Why diffusion on a domain with complex boundary appears anomalous

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We use volume averaging theory to show how the macroscopic appearance of a perfectly normal microscopic diffusion process is rendered anisotropic and even anomalous by confinement in complex boundaries. This is an attempt to explain the experimental observation that diffusion in the ER appears anomalous in FRAP (Fluorescence Recovery After Photobleaching, an organelle-scale method) assays, but at the same time perfectly normal in FCS (Fluorescence Correlation Spectroscopy, a molecular scale method).

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Consider a process of isotropic, linear, strongly self-similar [1] diffusion, governed by the equation:

$$\left( \partial_t - \nabla^2 \right) c(x,t) = 0 \quad , x \in \Omega \quad (1)$$

with a function $c : \Omega \times \mathbb{R}_0^+ \rightarrow \mathbb{R}$, $c \in C^\ell(\Omega \times \mathbb{R}_0^+)$, $\ell \geq 2$. Let this process take place inside a closed and connected domain $\Omega \subset \mathbb{R}^n$ with boundary $\partial \Omega$. The $n - 1$ dimensional manifold $\partial \Omega$ is assumed to have a "complex" shape with geometric features on a small length scale $\epsilon$. The whole process is observed by an imaginary observer on a larger length scale $E \gg \epsilon$ such that the ratio $\epsilon = c/E \ll 1$ is negligible. We denote the order of magnitude of the values of $c(x,t)$ by $k$. The limited resolution of the observer makes it impossible to fully resolve the shape of $\Omega$ on the observation length scale. All the observer can see is a volume average of the field $c(x,t)$:

$$\langle c(x,t) \rangle = \frac{1}{\mathcal{L}^n(V(x))} \int_{V_0(x)} c(y,t) \, d^n y \quad (2)$$

The average at each point $x$ is taken over an observation volume $V(x)$ with $\mathcal{L}^n(V(x)) = O(E^n)$ (which basically defines the resolution unit of the observer) centered at $x$. $V_0(x) = V \cap \Omega$ is the part of the averaging volume which is inside the domain (we did not require $c(x,t)$ to be defined outside $\Omega$). $\mathcal{L}^n$ is the $n$-dimensional Lebesgue measure (since we did not restrict the complexity of the averaging volume). To simplify the notation, we will write $V$ instead of $V(x)$ in the following. Above volume average basically amounts to convolving $c(x,t)$ with the indicator function $\chi(V_0)$. Since convolution and differentiation are commutative (thanks to Michael for pointing this out to me!), the resulting averaged function is again $C^\ell$ and all differential operators can be applied to it.

The volume averaging theorem [3] for the gradient of a scalar quantity $\psi \in C^\ell$, $\ell \geq 1$ on $\Omega$ is:

$$\langle \nabla \psi \rangle = \nabla \langle \psi \rangle + \frac{1}{\mathcal{L}^n(V)} \int_S \psi \, n \, dA \quad (3)$$

$S$ is the surface of the domain inside the averaging volume $S = \partial(V \cap \Omega)$. $n$ is the outward (i.e. out of $\Omega$) unit normal on $S$ and $dA$ is the surface element on $S$. Notice that the averaging volume $V$ is not restricted to $\Omega$.

For the divergence of a vector field $\Psi$, the corresponding theorem is:

$$\langle \nabla \cdot \Psi \rangle = \nabla \cdot \langle \Psi \rangle + \frac{1}{\mathcal{L}^n(V)} \int_S n \cdot \Psi \, dA \quad (4)$$

The volume average of a time derivative of a scalar quantity is:

$$\langle \partial_t \psi \rangle = \partial_t \langle \psi \rangle - \frac{1}{\mathcal{L}^n(V)} \int_S \psi \, u \cdot n \, dA \quad (5)$$

where $u$ is the velocity of the boundary $S$. This expression remains formally unchanged for vector quantities. Elegant proofs of these averaging theorems can be found in [2].

Using theorems (4) and (5) as well as the fact that the boundary is at rest, the volume average of equation (1) becomes:

$$\partial_t \langle c(x,t) \rangle = \nabla \cdot \langle \nabla c(x,t) \rangle \, + \, \frac{1}{\mathcal{L}^n(V)} \int_S \nabla c(x,t) \cdot n \, dA \quad (6)$$

Using theorem (3) to expand the average of the gradient, this becomes:

$$\partial_t \langle c(x,t) \rangle = \nabla^2 \langle c(x,t) \rangle \, + \, \frac{1}{\mathcal{L}^n(V)} \nabla \cdot \int_S c(x,t) n \, dA \quad$$

$$+ \, \frac{1}{\mathcal{L}^n(V)} \int_S \nabla c(x,t) \cdot n \, dA \quad (7)$$
The full solution $c(x, t)$ can always be written as the sum of the averaged solution plus small-scale fluctuations:

$$c(x, t) = \langle c(x, t) \rangle + \tilde{c}(x, t)$$  \hfill (8)

All terms in this equation are $O(k)$ in their value. The length scales of $c$ and $\tilde{c}$ are $O(e)$, the ones of $\langle c \rangle$ are $O(E)$. The equation for $\tilde{c}(x, t)$ is obtained by substituting equation (8) into the averaged equation (7) and subtracting it from the full equation (1):

$$\partial_t \tilde{c}(x, t) = \nabla^2 \tilde{c}(x, t) - \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S \langle c(x, t) \rangle n \, dA - \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \langle c(x, t) \rangle \cdot n \, dA$$  \hfill (9)

We expand the integral terms in this equation using equation (8) again:

$$\partial_t \tilde{c}(x, t) = \nabla^2 \tilde{c}(x, t) - \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S \langle c(x, t) \rangle n \, dA - \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \langle c(x, t) \rangle \cdot n \, dA - \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \tilde{c}(x, t) \cdot n \, dA$$  \hfill (10)

Consider the first integral term on the right hand side. $\langle c(x, t) \rangle$ is – by construction – approximately constant over $S$ and can be pulled out of the integral. The remaining integral is the surface area of $S$ and constant as well. The first term thus vanishes (divergence of a constant). The third term can be neglected as well, since the gradient of $\langle c(x, t) \rangle$ is approximately zero. These qualitative statements can be made more formal by order analysis. The second and fourth integral terms are $O(k/(eE))$ [4], the first and third ones are $O(k/E^2)$. The ratio of these orders is $\varepsilon$, which means that we can neglect the first and third integral. The final equation for the small-scale fluctuation thus becomes:

$$\partial_t \tilde{c}(x, t) = \nabla^2 \tilde{c}(x, t) - \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S \tilde{c}(x, t) n \, dA - \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \tilde{c}(x, t) \cdot n \, dA$$  \hfill (11)

To obtain the equation for the averaged field, we proceed in a similar way by substituting equation (8) into equation (7):

$$\partial_t \langle c(x, t) \rangle = \nabla^2 \langle c(x, t) \rangle + \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S \langle c(x, t) \rangle n \, dA + \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S \tilde{c}(x, t) n \, dA + \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \langle c(x, t) \rangle \cdot n \, dA + \frac{1}{\mathcal{E}_n(V)} \int_S \nabla \tilde{c}(x, t) \cdot n \, dA$$  \hfill (12)

By the same arguments as before, we can neglect the first and third integral term on the right hand side. For $\tilde{c}(x, t)$, we make the ansatz

$$\tilde{c}(x, t) = b(x, t) \cdot \nabla \langle c(x, t) \rangle$$  \hfill (13)

It has been shown (Ref.) that this kind of ansatz produces the unique solution of equation (11) if fluctuations exist (if they would not exist, this whole consideration would not make sense anyway). The value of $\tilde{c}$ is $O(k)$ and the one of $\nabla \langle c \rangle$ is $O(k/E)$ (gradient on the large scale). The value of $b$ thus is $O(E)$ with length scales being $O(e)$. Substituting this ansatz yields:

$$\partial_t \langle c(x, t) \rangle = \nabla^2 \langle c(x, t) \rangle + \frac{1}{\mathcal{E}_n(V)} \nabla \cdot \int_S (b(x, t) \cdot \nabla \langle c(x, t) \rangle) n \, dA + \frac{1}{\mathcal{E}_n(V)} \int_S \nabla (b(x, t) \cdot \nabla \langle c(x, t) \rangle) \cdot n \, dA$$  \hfill (14)

The first integral term is $O(k/(eE))$ [5] and the second one is of the same order of magnitude. Using the linearity of the divergence operator and the fact that $\nabla^2 = \nabla \cdot \nabla$, this can be approximated by:

$$\partial_t \langle c(x, t) \rangle = \nabla \cdot \left( [1 + \frac{1}{\mathcal{E}_n(V)} \int_S b(x, t) \otimes n \, dA] \nabla \langle c(x, t) \rangle \right) + \frac{1}{\mathcal{E}_n(V)} \int_S \nabla (b(x, t) \cdot \nabla \langle c(x, t) \rangle) \cdot n \, dA$$  \hfill (15)

where we have again used the approximation that $\langle c(x, t) \rangle$ is virtually constant over $S$. Both integrals are still $O(k/(eE))$.

This is as far as we can get without taking the original boundary conditions into account. Let the original problem (1) have a zero flux boundary condition on $\partial \Omega$:

$$n \cdot \nabla c(x, t) = 0, \quad x \in \partial \Omega.$$  

Using equation (8) this translates into the following condition for the fluctuations:

$$n \cdot \nabla \tilde{c}(x, t) = -n \cdot \nabla \langle c(x, t) \rangle$$  \hfill (16)

Using this together with ansatz (13), the last integral term of equation (15) can be written as:

$$\frac{1}{\mathcal{E}_n(V)} \int_S \nabla (b(x, t) \cdot \nabla \langle c(x, t) \rangle) \cdot n \, dA = -\frac{1}{\mathcal{E}_n(V)} \int_S \nabla \langle c(x, t) \rangle n \, dA$$  \hfill (17)

The term on the right hand side is of order $O(k/E^2)$. The second integral in equation (15) is thus $\varepsilon$ times smaller than the first one and can be neglected. The
final averaged equation (i.e. what is effectively observed by the observer) under homogeneous Neumann boundary conditions becomes:

\[ \partial_t \langle c(x,t) \rangle = \nabla \cdot \left( \left[ \mathbb{1} + \frac{1}{\mathcal{L}^n(V)} \int_S b(x,t) \otimes n \, dA \right] \nabla \langle c(x,t) \rangle \right) \]  

(18)

Both terms inside the parentheses are \( O(1) \), the divergence introduces a scale factor of \( O(1/e) \) (small scales in \( b \)) and the gradient of the averaged field is \( O(k/E) \). The whole equation is thus of order \( O(k/(eE)) = O(k) \) in value. This equation describes a diffusion process on the observation length scale \( E \). The effectively observed diffusion tensor on this scale is \( O(1) \) in value and given by:

\[ D_{eff} = \left[ \mathbb{1} + \frac{1}{\mathcal{L}^n(V)} \int_S b(x,t) \otimes n \, dA \right] \]  

(19)

Diffusion is called anisotropic if the tensor \( D \) is not a scalar multiple of the identity tensor. It is furthermore called anomalous if \( D \) is a function of time [6].

From equation (18) it can be seen that, macroscopically, diffusion can appear anisotropic even if the microscopic process is normal and isotropic diffusion! If \( b \) depends on time (which is possible if the fluctuations are time-dependent), diffusion also appears anomalous. To summarize we can say that a diffusion process given by equation (1) on length scales \( O(e) \) is perceived by an observer on length scales \( O(E) \) as:

\[ \partial_t \langle c(x,t) \rangle = \nabla \cdot \left( D_{eff} \nabla \langle c(x,t) \rangle \right) \]  

(20)

Diffusion is thus expected to appear anomalous and anisotropic on the observation length scale even if the underlying process is purely isotropic normal diffusion.

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[4] Note that integration over the surface \( S \) followed by division by the volume introduces a scale factor of \( O(1/E) \) in value.
[5] the integrand is \( O(k) \), the integration introduces a factor of \( O(E^{-n-1}) \), the divergence one of \( O(1/e) \) (small length scales in \( b \) cause large derivatives) and the division by the averaging volume is \( O(E^{-n}) \).
[6] In this case, the mean square displacement no longer scales linearly with time.