Diffusive flux in a model of stochastically gated oxygen transport in insect respiration

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Oxygen delivery to insect tissues is controlled by transport through a branched tubular network that is connected to the atmosphere by valve-like gates, known as spiracles. In certain physiological regimes, the spiracles appear to be randomly switching between open and closed states. Quantitative analysis of this regime leads a reaction-diffusion problem with stochastically switching boundary condition. We derive an expression for the diffusive flux at long times in this problem. Our approach starts with the derivation of the passage probability for a single particle that diffuses between a stochastically gated boundary, which models the opening and closing spiracle, and the perfectly absorbing boundary, which models oxygen absorption by the tissue. This passage probability is then used to derive an expression giving the diffusive flux as a function of the geometric parameters of the tube and characteristic time scales of diffusion and gate dynamics. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4950769>]

I. INTRODUCTION

Stochastic gating plays an important role in various biophysical processes such as transport through ligand- and voltage-gated ion channels,¹ gated ligand binding to proteins,^{2–10} small molecule migration in proteins, which is controlled by passage through fluctuating bottlenecks,^{11–23} etc. A common feature of all these processes is that their rates are determined by the so-called stochastic “gate” opening and closing, due to random transitions of the system between two or more states with different geometric parameters. In some cases, stochastic gating can be modeled as random switching of boundary conditions for diffusing species.

The focus of this paper is on stochastic gating in a simple model motivated by studies of insect respiration. In insects, gas exchange between atmosphere and tissues relies on diffusive transport through a tubular network.²⁴ Oxygen enters through the vascular openings in the exoskeleton, called spiracles, and diffuses through a series of tubes, called tracheae. The state of the spiracles is regulated by complex neuromuscular systems. Depending on the physiological conditions, insects can enter a regime of discontinuous gas exchange, in which the spiracle appears to be randomly switching between the open and closed states.^{25–29} The functional significance of this regime is still unclear, but several of the proposed mechanisms require quantitative analysis of diffusive fluxes through the tracheal network.²⁵

A first step in this direction was made by Lawley *et al.*³⁰ who proposed and analyzed a one-dimensional diffusion model, in which the absorbing boundary condition at the tube exit was used to describe oxygen consumption by the tissue, and randomly switching boundary conditions at the

tube entrance were used to describe the spiracle dynamics. The main result of Ref. 30 is the expression for the flux through the absorbing boundary at long times, which gives the flux as a function of the problem parameters. This expression predicts that the flux diverges as the tube length tends to zero, which is clearly unphysical.

In the present paper we derive an expression for the flux, which reduces to that obtained in Ref. 30 when the tube length significantly exceeds its radius and remains finite, as the tube length vanishes. The outline of the paper is as follows. We discuss the model in Sec. II. In Section III we derive an expression for the passage probability which is the probability that a particle entering a stochastically gated tube will traverse it and escape on the opposite side. This passage probability is then used in Section IV to find the expression for the diffusive flux through the tube when its entrance is stochastically gated. Some concluding remarks are made in the final Section V.

II. MODEL

Consider two reservoirs *A* (atmosphere) and *B* (tissue) connected by a cylindrical tube of radius *a* and length *L*. Our goal is to find the long time behavior of the diffusive flux *f* of particles (oxygen molecules) from reservoir *A* to reservoir *B* when the entrance to the tube from reservoir *A* randomly jumps between open and closed states as shown in Fig. 1. When the gate is open, particles freely enter the tube from reservoir *A* where their concentration and diffusivity, respectively, are *c_A* and *D_A*. The influx through the open gate, denoted by *f_{in}⁽⁰⁾*, is the product of the particle concentration *c_A* and the Hill rate constant *k_H*,³¹ *f_{in}⁽⁰⁾* = *k_Hc_A*,

FIG. 1. Schematic representation of two reservoirs, *A* and *B*, connected by a tube of length *L* and radius *a*. The gate at the tube entrance from reservoir *A* can randomly jump between open and close states.

where

$$k_H = 4aD_A. \quad (2.1)$$

As in Ref. 30, we take that the gate dynamics is Markovian and characterized by the rate constants r_0 and r_1 , where the subscripts 0 and 1 denote open and closed states of the gate, respectively. The probabilities $P_0(t)$ and $P_1(t)$ of finding the gate open and closed at time t satisfy the rate equations

$$\frac{dP_0(t)}{dt} = -\frac{dP_1(t)}{dt} = -r_0P_0(t) + r_1P_1(t). \quad (2.2)$$

As a consequence, the equilibrium probability of finding the gate open, P_0^{eq} , is

$$P_0^{eq} = \frac{r_1}{r_1 + r_0}. \quad (2.3)$$

The mean influx entering a stochastically gated tube from reservoir *A*, denoted by f_{in} , is the product of the influx, $f_{in}^{(0)} = k_H c_A$, through the open entrance and the probability, P_0^{eq} , of finding the gate open,

$$f_{in} = P_0^{eq} f_{in}^{(0)} = \frac{r_1}{r_1 + r_0} 4aD_A c_A. \quad (2.4)$$

A particle entering the tube from reservoir *A* either passes through the tube to reservoir *B*, contributing to the flux of interest, or returns to reservoir *A*. Let W be the probability of the particle passage through the tube and escape to reservoir *B*. The flux of interest, f , is the product of the influx f_{in} and the passage probability W ,

$$f = W f_{in} = W \frac{r_1}{r_1 + r_0} 4aD_A c_A. \quad (2.5)$$

Thus, the problem of finding the flux reduces to that of finding the passage probability. An expression giving this probability as a function of the parameters of the problem is derived in Sec. III.

III. THE PASSAGE PROBABILITY

We derive an expression for the probability W , by solving a one-dimensional diffusion problem on an interval of length L , $0 < x < L$, with stochastically switching boundary conditions on the right end of the interval, at $x = L$ (see Fig. 1). As in Ref. 30 we assume that the left boundary of the interval, at $x = 0$, is perfectly absorbing. The boundary condition on the right boundary depends on the state of the gate. The right boundary is perfectly reflecting when the gate is closed,

and partially absorbing when the gate is open. The effective boundary trapping rate entering the boundary condition in the gate-open state, denoted by κ_L , is given by^{32,33}

$$\kappa_L = \frac{4D_A}{\pi a}. \quad (3.1)$$

Roughly speaking, this expression follows from the condition of detailed balance. Specifically, when the exit to reservoir *B* at the left end of the tube is blocked, the system is in equilibrium, and the particle concentration in the tube is the same as in reservoir *A*. As a consequence, the one-dimensional concentration of the particles in the tube is $\pi a^2 c_A$. The expression in Eq. (3.1) follows from the requirement that, in equilibrium, the influx from the reservoir *A*, $k_H c_A = 4aD_A c_A$, must be compensated by the outflux $\kappa_L \pi a^2 c_A$ from the tube to the reservoir. One can find derivations of the expression for the trapping rate in Eq. (3.1) in Refs. 32 and 33.

Consider a particle that entered the tube from reservoir *A* at time $t = 0$ and has not escaped from the tube during time t . Let $g_0(x, t)$ and $g_1(x, t)$ be the probability densities of finding the particle at point x of the interval, $0 < x < L$, and the gate in open and closed states, respectively, at time t . These two probability densities are components of the two-component particle propagator, which satisfy

$$\frac{\partial g_0}{\partial t} = D \frac{\partial^2 g_0}{\partial x^2} - r_0 g_0 + r_1 g_1, \quad (3.2)$$

$$\frac{\partial g_1}{\partial t} = D \frac{\partial^2 g_1}{\partial x^2} + r_0 g_0 - r_1 g_1, \quad (3.3)$$

subject to the boundary conditions

$$g_0(0, t) = g_1(0, t) = \left. \frac{\partial g_1(x, t)}{\partial x} \right|_{x=L} = 0, \quad (3.4)$$

$$-D \left. \frac{\partial g_0(x, t)}{\partial x} \right|_{x=L} = \kappa_L g_0(L, t), \quad (3.5)$$

and the initial conditions

$$g_0(x, 0) = \delta(x - L), \quad g_1(x, 0) = 0. \quad (3.6)$$

Here D is the particle diffusivity in the tube, which may differ from its bulk value D_A in reservoir *A*.

The probability flux entering reservoir *B* from the tube at time t is $D [\partial (g_0 + g_1) / \partial x]_{x=0}$. The passage probability of interest is the integral of this flux with respect to time from zero to infinity,

$$\begin{aligned} W &= D \int_0^\infty \left[\frac{\partial}{\partial x} (g_0 + g_1) \right]_{x=0} dt \\ &= D \left[\frac{d}{dx} \int_0^\infty (g_0 + g_1) dt \right]_{x=0}. \end{aligned} \quad (3.7)$$

Introducing the notations $\hat{g}_0(x)$ and $\hat{g}_1(x)$ for the time integrated components of the propagator,

$$\hat{g}_0(x) = \int_0^\infty g_0(x, t) dt, \quad \hat{g}_1(x) = \int_0^\infty g_1(x, t) dt, \quad (3.8)$$

we can write Eq. (3.7) as

$$W = D \left[\frac{d}{dx} (\hat{g}_0(x) + \hat{g}_1(x)) \right]_{x=0}. \quad (3.9)$$

Integrating Eqs. (3.2)–(3.5) with respect to time from zero to infinity and using the initial conditions in Eq. (3.6), we find that functions $\hat{g}_0(x)$ and $\hat{g}_1(x)$ satisfy

$$D \frac{d^2 \hat{g}_0}{dx^2} - r_0 \hat{g}_0 + r_1 \hat{g}_0 = -\delta(x - L), \quad (3.10)$$

$$D \frac{d^2 \hat{g}_1}{dx^2} + r_0 \hat{g}_0 - r_1 \hat{g}_0 = 0, \quad (3.11)$$

subject to the boundary conditions

$$\hat{g}_0(0) = \hat{g}_1(0) = \left. \frac{d\hat{g}_1(x)}{dx} \right|_{x=L} = 0, \quad (3.12)$$

$$-D \left. \frac{d\hat{g}_0(x)}{dx} \right|_{x=L} = \kappa_L \hat{g}_0(L). \quad (3.13)$$

Integrating Eq. (3.10) with respect to x from $L - \varepsilon$ to L , where $\varepsilon \rightarrow 0$, one can move the boundary condition into the interval and impose it at $L - \varepsilon$, i.e., in front of the δ -function. As a result, one can ignore the δ -function on the right-hand side of Eq. (3.10) and replace the boundary condition in Eq. (3.13) by

$$D \left. \frac{d\hat{g}_0(x)}{dx} \right|_{x=L} = 1 - \kappa_L \hat{g}_0(L). \quad (3.14)$$

A solution to the resulting boundary value problem satisfying the boundary conditions at $x = 0$ is given by

$$\hat{g}_0(x) = \frac{1}{r_0 + r_1} (r_1 M x + N \sinh(qx)), \quad (3.15)$$

$$\hat{g}_1(x) = \frac{1}{r_0 + r_1} (r_0 M x - N \sinh(qx)), \quad (3.16)$$

where M and N are constants which can be determined from the boundary conditions at $x = L$, and q is a parameter related to the diffusivity D , and rate constants r_1 and r_0 by the relationship $q = \sqrt{(r_1 + r_0)/D}$. The reflecting boundary condition for $\hat{g}_1(x)$ at $x = L$ allows one to establish a relation between M and N ,

$$N = \frac{r_0}{q \cosh(\gamma)} M, \quad (3.17)$$

where

$$\gamma = qL = L \sqrt{\frac{r_1 + r_0}{D}} \quad (3.18)$$

is the dimensionless parameter introduced in Ref. 30. One can determine constant M using (3.14) and (3.17). The result is

$$M = \frac{r_1 + r_0}{D(r_1 + r_0) + \kappa_L L \left(r_1 + \frac{r_0}{\gamma} \tanh(\gamma) \right)}. \quad (3.19)$$

According to Eqs. (3.9), (3.15), (3.16), and (3.19), the passage probability is given by

$$W = DM = \frac{r_1 + r_0}{r_1 + r_0 + \frac{\kappa_L L}{D} \left(r_1 + \frac{r_0}{\gamma} \tanh(\gamma) \right)}. \quad (3.20)$$

Substituting here the expression for the effective trapping rate, κ_L , in Eq. (3.1), we arrive at

$$W = \frac{r_1 + r_0}{r_1 + r_0 + \left(r_1 + \frac{r_0}{\gamma} \tanh(\gamma) \right) \frac{4LD_A}{\pi a D}}. \quad (3.21)$$

Thus, the passage probability is a function of three dimensionless parameters: (1) the rate constant ratio, r_0/r_1 , (2) the square root of the ratio of the characteristic diffusion time, L^2/D , and the gate relaxation time, $(r_1 + r_0)^{-1}$, $\gamma = \sqrt{L^2(r_1 + r_0)/D}$, and (3) the parameter $4LD_A/(\pi a D)$, which is proportional to the ratio of the tube geometric parameters multiplied by the ratio of the diffusivities in reservoir A and in the tube.

When $r_0/r_1 \rightarrow 0$, the passage probability in Eq. (3.21) reduces to its counterpart for a permanently open gate, W_0 ,

$$W_0 = \frac{1}{1 + 4LD_A/(\pi a D)}. \quad (3.22)$$

W also reduces to W_0 as $\gamma \rightarrow 0$. In this limiting case the gate dynamics is so slow that a particle entering the tube from reservoir A through the open gate, escapes from the tube before the gate closes. As follows from Eq. (3.22), the passage probability W_0 monotonically decreases, as the tube length, L , increases, from unity at $L = 0$, to its large L asymptotic behavior given by $W_0|_{L \rightarrow \infty} \approx \pi a D/(4LD_A)$.

It is convenient to write Eq. (3.21) as

$$\frac{1}{W} = \frac{1}{W_0} - \frac{r_0}{r_1 + r_0} \left(1 - \frac{1}{\gamma} \tanh(\gamma) \right) \frac{4LD_A}{\pi a D}. \quad (3.23)$$

This shows that the passage probability W at a fixed value of the parameter $4LD_A/(\pi a D)$, determining W_0 , Eq. (3.22), is a monotonically increasing function of both r_0/r_1 and γ . At fixed γ , W increases with the rate constant ratio from W_0 at $r_0/r_1 = 0$ to its maximum value, $W_{\max}$, at $r_0/r_1 = \infty$ given by

$$W_{\max} = \frac{1}{1 + \frac{1}{\gamma} \tanh(\gamma) \frac{4LD_A}{\pi a D}}. \quad (3.24)$$

$W_{\max}$, in turn, grows from W_0 at $\gamma = 0$ to unity, as $\gamma \rightarrow \infty$. The latter limiting value, $W_{\max}|_{\gamma \rightarrow \infty} = 1$, reflects the fact that the particle cannot return to reservoir A when r_0/r_1 , $\gamma \rightarrow \infty$, since the gate is closed most of the time. Plots in Fig. 2 illustrate the dependence of the passage probability on the rate constant ratio at three values of the parameter γ , $\gamma = 1, 10$, and 100 (from top to bottom), for $4LD_A/(\pi a D) = 10$.

FIG. 2. Passage probability, W , as a function of the rate constant ratio, r_0/r_1 , at three values of the parameter $\gamma = \sqrt{L^2(r_1 + r_0)/D}$, $\gamma = 100, 10$, and 1 (from top to bottom), for $4LD_A/(\pi a D) = 10$.

The expression for the passage probability in Eq. (3.21) is the main result of this section. We use it in Sec. IV to find the flux.

IV. THE FLUX

Substituting W in Eq. (3.21) into Eq. (2.5), we arrive at

$$f = \frac{4aD_A c_A r_1}{r_1 + r_0 + \left[r_1 + \frac{r_0}{\gamma} \tanh \gamma \right] \frac{4LD_A}{\pi a D}}. \quad (4.1)$$

This expression for the flux is one of the main results of this paper. When the tube length significantly exceeds its radius, $L \gg a$, Eq. (4.1) reduces to

$$f = \frac{r_1}{r_1 + \frac{r_0}{\gamma} \tanh \gamma} \frac{\pi a^2 c_A D_A}{L}. \quad (4.2)$$

This is identical to the expression for the flux at long times obtained in Ref. 30, if we identify the product of the tube cross section area and the particle concentration in reservoir A, $\pi a^2 c_A$, with the constant b from Ref. 30. As $L/a \rightarrow 0$, Eq. (4.2) predicts an infinite flux that is clearly unphysical. At the same time, the flux in Eq. (4.1) remains finite in this limiting case and is given by

$$f = \frac{4aD_A c_A r_1}{r_1 + r_0} = P_0^{eq} f_{in}^{(0)}, \quad (4.3)$$

as might be expected based on common sense arguments.

The expression for the flux in Eq. (4.1) shows how the flux between the two reservoirs depends on the problem parameters: the length and radius of the connecting tube, L and a , the rate constants r_0 and r_1 , determining the gate dynamics, the particle diffusivities D and D_A in the tube and in the reservoir A, and the particle concentration c_A in reservoir A. When the rate constant ratio r_0/r_1 vanishes, the flux in Eq. (4.1) reduces to its counterpart in the absence of gating, denoted by f_0 ,

$$f_0 = \frac{4aD_A c_A}{1 + \frac{4LD_A}{\pi a D}} = \frac{\pi a^2 c_A D}{L + \frac{\pi a D}{4D_A}}. \quad (4.4)$$

Using f_0 , we can write the flux in Eq. (4.1) as

$$f = \frac{1}{1 + K} f_0. \quad (4.5)$$

Here K is a factor determining the decrease of the flux due to stochastic gating of the tube entrance from reservoir A given by

$$K = \frac{r_0}{r_1} \frac{\frac{\pi a D}{4LD_A} + \frac{\tanh \gamma}{\gamma}}{\frac{\pi a D}{4LD_A} + 1}. \quad (4.6)$$

As $\gamma \rightarrow 0$ (very slow gate dynamics), Eq. (4.6) simplifies and factor K reduces to the rate constant ratio, $K = r_0/r_1$. As a result, the flux in Eq. (4.5) takes the form

$$f = \frac{r_1}{r_1 + r_0} f_0 = P_0^{eq} f_0, \quad (4.7)$$

as might be expected in this limiting case, where the tube works for the fraction of time equal P_0^{eq} , as if there is no gating. In the opposite limiting case of $\gamma \rightarrow \infty$, Eq. (4.6)

FIG. 3. The flux ratio, f/f_0 , as a function of $\gamma = \sqrt{L^2(r_1 + r_0)}/D$ at four values of the rate constant ratio, r_0/r_1 , $r_0/r_1 = 0.2, 1, 5$, and 10 (from top to bottom), for $4LD_A/(\pi a D) = 10$.

reduces to

$$K = \frac{r_0}{r_1} \frac{\pi a D}{\pi a D + 4LD_A}. \quad (4.8)$$

As a result, the flux in Eq. (4.5) takes the form

$$f = \frac{r_1}{r_1 + r_0 \pi a D / (\pi a D + 4LD_A)} f_0. \quad (4.9)$$

According to Eqs. (4.5) and (4.6) the flux ratio, f/f_0 , is a monotonically decreasing function of the rate constant ratio, r_0/r_1 , and a monotonically increasing function of γ . Figure 3 shows the flux ratio dependence on γ at four values of the rate constant ratio, $r_0/r_1 = 0.2, 1, 5$, and 10 (from top to bottom), for $4LD_A/(\pi a D) = 10$.

V. CONCLUDING REMARKS

We presented an analytical approach to calculating the diffusive flux in a toy model of stochastically gated oxygen transport in insect respiration. The approach is based on the derivation of the passage probability that a single molecule entering the system diffuses to the absorbing boundary instead of escaping through the stochastically gated entrance. This probability is then used to find the flux through the system at long times. As the passage probability, the resulting flux depends on three dimensionless parameters: the ratio of the rate constants for the opening and closing of the gate, r_0/r_1 , the ratio of the time scales of diffusive transport through the tube and gate relaxation, $\sqrt{L^2(r_1 + r_0)}/D$, and the ratio of the tube geometric parameters multiplied by the ratio of the oxygen diffusivities in the atmosphere and in the tube, $4LD_A/(\pi a D)$.

This study focuses on the effect of stochastic gating on diffusive transport through the tube, which has never been considered in the literature. Although our work is motivated by studies in insect respiration, the model we analyze is too simple to be quantitatively compared to the experimental observations of time-dependent gas exchange in the organism.

A more detailed model of this process must take into account the branched geometry of the tracheal tree²⁴ and partially absorbing boundary conditions at the tracheal tips,^{32,33} as well as coordination of multiple spiracles. Each of these factors will affect the flux through the tube, especially the first one, which will affect the flux significantly. Currently, it is not clear how to describe diffusive transport through a branched tubular network. Therefore, further work is required to develop more realistic models of insect respiration.

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