Supplemental Material: Imaging Local Diffusive Dynamics Using Diffusion Exchange Spectroscopy MRI

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REGULARIZATION

After discretization, Eq. 2 from the main text can be written as

$$\mathbf{E} = \mathbf{K}\mathbf{F}\mathbf{K}', \tag{S1}$$

and Eq. 4 as

$$\mathbf{F}^{(\alpha)} = \arg\min_{\mathbf{F}\geq 0}(\|\mathbf{K}\mathbf{F}\mathbf{K}' - \mathbf{E}\|_2^2 + \alpha\|\mathbf{F}\|_2^2). \tag{S2}$$

The regularization parameter, α, was chosen based on the S-curve method [1], which uses the fit error, $\chi(\alpha) = \|\mathbf{K}\mathbf{F}^{(\alpha)}\mathbf{K}' - \mathbf{E}\|_2$. The regularization parameter was determined such that $\mathrm{d}(\log\chi)/\mathrm{d}(\log\alpha) = \mathrm{TOL}$, with $\mathrm{TOL} = 0.1$ [1], with α in the range of 10^-5 to 10^5.

APPARENT DIFFUSION COEFFICIENT OF THE RESTRICTED COMPARTMENT

The method used in the main text yields the apparent diffusion coefficient of the restricted compartment, D_{rest}. This diffusivity is determined by a combination of the medium diffusion coefficient, D_0, the shape and the size of the restriction, and the diffusion-encoding experimental parameters. To establish the ground truth of D_I we consider the confinement geometry, the cylinder, and its nominal diameter, 5 μm, as well as the diffusion time and the known water diffusivity. The Gaussian phase distribution (GPD) method [2] is a prevalent approach to approximate D_I^{GT}; however, the DEXSY experiment requires that $\tau_m \gg \Delta$ and, therefore, it was set as $\Delta = 15$ ms. The GPD approximation is only valid when all diffusing spins have encountered boundaries many times, i.e., $\Delta \gg R^2/D_0$, R being the pore radius [3]. This condition is violated; thus the GPD method cannot be used. We therefore must estimate D_I without imposing any assumptions regarding the diffusion-encoding timing parameters. The multiple correlation function (MCF) approach [4] can be used to calculate the theoretical signal attenuation from water diffusing in a cylinder, with arbitrary experimental parameters. For completeness, we detail here the the derivation of the diffusion equation to a matrix formalism that enabled the approximation of D_{rest} [4].

The Bloch-Torrey Equation [5] describes the evolution of the transverse magnetization $m(\mathbf{r},t)$ with a diffusive component comprised of the Laplace operator and an encoding component comprised of the magnetic field $B(\mathbf{r},t)$,

$$\frac{\partial}{\partial t}m(\mathbf{r},t) = D\nabla^2 m(\mathbf{r},t) - i\gamma B(\mathbf{r},t)m(\mathbf{r},t). \tag{S3}$$

This description neglects T_1 and T_2 relaxation of the spins. This equation is, in fact, the diffusion equation with an additional combined effect of diffusion in the presence of a varying magnetic field on the molecules. Note that here $B(\mathbf{r},t) = B_0 + f(t)(\mathbf{G}\cdot\mathbf{r})$ is the superposition of the constant magnetic field $\mathbf{B}_0$ and the linear magnetic field gradient $\mathbf{G}$, with a dependence on time in the form of the temporal profile $f(t)$ (i.e., the gradient waveform).

The Bloch-Torrey equation defines two influences on the magnetization—the diffusive migration of molecules and the magnetic field encoding. Therefore, there are two important length scales: the diffusion length $\sqrt{DT}$, which correlates to the average displacement of a molecule until the echo time T, and a gradient length $(\gamma GT)^{-1}$ which correlates to the displacement of a molecule under a magnetic field gradient G that results in a phase spread of the order of 2π. According to the two main length scales in the problem there is one dimensionless factor $\sqrt{DT}\gamma GT$. This is true for an unconfined geometry where the diffusion is free. For a restricting geometry, the typical size of the geometry L is introduced as a new dimensional parameter, thus creating two new dimensionless factors, which are defined as

$$p_1 = DT/L^2, \qquad p_2 = \gamma GLT. \tag{S4}$$

The Laplace operator ∇^2 can be represented by its set of eigenfunctions and eigenvalues, since it has a complete set of eigenfunctions for a bounded domain, $\mathbf{\Omega}$. The problem is described by expressing the eigenvalues in dimensionless units as

$$\nabla^2 u_m(\mathbf{r}) + \frac{\lambda_m}{L^2}u_m(\mathbf{r}) = 0. \qquad (\mathbf{r}\in\mathbf{\Omega}) \tag{S5}$$

Expressing the solution of Eq. S3 by the decomposition of the eigenfunctions results in

$$m(\mathbf{r},t)=\sum_{m'}c_{m'}(t)u_{m'}(\mathbf{r}), \tag{S6}$$

where $c_{m'}(t)$ are unknown coefficients. Plugging Eq. S6 in to Eq. S3, using Eq. S5, multiplying the equation by $u_m^*(\mathbf{r})$, and integrating over $\mathbf{\Omega}$ gives a set of differential equations

$$\frac{\partial}{\partial t}c_m(t)+\sum_{m'}\Big(\frac{D\delta_{m,m'}\lambda_m}{L^2}+i\gamma\mathbf{G}Lf(t)\int_\Omega d\mathbf{r}u_m^*(\mathbf{r})\mathbf{r}u_{m'}(\mathbf{r})\Big)c_{m'}(t)=0. \tag{S7}$$

Note that $B_{eff}(\mathbf{r})=\frac{f(t)(\mathbf{G}\cdot\mathbf{r})}{L}$ is the effective, normalized and dimensionless magnetic field gradient (the additional multiplication by L compensates for the dimensionless factoring). $f(t)$ is the temporal profile of the magnetic field. Since the static magnetic field $\mathbf{B}_0$ generates a constant term in Eq. S3 and does not contribute to the evolution of the signal, it can be dropped out. Therefore, $f(t)$ describes the temporal profile of the applied magnetic field gradients. The following infinite-dimensional matrices can be defined

$$\mathcal{B}_{m,m'}=\int_\Omega d\mathbf{r}u_m^*(\mathbf{r})\mathbf{r}u_{m'}(\mathbf{r}), \tag{S8}$$

$$\Lambda_{m,m'}=\delta_{m,m'}\lambda_m. \tag{S9}$$

Multiplying Eq. S7 by T and plugging the dimensionless parameters p_1 and p_2 yields

$$T\frac{\partial}{\partial t}c_m(t)+\sum_{m'}\Big(p_1\Lambda_{m,m'}+ip_2f(t)\mathcal{B}_{m,m'}\Big)c_{m'}(t)=0. \tag{S10}$$

$c_m(t)$ can be considered as components of an infinite vector $C(t)$ thus deriving a matricial first-order differential equation

$$T\frac{d}{dt}C(t)=-\Big(p_1\Lambda+ip_2f(t)\mathcal{B}\Big)C(t), \tag{S11}$$

for which the solution is

$$C(t)=\mathrm{e}^{-(p_1\Lambda+ip_2f(t)\mathcal{B})t/T}C(0). \tag{S12}$$

Before deriving the macroscopic NMR signal, consider that at $t=0$ the magnetization is uniform over $\mathbf{\Omega}$. Thus, if V is the volume of Ω then the initial condition is

$$m(\mathbf{r},t=0)=\frac{1}{V}. \tag{S13}$$

Note that $u_0^*(\mathbf{r})=V^{-1/2}$, thus $m(\mathbf{r},t=0)=V^{-1/2}u_0^*$. Applying the initial condition on Eq. S6 yields

$$C(0)=V^{-1/2}\delta_{m,o}. \tag{S14}$$

The NMR signal is determined by the transverse magnetization $m(\mathbf{r},t)$; therefore, the signal at the echo time T can be expressed by integrating $m(\mathbf{r},T)$ over the confined volume $\mathbf{\Omega}$

$$E=\int d\mathbf{r}m(\mathbf{r},T). \tag{S15}$$

Plugging Eq. S6 in to Eq. S15 and multiplying by $u_0^*(\mathbf{r})$ yields

$$\begin{aligned}E=\int d\mathbf{r}m(\mathbf{r},T)=V^{1/2}\sum_{m'}c_{m'}(T)\times\\ \int_\Omega d\mathbf{r}u_{m'}(\mathbf{r})u_0^*(\mathbf{r})=V^{1/2}c_0(T).\end{aligned} \tag{S16}$$

It can be seen that the macroscopic signal depends only on the state that corresponds to u_0, and, together with Eq. S14, the signal is the first diagonal element of the matrix

$$E=\Big[\mathrm{e}^{-(p_1\Lambda+ip_2f(t)\mathcal{B})}\Big]_{0,0}. \tag{S17}$$

This is true for $f(t)=\mathbf{const}$, but if the temporal profile is not constant, a numerical approximation is needed. Dividing T into a K number of equal intervals of duration $\tau=T/K$ yields

$$E=\Bigg[\prod_{k=0}^{K}\mathrm{e}^{-\tau(p_1\Lambda+ip_2f(\frac{k}{K}T)\mathcal{B})}\Bigg]_{0,0}. \tag{S18}$$

The matrices Λ and $\mathcal{B}$ depend on the confining geometry, and can be calculated for several well-defined geometries. For a cylindrical geometry, they are given by Grebenkov [4].

To estimate D_I^{GT}, we first compute the signal attenuation from Eq. S18 with $L = R$, $T = \Delta + \delta$, $D = D_0$, and $f(t)$ is the piecewise-constant profile of an SDE gradient waveform, denoted as E_I. We then find D_I that solves the problem

$$D_I^{GT} = \arg\min_{D_I} \|\mathrm{e}^{-q^2 \Delta D_I} - E_I\|_2^2 \tag{S19}$$

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