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Analytical Solution of a Model of Integrin-Cytoskeletal Interactions in Migrating Fibroblasts

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Abstract. — We demonstrate that an exact analytical solution can be constructed for an intracellular directed transport model of integrin developed by Schmidt *et al.* (1994). The model attempts to mimic the experimental observation that integrin is transported intermittently, by a combination of two-dimensional diffusion and cytoskeleton-mediated convective transport, towards the cell edge. In particular, the model assumes stochastic coupling and uncoupling of integrin molecules (described by first-order rate coefficients k_c and k_u) to a cytoskeletal element moving at a fixed velocity V_0 . Uncoupled integrins are assumed to undergo isotropic two-dimensional diffusion with a diffusion coefficient D_0 . We demonstrate for this model that, in the asymptotic limit of transport over large distances and long times, transport is described by parallel diffusion and convection processes with effective diffusivity $D = D_0 K_D / (1 + K_D)$ and effective velocity $V = V_0 / (1 + K_D)$, where $K_D = k_u / k_c$ is an equilibrium constant for decoupling. At shorter times, the mean-squared displacement cannot be described by superposing diffusion and convection; rather complicated transport arises from dynamical correlations associated with the coupled reaction, diffusion, and convection processes.

1. Introduction

There has recently been considerable interest in the biophysics underlying cell locomotion [1–4]. Adhesive contacts with external surfaces are facilitated by transmembrane adhesion receptors, such as integrins, which allow contractile forces generated by the cytoskeleton motors to be translated into cell motion [5–10]. Little is known, however, about the mechanism by which these adhesion receptors are supplied to the advancing edges of a cell.

Schmidt *et al.* [11] recently used video microscopy and image analysis techniques to demonstrate that $\beta 1$ integrins are transported towards the leading edge of mouse fibroblasts by an intermittent process that apparently involves both diffusive and convective (directed) motions. By means of related experiments on mutant integrins lacking a cytoplasmic domain, these authors were able to establish that the directed component of the motion arises from an interaction of integrin with a moving cytoskeletal component. Although Schmidt *et al.* [11] were not able to unambiguously identify this cytoskeletal component and the precise nature

of the interaction that temporarily binds integrin, in a subsequent paper [12] they were able to quantitatively reproduce experimental integrin trajectories by means of computer simulations of a simple transport model. The model assumes that integrin is transported by a two-dimensional diffusion process when uncoupled from the cytoskeleton, but that convective transport takes place when the coupling is active. The cytoskeletal component was taken to be moving unidirectionally at a constant velocity. Finally, stochastic coupling and uncoupling of the integrin-cytoskeleton complex was assumed to be described by two first-order kinetic rate coefficients, k_c and k_u .

Schmidt *et al.* [12] used computer simulations of the above model to reproduce trajectories of migrating integrin and by fitting the simulation data to experiment, were able to deduce values of the coupling and uncoupling rate coefficients: $k_c = 0.26 \text{ s}^{-1}$, $k_u = 2.5 \text{ s}^{-1}$. These values may prove useful in identifying the specific integrin-cytoskeletal linkage responsible for directed transport, but may also be incorporated into more ambitious models of integrin-mediated adhesion and cell locomotion.

The model for integrin transport proposed by Schmidt *et al.* [12] may have more general applicability beyond the specific system considered (see, e.g. Ref. [13]), so motivation exists for a more detailed study of its properties. In the present paper, we show that the model actually admits an analytical solution, rendering computer simulation studies unnecessary.

2. Model and Solution

We employ the same model devised by Schmidt *et al.* [12] with minor notational modifications. Adhesion receptors, e.g. integrins, are assumed to execute two-dimensional diffusion (in the $x - y$ plane of the cell substrate and characterized by a diffusivity D_0) when the receptor-cytoskeleton coupling is not active. When the coupling is active, the receptor is assumed to be transported at a constant velocity V_0 along the x -axis by a moving cytoskeletal component. A convenient way of representing these alternative channels of transport is through the following convected-diffusion (Fokker-Planck) equation:

$$\frac{\partial}{\partial t} P(\mathbf{r}, t) = D_0 [1 - \theta(t)] \nabla^2 P(\mathbf{r}, t) - V_0 \theta(t) \frac{\partial}{\partial x} P(\mathbf{r}, t) \quad (1)$$

where ∇^2 is the two-dimensional Laplacian operator. The fundamental quantity with which we work is $P(\mathbf{r}, t)$, the probability density that an adhesion receptor is at a point $\mathbf{r} = (x, y)$ in the cell substrate plane at a time t . The quantity $\theta(t)$ appearing on the right hand side of equation (1) is a discrete stochastic variable that assumes the value 0 at time t if the receptor-cytoskeleton coupling is inactive, and the value +1 at time t if the coupling is active. Equation (1) is clearly consistent with two-dimensional diffusion or convection, depending on the value of $\theta(t)$.

Next, we specify the dynamics of the stochastic variable $\theta(t)$ by assuming that the coupling-uncoupling dynamics are governed by first-order kinetic processes with rate coefficients k_c and k_u , respectively. For this purpose, it proves convenient to define a two-element column vector $\mathbf{p}(t)$ with elements

$$\mathbf{p}(t) = \begin{pmatrix} p_0(t) \\ p_1(t) \end{pmatrix} \quad (2)$$

Here, $p_0(t)$ is the probability that the variable θ assumes the value 0 at time t and $p_1(t) = 1 - p_0(t)$ is the probability that θ is in the other state (+1) at time t . The dynamics of the vector $\mathbf{p}(t)$ are described by a master equation ([14])

$$\frac{d}{dt} \mathbf{p}(t) = \mathbf{W} \cdot \mathbf{p}(t) \quad (3)$$

where \mathbf{W} is a 2×2 matrix that defines the probability per unit time of making transitions between the decoupled and coupled states. \mathbf{W} can be expressed in terms of the rate coefficients k_c and k_u by

$$\mathbf{W} = \begin{pmatrix} -k_c & k_u \\ k_c & -k_u \end{pmatrix} \quad (4)$$

At equilibrium, equation (3) is satisfied by the column vector $\mathbf{p}^e = (p_0^e, p_1^e)$ where the equilibrium probabilities of the uncoupled and coupled states are, respectively

$$p_0^e = K_D / (1 + K_D) \quad (5)$$

$$p_1^e = 1 / (1 + K_D) \quad (6)$$

and $K_D \equiv k_u / k_c$ is an equilibrium constant. For an arbitrary initial state $\mathbf{p}(0)$, equation (3) is formally solved as

$$\mathbf{p}(t) = \mathbf{G}(t) \cdot \mathbf{p}(0) \quad (7)$$

where $\mathbf{G}(t)$ is a propagator that describes the conditional probabilities of state changes during a time interval t :

$$\mathbf{G}(t) = \exp(\mathbf{W}t) \quad (8)$$

In the present paper, we shall be concerned with solving equation (1) subject to the coupling-decoupling dynamics governed by equation (7). Since the solution of equation (1) for an arbitrary initial condition can be obtained by superposition from the Green's function solution, we restrict consideration to the particular initial condition that corresponds to the adhesion receptor placed at the origin at time zero:

$$P(\mathbf{r}, 0) = \delta(\mathbf{r}) = \delta(x)\delta(y) \quad (9)$$

The functions $\delta(\mathbf{r})$ and $\delta(x)$ appearing in equation (9) are two-dimensional and one-dimensional Dirac delta functions, respectively. Our next step is to spatially Fourier transform equation (1) according to

$$R(\mathbf{q}, t) = \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dy \exp(i\mathbf{q} \cdot \mathbf{r}) P(\mathbf{r}, t) \quad (10)$$

where $\iota = \sqrt{-1}$. The solution of the transformed equation (1), consistent with equation (9), can be easily written in the form

$$R(\mathbf{q}, t) = \exp(-D_0 q^2 t) \exp \left[\beta \int_0^t ds \theta(s) \right] \quad (11)$$

where $q^2 \equiv \mathbf{q} \cdot \mathbf{q} = q_x^2 + q_y^2$ and β is defined by

$$\beta \equiv \iota q_x V_0 + D_0 q^2 \quad (12)$$

The object of primary theoretical interest is not $R(\mathbf{q}, t)$, but rather its average over all possible realizations of the stochastic variable $\theta(s)$ during the time interval $0 \leq s \leq t$. We denote this average (actually a path integral) by angular brackets; hence

$$\langle R(\mathbf{q}, t) \rangle = \exp(-D_0 q^2 t) \langle \exp \left[\beta \int_0^t ds \theta(s) \right] \rangle \quad (13)$$

The averaged quantity on the left hand side of this equation provides complete information about receptor transport at arbitrary times and for arbitrary distance scales. In practice,

we use it as a generating function to derive physical quantities of interest. For example, the mean-squared displacements along x and y follow from the definition of the Fourier transform:

$$\langle x^2(t) \rangle = -\frac{\partial^2}{\partial q_x^2} \langle R(\mathbf{q}, t) \rangle |_{\mathbf{q}=0} \quad (14)$$

$$\langle y^2(t) \rangle = -\frac{\partial^2}{\partial q_y^2} \langle R(\mathbf{q}, t) \rangle |_{\mathbf{q}=0} \quad (15)$$

Our next task is to evaluate the averaged quantity appearing on the right hand side of equation (13), making use of the stochastic dynamics defined in equation (7). For this purpose it proves convenient to temporarily discretize the time interval $0 \leq s \leq t$ by dividing it up into n equally spaced time intervals of length Δ . We shall subsequently take the limits $n \rightarrow \infty$ and $\Delta \rightarrow 0$, constrained by $t = \Delta n$, so this temporary representation will have no permanent effect. The object of interest on the right hand side of equation (13), denoted by Q for convenience, thus reduces to

$$Q \equiv \langle \exp \left[\beta \int_0^t ds \theta(s) \right] \rangle \approx \left\langle \prod_{j=1}^n \exp(\beta \Delta \theta_j) \right\rangle \quad (16)$$

with errors that are first order in Δ . In the present form, the θ average implicit in the angular brackets can be made explicit:

$$Q \approx \sum_{\theta_1, \dots, \theta_n} \exp(\beta \Delta \theta_n) \dots G_{\theta_3, \theta_2} \exp(\beta \Delta \theta_2) G_{\theta_2, \theta_1} \exp(\beta \Delta \theta_1) p^e(\theta_1) \quad (17)$$

where $p^e(\theta)$ for $\theta = 0$ or $+1$ denote the two elements of the column vector \mathbf{p}^e defined above. The quantities G_{θ_i, θ_j} appearing in this expression are matrix elements of the propagator defined in equation (8), $\mathbf{G}(\Delta)$, and connect states separated in time by a small interval Δ . Equation (17) can be written more compactly in matrix notation if we introduce a new (2-element) column vector \mathbf{e}_R , a new (2-element) row vector \mathbf{e}_L , and a new 2×2 matrix \mathbf{M} . The elements of these vectors and matrices are defined by ($\theta = 0, +1$)

$$e_R(\theta) = \exp(\beta \Delta \theta / 2) p_\theta^e \quad (18)$$

$$e_L(\theta) = \exp(\beta \Delta \theta / 2) \quad (19)$$

$$M_{\theta_1, \theta_2} = \exp(\beta \Delta \theta_1 / 2) G_{\theta_1, \theta_2}(\Delta) \exp(\beta \Delta \theta_2 / 2) \quad (20)$$

With these definitions, our expression for Q becomes

$$Q \approx \mathbf{e}_L \cdot (\mathbf{M})^{n-1} \cdot \mathbf{e}_R \quad (21)$$

In order to restore the continuum limit, we only require a representation of the matrix \mathbf{M} valid to first-order in Δ . It proves convenient to express this as

$$\mathbf{M} = \mathbf{I} + \Delta \mathbf{N} \quad (22)$$

where \mathbf{I} is the identity matrix and \mathbf{N} is explicitly obtained by expanding equation (8) for $\mathbf{G}(\Delta)$ to first-order in Δ :

$$\mathbf{N} = \begin{pmatrix} -k_c & k_u \\ k_c & \beta - k_u \end{pmatrix} \quad (23)$$

The continuum limit of equation (21) can now be easily taken by making use of the matrix identity

$$\lim_{n \rightarrow \infty} \mathbf{M}^n = \lim_{n \rightarrow \infty} [\mathbf{I} + (t/n)\mathbf{N}]^n = \exp(t\mathbf{N}) \quad (24)$$

Thus, reversing our discretization by taking the simultaneous limits of $n \rightarrow \infty$ and $\Delta \rightarrow 0$ (with $t = \Delta n$ held fixed), the quantity Q is given exactly by .

$$Q = \mathbf{e} \cdot \exp(t\mathbf{N}) \cdot \mathbf{p}^e \tag{25}$$

where $\mathbf{e} = (1, 1)$ is the $\Delta \rightarrow 0$ limit of the row vector \mathbf{e}_L and \mathbf{p}^e is recovered as the $\Delta \rightarrow 0$ limit of the column vector \mathbf{e}_R .

The exponential matrix in equation (25) is easily evaluated and the final matrix algebra can be explicitly performed. Since our final result for $\langle R(\mathbf{q}, t) \rangle$ depends on the two eigenvalues of the matrix \mathbf{N} , we provide them in advance:

$$\lambda_{\pm} = [\beta - k_u - k_c \pm \sqrt{(k_u + k_c - \beta)^2 + 4\beta k_c}]/2 \tag{26}$$

In terms of these eigenvalues, the following exact analytical expression for $\langle R(\mathbf{q}, t) \rangle$ can be written:

$$\begin{aligned} \langle R(\mathbf{q}, t) \rangle &= \frac{K_D \exp(-D_0 q^2 t)}{(\lambda_+ - \lambda_-)(1 + K_D)} \{ \exp(\lambda_+ t) [(k_u + k_c + \lambda_+)(1 + 1/K_D) - \beta] \\ &- \exp(\lambda_- t) [(k_u + k_c + \lambda_-)(1 + 1/K_D) - \beta] \} \end{aligned} \tag{27}$$

3. Results and Discussion

Equation (27) provides a basis for analyzing the transport behavior of adhesion receptors within the context of the model summarized in the above section. In the present section, we explore the implications of this expression.

We begin by considering the asymptotic transport behavior in the limit of large displacements and long times. Such asymptotic behavior can be extracted from the $\mathbf{q} \rightarrow 0$ and $t \rightarrow \infty$ limiting form of $\langle R(\mathbf{q}, t) \rangle$. In particular, by replacing the eigenvalues with their $\beta \rightarrow 0$ limiting forms

$$\lambda_+ \approx \beta/(1 + K_D) \tag{28}$$

$$\lambda_- \approx -(k_u + k_c) + \beta K_D/(1 + K_D) \tag{29}$$

and retaining only the leading terms for $t \rightarrow \infty$, equation (27) reduces to the simple expression

$$\langle R(\mathbf{q}, t) \rangle \approx \exp(-Dq^2 t + i q_x V t) \tag{30}$$

The *effective diffusion coefficient and velocity* appearing in this equation are given by

$$D \equiv D_0 K_D/(1 + K_D) = D_0 p_0^e \tag{31}$$

$$V \equiv V_0/(1 + K_D) = V_0 p_1^e \tag{32}$$

These equations indicate that the asymptotic transport behavior of the model can be described by *parallel* diffusion and convection processes, with characteristic diffusivity D and streaming velocity V . Moreover, this asymptotic behavior can evidently be reproduced by simply preaveraging the coefficients on the right hand side of equation (1) with the equilibrium distribution of θ , \mathbf{p}^e . The mean-squared displacements along x and y in this asymptotic regime follow simply from equations (14) and (15):

$$\langle x^2(t) \rangle \approx (Vt)^2 \quad t \rightarrow \infty \tag{33}$$

$$\langle y^2(t) \rangle \approx 2Dt \quad t \rightarrow \infty \tag{34}$$

Similar expressions were written by Schmidt *et al.* [12], although no attempt was made to distinguish the bare diffusivity and velocity of the model (D_0 and V_0) from the effective (observed) diffusivity and velocity (D and V).

Outside of this asymptotic regime, i.e. at shorter times and displacements, the receptor transport is much more complicated because the convection and diffusion processes are dynamically correlated. Indeed, the analytic structure of equation (27) is quite complicated due to the fact that β is a complex parameter. To clearly illustrate these dynamical correlations, we focus on the mean-squared displacements, given in terms of $\langle R(\mathbf{q}, t) \rangle$ by equations (14) and (15). By explicitly performing the indicated operations on equation (27), it is possible to derive the following *exact* expressions for the two mean-squared displacements:

$$\langle x^2(t) \rangle = 2Dt + \frac{2K_D V^2}{(k_u + k_c)^2} [\exp(-(k_u + k_c)t) - 1] + \frac{2K_D V^2 t}{k_u + k_c} + (Vt)^2 \quad (35)$$

$$\langle y^2(t) \rangle = 2Dt \quad (36)$$

where D and V are the effective diffusivity and velocity given previously in equations (31) and (32). We note that equations (35) and (36) can be used directly to fit experimental data for receptor trajectories, following a procedure similar to that used by Schmidt *et al.* [12] to compare experimental and simulated trajectories.

Equations (35) and (36) demonstrate that although transport in the y -direction (non-directed axis) remains purely diffusive at all times, transport along the directed x -axis has associated memory effects that die off with a characteristic time constant $\tau_m \equiv 1/(k_u + k_c)$. We also note that in the asymptotic limit of long times, equation (35) is clearly consistent with dominant convective transport, reproducing equation (33). To discuss the behavior of equation (35) at short and intermediate times it is useful to introduce a *second* characteristic time constant, $\tau_c \equiv D/V^2$, which is the timescale at which convection and diffusion are competitive. With these definitions, two types of behavior are possible for $\langle x^2(t) \rangle$, depending on the relative values of τ_m and τ_c .

If $\tau_m \ll \tau_c$, a situation in which the adhesion receptor coupling-uncoupling dynamics is very fast relative to the timescale set by the combination of convection and diffusion (τ_c), then equation (35) predicts that $\langle x^2(t) \rangle \approx 2Dt$ for the entire time interval $0 \leq t \leq \tau_c$. Thus, diffusive transport is expected up to a mean-squared displacement that is characteristically of order $2D\tau_c \sim (D/V)^2$. For $t \gg \tau_c$, equation (35) predicts convective transport, $\langle x^2(t) \rangle \approx (Vt)^2$, consistent with equation (33). Overall, for $\tau_m \ll \tau_c$, the model predicts a smooth crossover from diffusive transport at short times to convective transport at long times, the crossover occurring for $t \approx \tau_c$. The adiabatic approximation of preaveraging the θ -dependent coefficients in equation (1) is quantitative in this situation of fast reaction kinetics.

In contrast, if the coupling-uncoupling reaction kinetics are slow compared with the transport timescale, $\tau_c \ll \tau_m$, the situation is more interesting. For $t \ll \tau_c$, equation (35) again predicts simple diffusion, $\langle x^2(t) \rangle \approx 2Dt$. Moreover, for $t \gg \tau_m$, equation (35) reproduces the convective behavior summarized in equation (33), namely $\langle x^2(t) \rangle \approx (Vt)^2$. However, in the intermediate time regime of $\tau_c \ll t \ll \tau_m$, equation (35) predicts an *anomalous convection* that displaces receptors faster than equation (33), namely $\langle x^2(t) \rangle \approx (1 + K_D)(Vt)^2$. The crossover between diffusion and anomalous convection occurs at a mean-squared displacement that is characteristically of order $(D/V)^2$, while the anomalous to normal convection crossover occurs at a mean-squared displacement of order $(1 + K_D)(V\tau_m)^2$.

For the experimental system studied by Schmidt *et al.* [11], where integrin transport was monitored within mouse fibroblasts, the following estimates were made of the coupling and uncoupling rate coefficients [12]: $k_c \approx 0.26 \text{ s}^{-1}$, $k_u \approx 2.5 \text{ s}^{-1}$, $K_D \approx 9.5$. In addition, as

described by Schmidt *et al.* [12], the parameters D_0 and V_0 were independently estimated to be $D_0 \approx 3.5 \times 10^{-10}$ cm²/s and $V_0 \approx 37$ μ m/mn. Thus, we are able to make estimates of the relevant timescales for their system: $\tau_m \approx 0.36$ s, and $\tau_c = D/V^2 = D_0 K_D(1+K_D)/V_0^2 \approx 9.2$ s. Since $\tau_m \ll \tau_c$, we anticipate for this particular experimental system the single crossover behavior between diffusion and convection summarized above. Indeed, Schmidt *et al.* were able to fit their mean-squared displacement data to $\langle x^2(t) \rangle = 2Dt + (Vt)^2$, which can be deduced from equation (35) for $\tau_m \ll \tau_c$. We should point out, however, that other adhesion receptors in different types of cells may fall into the second class of systems that possess an intermediate regime of anomalous convection.

In summary, our exact solution of the model proposed by Schmidt *et al.* [12] is useful for several reasons. First of all, equations (35) and (36) provide a direct means of using experimentally determined adhesion receptor trajectories to extract kinetic information about the coupling-uncoupling reactions with the cytoskeleton. The simulation method employed by Schmidt *et al.* [12], while in principle capable of reproducing the properties of the model, is less straightforward to apply and requires significant computational effort. Secondly, our analytic solution has clarified the difference between the intrinsic transport parameters of the model, D_0 and V_0 , and the effective parameters D and V that apply when coupling-uncoupling reactions, convective transport, and diffusive transport processes act in concert. Finally, we have been able to classify the general transport behavior of adhesion receptors that conform to the model into two groups. The first group, to which the integrin model system studied by Schmidt *et al.* [11] belongs, corresponds to fast cytoskeletal coupling-uncoupling reaction kinetics and diffusion limited transport. The second group, for which there may or may not exist experimental realizations, possesses a regime of "anomalous" convection arising from correlated transport on the timescale for the reaction kinetics to equilibrate. We hope that future applications of the model will unearth such biological systems and lead to an improved understanding of the underlying mechanisms of cell motility.

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