)^{-n} \right)^{-1/n}. \quad (6)$$

Here, n is a parameter chosen to fit the data and is hopefully independent of P . Equation (6) reduces to Eq. (4b) for $n = 1$. In Sect. 5, we will combine these approximate methods with the theory derived from singular perturbation methods and compare their results with those of the simulations.

3.3 Formal perturbation expansion

When $P \ll 1$, we expect to observe different physics at two distinct length scales (the so-called inner and outer regions of the perturbation expansion). At wall-normal distances on the order of the pore's radius (the inner region), the particles will simply diffuse to the pore. At distances far from the pore (the outer region, where $z, \rho \sim O(P^{-1/2})$), convection effects eventually balance diffusion, with the concentration varying smoothly between the near- and far-field limits. This separation of length scales makes this problem ideal for the classic method of matched asymptotic expansions as pioneered by Milton Van Dyke, among others. Subsequently, we will write the expansion for the inner and outer regions and, in the following subsections, solve for the concentration fields. We denote the fields in the inner expansions with lowercase letters and those in the outer expansions with uppercase letters.

The concentration in the inner region ($z, \rho \sim O(1)$) satisfies Laplace's equation through all orders of P considered here: $\nabla^2 c = 0$. An appropriate form for the expansion takes the form

$$c(\vec{r}) = g(P) c_0(\vec{r}) + h(P) c_1 + o(h(P)), \quad (7)$$

where $g(P)$ and $h(P)$ are scaling factors, which we will determine, and $h(P)$ is $o(g(P))$. Convection effects balance bulk diffusion when z and ρ are $O(P^{-1/2})$. Using the stretched variables $Z = P^{1/2}z$, $R = P^{1/2}r$, and $X = P^{1/2}x$, where r the radial distance in spherical

coordinates ($r^2 = x^2 + y^2 + z^2$), the concentration field in the outer region satisfies the advection-diffusion equation

$$\nabla^2 C = Z \frac{\partial C}{\partial X}, \quad (8a)$$

with

$$\frac{\partial C}{\partial Z} = 0 \quad \text{at } Z=0, \quad R > P^{1/2}, \quad (8b)$$

and a matching condition with the inner solution at $R \sim P^{1/2}$. Since $C = 1$ is a solution of Eqs. (8a, b), the outer expansion takes the form

$$C = 1 + f(P) C_0 + o(f(P)), \quad P \rightarrow 0. \quad (9)$$

Again, $f(P)$ is a scaling factor to be determined through the method of matched asymptotic expansions. The following subsections will provide expressions for the leading-, i.e., zeroth-, order inner and outer concentration fields. Once we obtain these solutions, we extract the nondimensional extravasation rate based on the inner terms:

$$S(P, \kappa) = \frac{1}{\pi_{\text{pore}}} \int \frac{\partial c}{\partial z} dA. \quad (10)$$

3.4 Inner expansion: leading term

To the leading order in P , the advection–diffusion equation reduces to Laplace’s equation ($\nabla^2 c_0 = 0$). Because our problem geometry is axisymmetric, the concentration field admits a cylindrical harmonic solution of the form:

$$c_0 = 1 + \int_0^\infty A(k) e^{-kz} J_0(k\rho) dk. \quad (11)$$

Here, the integral represents a continuous superposition of modes in Laplace space, with $A(k)$ the coefficients of the basis function $e^{-kz} J_0(k\rho)$. Substituting this form into the mixed boundary conditions (2b, 2c) gives us two integral equations, and thus we use the classical theory of dual integral equations arising in mixed boundary value problems in potential or elasticity theory. In this context, we build an expression for solving the dual equations using a technique developed by Gladwell et al. [16].

We break $A(k)$ into Fourier modes via the finite cosine transform

$$A(k) = \int_0^1 f(t) \cos(kt) dt, \quad (12)$$

with $f(1) = 0$. The advantage of this expression is that it automatically satisfies the no-flux condition at the channel wall (for details, see Duffy [17]). Gladwell et al. [16] arrive at the same expression for $A(k)$ using cyclic identities involving coupled Abel, Hankel, and Fourier transforms. To satisfy the flux boundary condition over the pore (Eq. 2b), the Fourier coefficients $f(t)$ must satisfy a Fredholm integral equation below, viz.,

$$f(t) + \frac{\kappa}{\pi} \int_0^1 f(y) K(t, y) dy = \frac{2\kappa}{\pi} \sqrt{1-t^2}, \quad (13a)$$

$$K(y, t) = \ln \left| \frac{\sqrt{1-t^2} + \sqrt{1-y^2}}{\sqrt{1-t^2} - \sqrt{1-y^2}} \right|. \quad (13b)$$

To solve this integral equation, we expand the modes $f(t)$ and the integral kernel $K(t, y)$ in a complete basis of trigonometric functions:

$$f(t) = F(\theta) = \sum_{n=0}^{\infty} a_n \sin((2n+1)\theta),$$

$$K(t, y) = \sum_{n=0}^{\infty} \frac{4}{2n+1} \sin((2n+1)\theta) \sin((2n+1)\phi),$$

where $t = \cos \theta$, $y = \cos \phi$. After some algebra, we obtain the infinite set of linear equations for the spectral coefficients a_k :

$$a_n + \frac{\kappa}{2n+1} \frac{1}{\pi} \sum_{m=0}^{\infty} d_{mn} a_m = \frac{2\kappa}{\pi} \delta_n, \quad (14a)$$

where the coefficients d_{mn} are given as follows:

$$d_{mn} = \frac{1}{2n-2m+1} - \frac{1}{2n-2m-1} - \frac{1}{2n+2m+3} + \frac{1}{2n+2m+1}. \quad (14b)$$

It is shown in [18] that the preceding set of equations is regular, so a truncated set can be solved for the first few coefficients, specifically for the all-important coefficient a_0 , as we will see in Sect. 3.5. The numerical solution of these linear equations is outlined in Appendix B. We typically truncate the series to 12 terms, which we find yields an error of at most 0.1% for the Damköhler numbers we consider in this paper. Using some trigonometric identities and identities with Chebyshev polynomials and Bessel functions (Appendix A), we obtain the following simplified expression for $A(k)$:

$$A(k) = \sum_{n=0}^{\infty} (-1)^n (2n+1) \pi \frac{a_n}{2} \frac{J_{2n+1}(k)}{k}. \quad (15)$$

Thus, the leading term of the inner solution is given by

$$c_0 = 1 - \frac{\pi}{2} \sum_{n=0}^{\infty} (-1)^n (2n+1) a_n \left[\int_0^{\infty} \frac{1}{k} e^{-kz} J_{2n+1}(k) J_0(k\rho) dk \right]. \quad (16)$$

3.5 Outer expansion: leading terms

Recall that $C \approx 1 + f(P)C_0$ and the fact that C_0 denotes the concentration profile created by a sink at the origin and thus has bulk diffusion balancing convection from the external shear flow: $\nabla^2 C_0 = Z C_0 / X$. We decompose the concentration into Fourier modes in the flow direction (X) and vorticity direction (Y) as follows:

$$\tilde{C}_0 = \iint C_0 \exp(iKX + iLY) dX dY.$$

With these definitions, the transformed concentration field satisfies Airy's equation:

$$\frac{\partial^2 \tilde{C}_0(s)}{\partial s^2} = s \tilde{C}_0(s), \quad s = e^{-\pi i/6} K^{1/3} \left(Z + i \frac{K^2 + L^2}{K} \right). \quad (17)$$

The solution to this differential equation is $\tilde{C}_0 = H(K, L) \text{Ai}(s)$, where $\text{Ai}(s)$ is the Airy function of the first kind, and $H(K, L)$ is a wave-vector-dependent amplitude that must be chosen in such a way that satisfies the boundary conditions at the channel wall. This was done by Kalumuck [19] for the no-flux condition at the channel wall (Eq. 8b). Noting that the equations are homogeneous, we state the final concentration field below (with our preferred scaling), referring the interested reader to Kalumuck [19] or Phillips [6] for more details:

$$C_0 = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \tilde{C}_0 \exp(-iKX - iLY) dK dL; \quad (18)$$

$$\tilde{C}_0 = \frac{1}{\pi^2} e^{\pi i/6} K^{-1/3} \left(\frac{\text{Ai}(s)}{\text{Ai}(s_0)} \right), \quad s_0 = s \Big|_{Z=0}. \quad (19)$$

3.6 Matching

3.6.1 Far-field solution, inner expansion—In the far-field limit ($r \gg 1$), the long wavelength modes in the region $k \sim O(1/r)$ dominate the inner solution to the concentration field. To see this, we take the leading-order solution in Eq. (16) and perform the spherical coordinate substitutions $\rho = r \sin \theta$ and $z = r \cos \theta$. The asymptotic approximation to the concentration field is thus (for $r \gg 1$)

$$\begin{aligned} c_0 - 1 &= -\frac{\pi}{2} \sum_{n=0}^{\infty} (-1)^n (2n+1) a_n \left[\int_0^{\infty} e^{-kr \cos \theta} J_0(kr \sin \theta) \frac{J_{2n+1}(k)}{k} dk \right], \\ &\sim -\frac{\pi}{2} \sum_{n=0}^{\infty} (-1)^n (2n+1) a_n \left[\int_0^{\infty} e^{-kr \cos \theta} J_0(kr \sin \theta) \left(\lim_{k \rightarrow 0} \frac{J_{2n+1}(k)}{k} \right) dk \right], \\ &\sim -\frac{\pi}{4} \sum_{n=0}^{\infty} (-1)^n (2n+1) a_n \delta_{n0} \left[\int_0^{\infty} e^{-kr \cos \theta} J_0(kr \sin \theta) dk \right]; \\ c_0 - 1 &\sim -\frac{\pi a_0}{4r}. \end{aligned} \quad (20)$$

The leading term in the inner solution decays as $1/r$ in the far-field limit, which is the classical scaling for a point source solution. Interestingly, it depends on the Damköhler number only via the leading coefficient a_0 , which is numerically determined by the truncated set of Eqs. (14a, 4b).

3.6.2 Near-field solution, outer expansion—Phillips [6] determined the near-field behavior of the outer solution as described by Eqs. (18) and (19). Again, we state the results and refer readers to Phillips for more details. As $R \rightarrow 0$, the asymptotic expansion for the concentration is

$$1 + f(P) C_0 \sim 1 - f(P) \frac{2}{\pi} \left[\frac{1}{R} - A \right] + O(R) \text{ terms antisymmetric in } X \text{ and symmetric in } Y + O(R^2), \quad (21)$$

where $A = 0.318 \dots$. We note that the leading term of the near-field solution is proportional to $1/R$, as is the leading term in the far-field limit of the inner solution (Eq. (19)). In addition, $f(P)$ is to be determined by matching. We also note that the $O(R)$ terms in the near-field solution are antisymmetric in the flow direction X and symmetric in the vorticity direction Y . This implies that the extravasation rate we derive in Sect. 3.7 has errors smaller than $O(P)$.

3.6.3 Matching—Recall that the leading-order inner and outer solutions are of the form $c = g(P)c_0 + h(P)c_1$, and $C = 1 + f(P)C_0$, where $g(P)$, $h(P)$, and $f(P)$ are undetermined scaling factors. In this subsection, we will determine these factors by matching the two solutions in an intermediate region $1 \ll r \ll P^{-1/2}$. Matching the asymptotic expressions from Eqs. (19) and (20), we obtain

$$\begin{aligned} 1 - f(P) \frac{2}{\pi} \left[\frac{1}{R} - A \right] &\sim g(P) \left(1 - \frac{\pi a_0}{4r} \right) = g(P) \left(1 - P^{1/2} \frac{\pi a_0}{4R} \right), \\ f(P) &= \frac{\pi^2 a_0}{8} P^{1/2} g(P). \end{aligned}$$

Note that $f(P)$ is $o(g(P))$.

We can choose $g(P) = 1$ and obtain $f(P) = \pi^2 a_0 P^{1/2}/8$, leaving only the $O(P^{1/2})$ term $2A f(P)/\pi$ in the outer asymptotic expression unmatched. It will have to be matched with the far-field limit of the $O(P^{1/2})$ term $h(P)c_1$ in the inner expansion. We note that $c_1 = c_0$ as they both satisfy the same set of homogeneous equations. The far-field asymptotic expansion of $h(P)c_1$ is $\sim h(P)(1 - \pi a_0/4r)$, which must match $2A f(P)/\pi$. This leads us to the equations

$$\begin{aligned} h(P) &= \frac{2}{\pi} A f(P), \\ c &= \left(1 + \frac{2}{\pi} A f(P) + O(P) \right) c_0 = \left[1 + \frac{\pi a_0 A}{4} P^{1/2} + O(P) \right] c_0 = \left[1 + 0.25 \dots a_0 P^{1/2} + O(P) \right] c_0. \end{aligned} \quad (22)$$

3.7 Extravasation rate

Because c_0 is a harmonic function, by the divergence theorem, it is seen from the form of the leading term of the inner solution (Eqs. (16), (22)) that the extravasation rate (Eq. (10)) is

$$S(0, \kappa) = \frac{\pi a_0}{2}. \quad (23)$$

Thus Eq. (22) can also be written as

$$c = \left[1 + \frac{S(0, \kappa)}{2\pi} P^{1/2} + O(P) \right] c_0. \quad (24)$$

We plot the dependence of a_0 , which is proportional to $S(0, \kappa)$, on the Damköhler number in Fig. 3. We recall the two asymptotic behaviors of $S(0, \kappa)$ for $\kappa \ll 1$ and $\kappa \gg 1$:

$$S(0, \kappa) \sim \kappa \quad \text{for } \kappa \ll 1, \quad (25a)$$

$$S(0, \kappa) \sim S(0, \infty) = \frac{4}{\pi} \quad \text{for } \kappa \gg 1; \quad (25b)$$

$$\text{thus, } a_0 \rightarrow \frac{8}{\pi^2} = 0.81$$

We can see immediately from Eqs. (10) and (24) that the change in the extravasation rate as P is increased from zero is given, to leading order, by

$$S(P, \kappa) = S(0, \kappa) \left[1 + \frac{S(0, \kappa)}{2\pi} P^{1/2} + O(P) \right]. \quad (26)$$

$S(0, \kappa)$ can be computed numerically using Eqs. (14a–b) and (23) or approximately using Eqs. (5a) and (23) (with $n = 0.93$, $P = 0$):

$$a_0 = \frac{2}{\pi} S(0, \kappa) \approx \frac{2}{\pi} \left(\kappa^{-0.93} + \left(\frac{4}{\pi} \right)^{-0.93} \right)^{-1/0.93}. \quad (27)$$

Equation (27) turns out to be a remarkably accurate fit, as seen in Fig. 3.

We can combine Eqs. (26)–(27) to find the following expression illustrating the explicit dependence of $S(P, \kappa)$ on P and κ ($n = 0.93$):

$$S(P, \kappa) \approx \left(\kappa^{-n} + \left(\frac{4}{\pi} \right)^{-n} \right)^{-1/n} \left[1 + \frac{\left(\kappa^{-n} + \left(\frac{4}{\pi} \right)^{-n} \right)^{-\frac{1}{n}}}{2\pi} P^{1/2} \right]. \quad (28)$$

Let us make a few observations regarding the expression (26). At zero Péclet number, the extravasation rate should be a weak function of the shape of the pore since there is only pure diffusion over the pore and reaction at the pore surface. Second, this flux has errors smaller than $O(P)$, as the next terms in the inner expansion do not contribute to the extravasation rate. To see this, we refer to the near-field asymptotic form for the outer expansion as discussed in Sect. 3.6.2, Eq. (21). The next term in the inner expansion must match the $O(R)$ terms in the outer expansion, which are symmetric in the vorticity direction Y but antisymmetric in the flow direction X . This matching requires that the inner solution possess the same symmetry, which leads to a vanishing extravasation rate when it is integrated over the circular pore. Thus, although our expression for the extravasation rate is valid to $O(P^{1/2})$, it is accurate for a wide range of P and in fact works reasonably well for $P < 1$ ($P = 0$ to $P = 0.3$) (see Sect. 5 for discussion). Note that Eq. (26) is essentially identical to the expression for the Nusselt number for a heat transfer analog with shear flow at small Reynolds numbers [13,14].

4 Brownian dynamics simulations

To test our theory, we performed Brownian dynamics simulations over a whole range of P and κ . The geometry of the Brownian dynamics simulations we performed is shown in Fig. 4. The simulation domain is a box of size $L_1 \times L_2 \times L_3 = 30 \times 30 \times 25$, with the bottom face ($x_3 = 0$) being a rigid wall with a circular pore of radius one. We randomly introduce a large number of Brownian particles into the box with an external shear flow $U_1^\infty = x_3$, and we track

the number of particles exiting the pore over time, which we denote as $N(t)$. We determine the flux across the pore by calculating the time derivative of $N(t)$, normalized by the far-field concentration of particles ϕ_∞ .

The simulation domain is periodic in the flow (x_1) and vorticity (x_2) directions, while a particle escaping from the top of the box is placed back just below the face in a random fashion to be consistent with the approximately zero net flux condition across the top face. We evolve the positions of each particle in the flow and vorticity directions via the classical Langevin equation (in dimensionless form):

$$\Delta x_i = P U_i \Delta t + \sqrt{2\Delta t} N_i(0, 1), \quad i=1, 2, \quad (29)$$

where N_i are standard Gaussian random variables with mean zero and variance one. To update the motion in the wall-normal direction (x_3), we implement a Monte Carlo algorithm proposed by Lamm and Schulten [20] that employs the solution of a one-dimensional Smoluchowski diffusion equation with a reactive boundary at one end. The details of this algorithm are described in Appendix C. When a particle is over the no-flux wall, its x_3 component is updated with no reaction (i.e., full reflection). When it is over the pore, the x_3 component is updated with a reaction rate set by the Damköhler number. An advantage of this method is that the boundary conditions are naturally incorporated into the equations of motion, avoiding the introduction of artificial schemes that approximate when a particle is about to cross a reflection boundary. In our simulations, particles never cross the wall surface.

It should be noted that the flux from the simulations is computationally sensitive to the normalization concentration (ϕ^∞) and, hence, the region over which the concentration is computed. We typically calculate ϕ^∞ by averaging over the top 70 % of the simulation box. Small errors may also occur because of pore-edge effects as the Brownian particles experience a sudden jump in reaction rate at the edge. These are accounted and corrected for by making the transition smooth and continuous within a very short radial segment located at the pore boundary.

Simulations are performed for Péclet numbers ranging from 0 to 100 and for Damköhler numbers ranging from 0.1 to 300. The simulation is run with time step $\Delta t = 10^{-4}$ until $t = 100$, with the flux calculated over the last two-thirds of the interval. Since each particle is simulated individually and there is no interaction between particles, the extravasation rate can be computed by simply increasing the number of particles in each run and averaging over a few runs. We use 400,000 particles in each simulation and average results over 5 runs. The standard deviation of the flux across these runs is quite small (<0.5 %). In the following section, we compare the extravasation rates from this simulation to those predicted by the analytical theory.

5 Discussion and conclusion

We performed simulations for a wide range of Péclet and Damköhler numbers, and the comparisons between the theory and simulation are discussed in the following sections. We identified three primary cases, corresponding to the different Péclet number regimes. Equation (6) (with $n = 1.1$), coupled with Eq. (5a), is found to fit our analytical formula and simulation data relatively well for the entire range of κ at every P . However, expression (28) turns out to be a very accurate fit for the analytical Eq. (26) simply because Eq. (27) is a very good approximation to begin with, as evident from Fig. 3.

5.1 Case I: $P = 0$

We are interested in determining the dependence of the extravasation rate, or S , on the two dimensionless parameters P and κ . The simplest case is $P = 0$, where our analytic solution is exact for all κ . Thus, we can use this case to benchmark our simulations.

Figure 5 shows very good agreement between the perturbation theory (Eq. (26)) and simulations over the entire range of κ , as expected. Two distinct limits appear for $\kappa \ll 1$ and $\kappa \gg 1$. As expected, when κ is increased, S increases linearly for small κ and then begins to plateau for $\kappa \sim O(1)$. At larger κ , the total mass transfer becomes limited by the rate at which particles can diffuse to the boundary, and S approaches asymptotically to the value of $4/\pi$. Both of these asymptotes are presented in Fig. 5a. Again, as is known from Sect. 3.7, Eq. (27) [or Eq. (28)] provides a very good approximation to the theoretical curve. As P is increased, we will show in the following sections a similar dependence of S on κ for the entire range of P .

5.2 Case II: $P \ll 1$ and $P \sim O(1)$

Since we found good agreement between perturbation theory (Eq. (26)) and the simulation for $P = 0$, we can safely assume that our simulations give the correct value of S for reasonable values of P and κ . This allows us to establish the range of validity of our theory (Eq. (26)), which is strictly valid only for $P \ll 1$. Figure 6 shows the corresponding plot of S , with P held constant at 0.3. As discussed earlier in Sect. 3, the curve is very similar to the $P = 0$ case, but with a slightly different growth rate for $\kappa \ll 1$ and different asymptote for $\kappa \gg 1$. Again, we see very good between theory (Eq. (26)), simulation, and the explicit expression in Eq. (28).

We test the limits of our theory by evaluating S for $P = 5$, shown in Fig. 7. Our theory is remarkably robust for $\kappa < 1$ but is incapable of capturing the full effect of convection for moderate to high values of κ ($\kappa > 10$). Recall that the physically relevant parameters are $P \sim O(1)$ and $\kappa \sim O(1)$, so our theory does a reasonable job of calculating S . As expected, Eq. (28) is a remarkable approximation for the analytical result at $P = 0.3$ (within 0.5% error).

5.3 Case III: entire range of P

To highlight the effect of convection, we plot S as a function of P while holding κ fixed. In Figs. 8a, b and 9a-d, we show the growth of S with P over several decades. Once again, we see good agreement between our theory and the simulation for $P < 1$, with significant deviations occurring for larger values of P . For $\kappa < 1$, quantitative agreement is shown even as P approaches 20, as resistance to mass transfer at the interface dominates convection. Again, as expected, a good agreement (within 0.5% error) still holds between the approximate expression (Eq. (28)) and the theory (Eq. (26)) for both $\kappa < 1$ and $\kappa \gg 1$ (Figs. 8 and 9).

Note that there exists a point sensitive to κ where S starts increasing rapidly with P . Increasing κ reduces the mass transfer resistance and moves the “turning point” to smaller values of P , whereas decreasing κ has the reverse effect. We note that this point is at reasonably large P for small κ , and thus we have good agreement between simulations and theory for a wide range of P (Fig. 8a, b).

For very large values of P and κ , the mass transfer across the pore can be approximated by Graetz–Lvque theory [8,21]. Across the pore, we integrate the diffusive flux from the self-similar solution to obtain a different asymptotic expression for the extravasation rate (S):

$$S=0.687P^{1/3}+O\left(P^{-1/6}\right). \quad (30)$$

As seen in Fig. 9d, when $\kappa = 300$, the Sherwood number from our simulations seems to slowly and smoothly transition between the large and small P asymptotes, with reasonable agreement at both ends. Since we are not interested in $P \gg 1$, we have not pursued finding a large P limit for S at finite κ .

5.4 Implications and future work

We have built a simple theory to quantify the extravasation of particles through pores that can be used to obtain estimates of mass transfer coefficients in a physical setting. To perform a valid comparison with experiments, we must measure the extravasation rate and then fit it to the theoretical expressions (22) and (23a, b) with the known Péclet number. Moreover, using the law of additive resistances, a relationship (Eq. (28)) was determined that shows the explicit dependence of S on the Damköhler number and Péclet number.

Typically, small particles experience less mass transfer resistance and correspond to large κ , while large particles correspond to small κ . Thus, although our model does not explicitly incorporate the effect of particle size, it can still be used to make qualitative predictions on the effects of particle size on extravasation. With this theory in hand, we are currently extending the model to account for other physical phenomena that have been postulated to impact extravasation rates. Specifically, we are working to incorporate volume exclusion and particle geometry (both aspect ratio and size) into our simulations. These effects are expected to play an important role for larger nanoparticles that are similar in size to the pore [1]. As for the pore geometry, we chose a circular pore for simplicity, but there is every reason to expect that pore shape has an effect on the extravasation process. Moreover, we are working toward finding a similar perturbation-based analysis for point-orientable (skewed aspect ratio) particles. Finally, we are interested in the effects of suction on the extravasation rate as there can be appreciable pressure drop across the endothelium in certain tumors [1].

Acknowledgments

One of the coauthors of this article, E.S.G.S., was a graduate student at Stanford during the days when Milton Van Dyke was a “giant” on campus. He was proud to have taken all available advanced courses from Prof. Van Dyke, including his perturbation theory course. The course was a revelation, and E.S.G.S. remembers the humorous and incisive lectures that introduced the subject. E.S.G.S. is eternally grateful for that experience. The perturbation theory in this manuscript is just a small example of the preparation that E.S.G.S. credits in large part to the introduction by Prof. Van Dyke. The authors are also thankful for the many fruitful discussions with Prof. Andreas Acrivos and the critical feedback they received from him. The authors are grateful for the funding support provided by the National Institutes of Health National Cancer Institute Grant U54 CA 151459-02, Stanford Graduate Engineering Fellowship, and NSF-MRI2 Award 0960306 for providing computing resources that contributed to the research. V.N. is supported by the National Science Foundation through a graduate research fellowship.

Appendix A: Derivations

Expression for $A(k)$ thus,

$$\begin{aligned} A(k) &= \sum_{n=0}^{\infty} a_n \int_0^{\pi/2} \sin((2n+1)\theta) \sin \theta \cos(k \cos \theta) d\theta, \\ &= \sum_{n=0}^{\infty} \frac{a_n}{2} \int_0^{\pi/2} \cos((2n)\theta) - \cos((2n+2)\theta) \cos(k \cos \theta) d\theta; \end{aligned}$$

thus,

$$\begin{aligned} A(k) &= \sum_{n=0}^{\infty} \frac{1}{4} a_n \int_{-1}^{+1} \frac{T_{2n}(t) - T_{2n+2}(t)}{\sqrt{1-t^2}} \cos(kt) dt, \\ &= \sum_{n=0}^{\infty} \frac{a_n}{4} \pi (-1)^n [J_{2n}(k) + J_{2n+2}(k)], \\ &= \sum_{n=0}^{\infty} (-1)^n (2n+1) \pi \frac{a_n}{2} \frac{J_{2n+1}(k)}{k}, \end{aligned}$$

where $T_n(t)$ is the n th Chebyshev polynomial of the first kind.

Appendix B: Numerical solution for leading-order inner term

The regular system of linear equations (Eqs. (14a, b)) that we solve are (after truncation) of the form

$$[\mathbf{I} + \kappa \cdot \mathbf{T}] \mathbf{A} = \frac{2\kappa}{\pi} \mathbf{e}_1,$$

where $\mathbf{A} = [a_0, a_1, \dots, a_n]^T$, $\mathbf{e}_1 = [1, 0, \dots, 0]^T$, and $\mathbf{I}$ is the identity matrix. Typically, we truncate the series to 12 terms, which we find yields an error of at most 0.01 % for the Damköhler numbers we consider. Figure 10 shows a variation of a_0 computed for the sample case of $\kappa = 300$ for various truncation lengths.

Appendix C: Monte Carlo methods for one-dimensional Smoluchowski equation with reaction boundary

The diffusion of particles can be viewed as an evolution of the probability density function $p(z, t)$ with space (z) and time (t). The one-dimensional Smoluchowski pure diffusion equation is

$$\frac{\partial}{\partial t} p(z, t|z_0) = \frac{\partial^2}{\partial z^2} p(z, t|z_0), \quad (31a)$$

subject to the initial condition that the particle is at (z_0, t_0) in space-time,

$$p(z, t=0|z_0) = \delta(z - z_0). \quad (31b)$$

It is subject to the reactive boundary condition

$$\left. \frac{\partial}{\partial z} p_k(z, t|z_0) \right|_{z=0} = k p_k(z, t|z_0) \Big|_{z=0}, \quad (31c)$$

with $k = 0$ implying no reaction (i.e., full reflection) and $k \rightarrow \infty$ implying complete adsorption at the boundary upon every interaction of a particle with the boundary. In this work, $k = \kappa$ when a particle is over a pore and $k = 0$ when it is over a wall. The exact analytical solution to this is given as

$$p_k(z, t|z_0) = \sum_{i=0,1,2} p_{ki}(z, t|z_0), \quad (32a)$$

where

$$p_{k0}(z, t|z_0) = (4\pi t)^{-1/2} \exp\left(-(z - z_0)^2/4t\right), \quad (32b)$$

$$p_{k1}(z, t|z_0) = (4\pi t)^{-1/2} \exp\left(-(z + z_0)^2/4t\right), \quad (32c)$$

$$p_{k2}(z, t|z_0) = \frac{1}{2} (-2k) \exp(k(z + z_0 + kt)) \operatorname{erfc}\left((z + z_0 + 2kt)/\sqrt{4t}\right). \quad (32d)$$

A Brownian particle will jump from z_0 to z_f in time t with a probability drawn from one of the three distributions, p_{ki} , $i = 0, 1, 2$. To ensure the relative number of jumps made with each distribution is statistically correct, a distribution is chosen according to its relative contribution to making the jump, given by

$$N_i(t|z_0) = \int_0^\infty p_{ki}(z, t|z_0) dz, \quad i=0, 1, 2. \quad (33)$$

Certainly $\sum_{i=0,1,2} N_i = 1$. A jump is made assuming there is a wall at $z = 0$ (pure reflection, $k = 0$) and the jump endpoint is decided by only using N_1 and N_2 . Then a survival probability is assigned to the particle for the jump made as a way to account for the contribution from N_3 . This survival probability P_s is compounded for each particle as it jumps at each time step in our simulation, and the yield is given by $(1 - P_s)$ per particle at the end of time t . This provides net-yield-versus-time data, which can be used to compute the flux or, equivalently, the extravasation rate (S). The aforementioned steps are described in brief in what follows.

1. A random number r_1 is chosen from a uniform distribution on $(0, 1]$, and a probability distribution function is chosen from p_{00} if $0 < r_1 < N_0$, else it is chosen from p_{01} if $N_0 < r_1 < N_0 + N_1$.
2. Another random number r_2 is drawn from a uniform distribution on $(0, 1]$, and the following integral is inverted analytically for that density function to obtain the endpoint z_f at time t , having started from z_0 :

$$r_2 = \left[\int_0^{z_f} p_{0i}(z, t|z_0) dz \right] / N_i. \quad (34)$$

Thus we choose one of the following two equations to compute the jump endpoint:

$$z_f = z_0 + \sqrt{4t} \operatorname{erfc}^{-1}\left(r_2 \operatorname{erfc}\left(\frac{-z_0}{\sqrt{4t}}\right)\right), \quad (35)$$

$$z_f = -z_0 + \sqrt{4t} \operatorname{erfc}^{-1}\left(r_2 \operatorname{erfc}\left(\frac{z_0}{\sqrt{4t}}\right)\right). \quad (36)$$

3. The survival probability is computed by taking the ratio of the probability of having made the jump $z_0 \rightarrow z_f$ in time t in the presence of a reactive boundary to the probability of having made the same jump in the presence of a reflective boundary:

$$S = \frac{p_k(z_f, t|z_0)}{p_0(z_f, t|z_0)}. \quad (37)$$

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Fig. 1. Simulation domain of κ versus P , with the region for which the present theory is developed as shown. Previous work is done only in the adsorption-dominated regime (Phillips [6], Stone [8], Lévêque [9])

Fig. 2. Schematic of our model. The axes are fixed with the origin at the center of the pore embedded in the flat plate with shear flow on it

Fig. 3.

Values of a_0 , i.e., $2S(P=0, \kappa)/\pi$, from Eqs. (14a, b) are plotted for the entire range of κ . The expression resulting from the law of additive resistances (Eq. 4a) and the approximation from Eq. (27) are also plotted for comparison. **a** a_0 plotted for $\kappa \ll 1$ and $\kappa \sim O(1)$, along with the two asymptotes. **b** a_0 plotted for $\kappa \gg 1$ and $\kappa \sim O(1)$

Fig. 4. Schematic of simulation domain indicating various coordinate directions and corresponding boundary conditions, along with pore on floor

Fig. 5. Singular perturbation theory (Eq. 26), simulation values, the law of additive resistances (Eq. 4a), and the approximation from Eq. (28) for the extravasation rate at $P = 0$ for $0 < \kappa < 100$, along with the two asymptotes at the extremes of the domain. **a** $\kappa < 1$ and $\kappa \sim 1$. **b** $\kappa \sim 1$ and $\kappa \gg 1$

Fig. 6.

Theory (Eq. (26)), approximation (Eq. 28), and Brownian dynamics simulation values of S at $P = 0.3$ for $0 \leq \kappa \leq 110$. **a** $\kappa \ll 1$ and $\kappa \sim 1$. **b** $\kappa \sim 1$ and $\kappa \gg 1$

Fig. 7.

Theory (Eq. 26), approximation (Eq. 28), and Brownian dynamics simulation values of S at $P = 2$ for $0 \leq \kappa \leq 110$. **a** $\kappa \ll 1$ and $\kappa \sim 1$. **b** $\kappa \sim 1$ and $\kappa \gg 1$

Fig. 8. Theory (Eq. 26) (*dashed*), approximation (Eq. 28) (*triangles*), and Brownian dynamics simulation (*boxes*) extravasation rates plotted for P ranging from 0 to 100 and $\kappa = 1$. **a** $\kappa = 1$. **b** $\kappa = 0.5$

Fig. 9.

Theory (Eq. 26) (*dashed*), approximation (Eq. 28) (*triangles*), and Brownian dynamics simulation (*connected boxes*) extravasation rates plotted for P ranging from 0 to 100 and $\kappa > 1$. Graetz-Lévêque asymptote (*solid line*) plotted for $\kappa = 300$. **a** $\kappa = 5$. **b** $\kappa = 10$. **c** $\kappa = 100$. **d** $\kappa = 300$.

Fig. 10.
Variation of a_0 with truncation length in Eq. (14a, 14b) for $\kappa = 300$