Diffusion-Reaction in Branched Structures: Theory and Application to the Lung Acinus

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An exact "branch by branch" calculation of the diffusional flux is proposed for partially absorbed random walks on arbitrary tree structures. In the particular case of symmetric trees, an explicit analytical expression is found which is valid whatever the size of the tree. Its application to the respiratory phenomena in pulmonary acini gives an analytical description of the crossover regime governing the human lung efficiency.

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The supply of nutritive or other substances from the source to the periphery of an extended biological system frequently involves branched structures. Typical examples are plant roots and branches, animal circulatory and respiratory systems, as well as river basins. A ramified geometry ensures capillary distribution to large exchange surfaces. In mammalian lungs, the bronchial tree is responsible for the convective transport of fresh air from the mouth to the gas exchange units, called pulmonary "acini". The acini comprise the last generations of airways where oxygen is transported by molecular diffusion in air and transferred to blood through the alveolar membrane [1]. The diffusion transport in branched structures has been addressed in several papers (see [2,3], and references therein). The important point here is that we consider the stationary diffusion described by the Laplace equation for oxygen concentration, with a *finite* absorption rate at the alveolar membrane. Recently, it has been shown that this partial differential equations problem (PDE) in a branched geometry can be mapped into a discrete problem defined by random walks on a finite Cayley tree, obtained from the skeleton of the three-dimensional branched structure. Random walks figuring oxygen diffusion on this skeleton tree were used to compute the human acinus efficiency [4]. The very slow decrease of branch diameters into the acinus is known to be irrelevant for *diffusional* flow (the problem of extreme sensitivity of a branched system to *hydrodynamic* flow is discussed in [5]).

In the present Letter, we describe an efficient "branch by branch" procedure providing an *exact* resolution of this discrete problem. The flux of particles diffusing on arbitrary trees with partial absorption at the boundary is derived analytically. Its application to symmetric trees provides an exact explicit relation for this diffusional flux. The branch by branch approach can also be used for asymmetric trees and is applied to calculate the flux into the real pulmonary acinus described in [6].

The PDE problem for oxygen concentration is expressed by the Laplace equation $\Delta c = 0$ with the mixed boundary condition at the partially absorbing surface

$$\frac{\partial c}{\partial n} = \frac{1}{\Lambda} c, \tag{1}$$

where n is the normal to the surface. A fixed concentration c_0 is set at the source of diffusion. The parameter Λ is the ratio D/W of the oxygen diffusivity in air D and membrane permeability W [7]. In the healthy human lungs, the value of Λ is around 30 cm. It is of practical importance to know how the transport properties of the human acini depend on this physical (and physiological) parameter as, for example, pulmonary edema degrades the membrane permeability leading to a significant increase of Λ. The oxygen flux through the membrane of total surface S is given by $\Phi = W \int c dS$. The system behavior as a gas exchanger is well described by a quantity η called efficiency and defined as

$$\eta = \frac{\Phi}{W c_0 S}. \tag{2}$$

Therefore, η is a number between zero and one representing the fraction of the surface which is active. It only depends on the physical parameter Λ and the morphology of the branched structure [7].

Let us introduce the discrete representation of this PDE problem. First, we note that the stationary diffusion with partial absorption at the boundary can be modeled by d-dimensional partially absorbed random walks on a lattice of parameter a [Fig. 1(a)]. In this frame, the mixed boundary condition (1) means that a particle hitting the boundary can be absorbed with probability σ, or reflected to its preceding position with probability $(1 - \sigma)$. The absorption probability σ is related to the parameter Λ of the equivalent PDE problem by the following relation: $\sigma = (1 + \Lambda/a)^{-1}$ [8]. Dealing with thin channels of square profiles, there are $2d - 2$ directions to the boundary. Then, the total probability to be absorbed at one step is $\sigma(2d - 2)/(2d)$. So, d-dimensional random walks in a thin channel of "diameter" a can be considered as one-dimensional longitudinal walks with the following dynamic "rules": being on an intermediate site k, the random particle can jump to the left (site $k - 1$) with probability

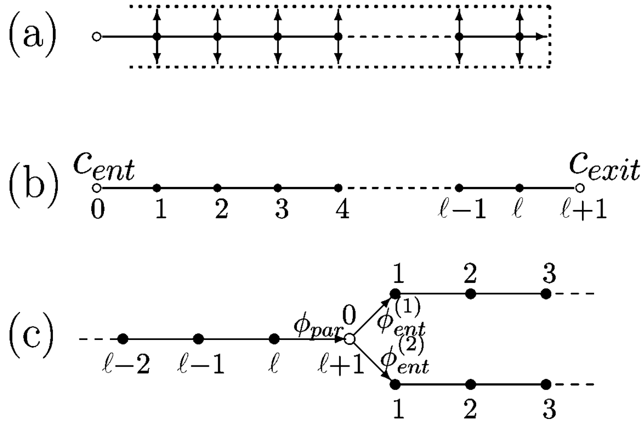

FIG. 1. (a) The stationary diffusion in a rectangular pore with partial absorption at the boundary (dotted contour) can be modeled as a one-dimensional partially absorbed random walk; (b) Linear chain of ℓ intermediate sites with the entrance (site 0) and the exit (site $\ell+1$); (c) At the branching point $\ell+1$, the parent branch (on the left) is divided into daughter branches (on the right).

$1/2d$, or to the right (site $k+1$) with the same probability $1/2d$; or it can stay on the same site k with probability $(1-\sigma)(1-1/d)$ (that is equivalent to the reflection from the boundary); or the random particle can be absorbed with probability $\sigma(1-1/d)$.

These rules can be written in the form of discrete differential equations for concentrations c_k (with $k = 1, ..., \ell$) [9,10]:

$$\frac{1}{2}(c_{k-1}+c_{k+1}) - c_k = (d-1)\sigma c_k, \tag{3}$$

where the left hand side represents the discrete Laplace operator.

For finite channels, boundary conditions should be defined for the *entrance* and *exit* sites. These sites will be labeled by 0 and $\ell+1$ for convenience [see Fig. 1(b)]. Imposing the values of the concentration at the entrance and the exit of the chain as respectively $c_0 = c_{\rm ent}$ and $c_{\ell+1} = c_{\rm exit}$, one can solve the discrete one-dimensional Eq. (3) explicitly by Fourier transform. In particular, the following linear relations hold:

$$c_1 = (1-u_{\sigma,\ell})c_{\rm ent} + v_{\sigma,\ell}c_{\rm exit}$$
$$c_\ell = v_{\sigma,\ell}c_{\rm ent} + (1-u_{\sigma,\ell})c_{\rm exit},$$

where coefficients $u_{\sigma,\ell}$ and $v_{\sigma,\ell}$ depend only on the branch length ℓ and the absorption probability σ:

$$u_{\sigma,\ell} = 1 - \frac{s_{\sigma,\ell}}{([1+(d-1)\sigma]s_{\sigma,\ell}+1/2)^2 - s_{\sigma,\ell}^2}$$
$$v_{\sigma,\ell} = 1 - \frac{[1+(d-1)\sigma]s_{\sigma,\ell}+1/2}{([1+(d-1)\sigma]s_{\sigma,\ell}+1/2)^2 - s_{\sigma,\ell}^2},$$

with

$$s_{\sigma,\ell} = \frac{1}{2\ell}\sum_{\alpha=0}^{\ell-1}[1+(d-1)\sigma - \cos 2\pi\alpha/\ell]^{-1}.$$

The entering flux $\phi_{\rm ent}$ and the exiting flux $\phi_{\rm exit}$ can be defined as

$$\phi_{\rm ent} = DS_0\frac{c_0 - c_1}{a} \qquad \phi_{\rm exit} = DS_0\frac{c_\ell - c_{\ell+1}}{a},$$

where the constant D corresponds to the diffusion coefficient, and S_0 stands for cross section area ($S_0 = a^{d-1}$ for a square profile). In conclusion, the concentration $c_{\rm ent}$ and the entering flux $\phi_{\rm ent}$ depend on $c_{\rm exit}$ and $\phi_{\rm exit}$ through *linear* functions

$$c_{\rm ent} = \frac{u_{\sigma,\ell}}{v_{\sigma,\ell}}c_{\rm exit} + \frac{a}{DS_0}\frac{1}{v_{\sigma,\ell}}\phi_{\rm exit}, \tag{4}$$

$$\phi_{\rm ent} = \frac{u_{\sigma,\ell}}{v_{\sigma,\ell}}\phi_{\rm exit} + \frac{DS_0}{a}\frac{u_{\sigma,\ell}^2 - v_{\sigma,\ell}^2}{v_{\sigma,\ell}}c_{\rm exit}. \tag{5}$$

The coefficients are complicated but *explicit* functions of the parameters σ and ℓ.

Now, in order to compute the flux within a complex tree, we divide it into branches. The thin channel description holds for each single branch. It is then possible to solve the problem for the entire system by using an iterative branch by branch procedure from the last generation up to the root, once some suitable condition has been defined for the branching points.

Let us consider the last branches. The mixed boundary condition (1) is applied on the terminal site $\ell+1$

$$\phi_{\rm exit} = DS_0\left(\frac{\partial c}{\partial n}\right)_{\rm exit} = \frac{DS_0}{\Lambda}c_{\rm exit}. \tag{6}$$

From the last equations, one obtains a direct relation between $c_{\rm ent}$ and $\phi_{\rm ent}$:

$$\phi_{\rm ent} = \frac{DS_0}{f_{\sigma,\ell}(\Lambda)}c_{\rm ent}. \tag{7}$$

Here $f_{\sigma,\ell}(\Lambda)$ is the new function

$$f_{\sigma,\ell}(\Lambda) = a\frac{(\Lambda/a)u_{\sigma,\ell}+1}{(\Lambda/a)(u_{\sigma,\ell}^2 - v_{\sigma,\ell}^2) + u_{\sigma,\ell}}. \tag{8}$$

This means that the relation (6) remains valid at the entrance but with a modified parameter $\Lambda' = f_{\sigma,\ell}(\Lambda)$. In the particular case of a single deep pore of length $\ell \gg 1$ (one branch alone), there is a region of values Λ/a (of order of ℓ^2) where the function $f_{\sigma,\ell}(\Lambda)$ behaves like $(\Lambda/a)^{1/2}$. One thus retrieves the flux $\phi_{\rm ent}$ following a power law with the classical exponent $-1/2$ [11].

The next step is to consider the branching point where the parent branch divides into M daughter branches of lengths $\ell_1, \ldots, \ell_M$ [see Fig. 1(c)]. For each of these daughter branches, one can apply the relation (7) between the concentration $c_{\rm ent}$ and the entering flux $\phi_{\rm ent}$. We will use the superscript to distinguish different daughter branches,

$$\phi_{\rm ent}^{(m)} = \frac{DS_0}{f_{\sigma,\ell_m}(\Lambda)} c_{\rm ent}^{(m)} \qquad (m = 1, \ldots, M) \tag{9}$$

At the branching point, one has the following conditions:

$$\begin{aligned} c_{\rm ent}^{(1)} = c_{\rm ent}^{(2)} = \ldots = c_{\rm ent}^{(M)} = c_{\rm par} \\ \phi_{\rm ent}^{(1)} + \phi_{\rm ent}^{(2)} + \ldots + \phi_{\rm ent}^{(M)} = \phi_{\rm par}. \end{aligned} \tag{10}$$

The first condition holds since the branching point connects the parent branch exit with the daughter branch entrances. The second condition provides the conservation of flux at the branching point: the exiting flux $\phi_{\rm par}$ of the parent branch is distributed into M daughter branches. If the branching point can also absorb the particles, the corresponding flux ought to be taken into account on the left hand side. Using these two conditions and relations (9), one has

$$\phi_{\rm par} = \frac{DS_0}{\Lambda'} c_{\rm par} \qquad \frac{1}{\Lambda'} = \sum_{m=1}^{M} \frac{1}{f_{\sigma,\ell_m}(\Lambda)}. \tag{11}$$

Now, one can forget the branching point and the daughter branches and use the relation between the concentration and flux at the end of the parent branch. Performing iteratively this branch by branch procedure up to the tree entrance, one obtains a similar expression for the total flux Φ,

$$\Phi = \frac{DS_0}{\Lambda_{\rm eff}} c_0, \tag{12}$$

where c_0 is the concentration at the main entrance. The function $\Lambda_{\rm eff}$ (depending on σ and, consequently, on Λ) provides the response of the branched tree, and the efficiency η can be written as

$$\eta(\Lambda) = \frac{\Phi}{Wc_0S} = \frac{S_0}{S}\frac{\Lambda}{\Lambda_{\rm eff}}. \tag{13}$$

A particular simplification appears in the case of a symmetric tree of constant branching number M when all branches have the same length ℓ. Let us consider such a tree of depth n (containing n branching levels). In this case, the relation (11) becomes

$$\Lambda_1 = \kappa f_{\sigma,\ell}(\Lambda) \equiv \tilde{f}_{\sigma,\ell}(\Lambda),$$

with $\kappa \equiv 1/M$. On the second level, one applies again this relation: $\Lambda_2 = \tilde{f}_{\sigma,\ell}(\Lambda_1) = \tilde{f}_{\sigma,\ell}(\tilde{f}_{\sigma,\ell}(\Lambda))$. Repeating this procedure, one finds for the main entrance:

$$\Lambda_{\rm eff} \equiv \Lambda_n = \underbrace{\tilde{f}_{\sigma,\ell}(\tilde{f}_{\sigma,\ell}(\ldots\tilde{f}_{\sigma,\ell}}_{n\ \text{times}}(\Lambda)\ldots)). \tag{14}$$

Since $\tilde{f}_{\sigma,\ell}(\Lambda)$ is the linear fractional transformation of Λ, its successive application of itself gives again a linear fractional transformation. One can calculate its coefficients explicitly

$$\Lambda_{\rm eff} = \kappa a \frac{\Lambda\left(u_{\sigma,\ell} - v_{\sigma,\ell}^2 \frac{\lambda_1^{n-1}-\lambda_2^{n-1}}{\lambda_1^n-\lambda_2^n}\right) + a}{\Lambda(u_{\sigma,\ell}^2 - v_{\sigma,\ell}^2) + a\left(\frac{\lambda_1^{n+1}-\lambda_2^{n+1}}{\lambda_1^n-\lambda_2^n} - \kappa u_{\sigma,\ell}\right)}, \tag{15}$$

with

$$\lambda_{1,2} = \frac{(1+\kappa)u_{\sigma,\ell} \pm \sqrt{(1+\kappa)^2 u_{\sigma,\ell}^2 - 4\kappa v_{\sigma,\ell}^2}}{2}. \tag{16}$$

Eqs. (13) and (15) give then an analytical expression for the efficiency η of a symmetric tree as a function of Λ and of the tree characteristics κ, ℓ, and n.

Figure 2 shows the dependency of the efficiency η as a function of Λ/L_p, where the length scale $L_p = S/a$ qualitatively corresponds to the perimeter of a cut of the acinus from the model of Kitaoka [12]. The observed behavior may be quite different from that of large trees for which one expects a power law with an exponent equal to 1 [13]. This last behavior can be derived from the above equations by taking the tree depth n sufficiently large. It can be shown that in this case the length $\Lambda_{\rm eff}$ becomes very close to the fixed point $\Lambda_{\rm eff}^{(\infty)} = a(\ell+1)/(M-1)$ of the linear fractional transformation $\tilde{f}_{\sigma,\ell}(\Lambda)$ (for small σ). In this regime, the efficiency η given by (14) varies linearly with Λ. This behavior is observed in Fig. 2 for the larger tree corresponding to $M = 4$ and (Λ/L_p) not too large. Consequently, a particular property of a large tree is that the flux given by Eq. (12) is constant and independent of the permeability W: the change in permeability is exactly compensated by the change in the size of the active zone. In this regime, the global flux is "robust" against permeability changes.

On the opposite, for the smaller tree corresponding to $M = 2$, which is representative of the human acinus, one observes a nontrivial behavior. This means that, due to finite size effects, the system always works in the crossover regime for which we now have an exact theory. In other words, the whole function $\eta(\Lambda)$ (instead of a single power

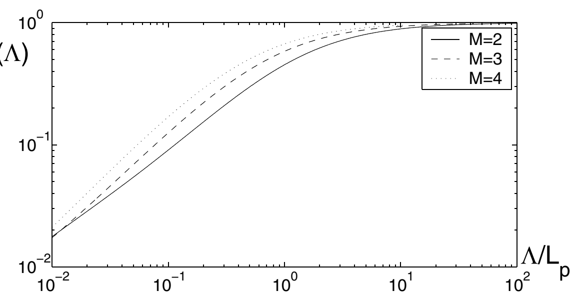

FIG. 2. Efficiency of finite symmetric trees with different branching numbers $M = 2$, 3, 4, fixed branch length $\ell = 2$, and five levels of branching (depth $n = 5$).

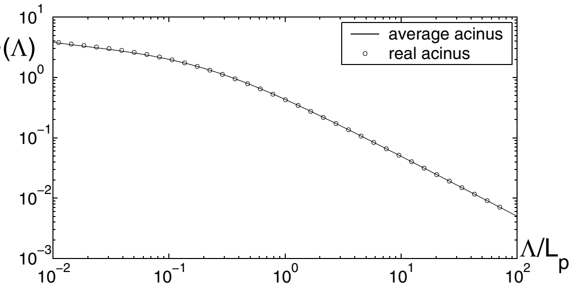

FIG. 3. Comparison between the flux (at constant D) in the average symmetrized acinus and the real acinus.

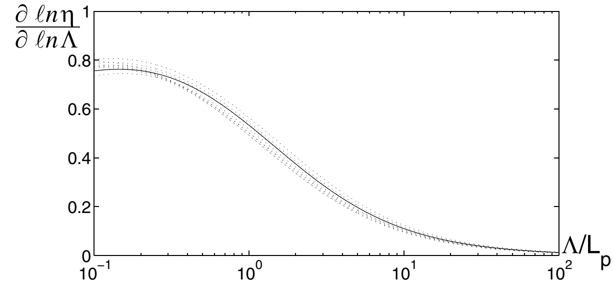

FIG. 4. Logarithmic derivatives of the efficiency of eight real subacini (dotted lines) compared to that of the symmetric dichotomic tree with $\ell = 2$ and $n = 5$.

law) has to be considered to correctly reproduce the complex response of the branched structure.

The human lung works in a different manner at rest and in exercise conditions because the region where the convection-diffusion transition occurs depends directly on the air flow velocity [7]. At rest the diffusion source is situated at the entry of what is called a "1/8 subacinus". Although always dichotomic ($M = 2$), the real subacini are slightly different in size and the corresponding trees are not symmetric: the branch lengths vary and some of them are terminated earlier than others [6]. It is then of interest to compare the properties of an "average" symmetrized structure to the different real subacini. The branch by branch method presented above can be used to compute the flux in the real acinus as the sum of the fluxes in its eight subacini. One can then compare this real flux with 8 times the flux in the dichotomic symmetric tree with the same average length of branches ($\ell = 2$) and the same average total area (corresponding to the depth $n = 5$). The result is shown in Fig. 3. One observes that the simplified acinus provides a good analytical approximation for the flux in the real pulmonary acinus. Figure 4 shows the detailed comparison between the logarithmic derivatives of the efficiency of the eight real subacini with the same quantity for the average symmetrized subacinus.

In summary, an exact branch by branch calculation of the diffusional flux has been developed for arbitrary trees. For symmetric trees, one obtains an explicit analytical expression. In a general case, one can use this branch by branch procedure as a theoretical basis for efficient numerical calculations. Indeed, this method opens the possibility to investigate various transport phenomena on large trees. In particular, it is found that large trees present a flux which corresponds to a limited efficiency but, remarkably, the global flux remains independent of the permeability. The particular application of this approach to the respiratory processes in human lungs provides an explicit analytical approximation for the efficiency of pulmonary acini for which a symmetrized acinus approximation is shown to be valuable. This last result is important for future studies of the convection-diffusion transition in the human lung. This theoretical approach could be useful for studying other phenomena on branched structures such as, e.g., spectral dimension of fractal trees [14,15].

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