

What are the time scales for diffusion in cells?

One of the most pervasive processes that serves to determine the reference time scale for all other processes in cells is that of diffusion. Molecules are engaged in an incessant, chaotic dance, as characterized in detail by the botanist Robert Brown in his paper with the impressive title “A Brief Account of Microscopical Observations Made in the Months of June, July, and August, 1827, On the Particles Contained in the Pollen of Plants, and on the General Existence of Active Molecules in Organic and Inorganic Bodies”. The subject of this work has been canonized as Brownian motion in honor of Brown’s seminal and careful measurements of the movements bearing his name. As observed by Brown, diffusion refers to the random motions undergone by small scale objects as a result of their collisions with the molecules making up the surrounding medium.

The study of diffusion is one of the great meeting places for nearly all disciplines of modern science. In both chemistry and biology, diffusion is often the dynamical basis for the reactions of interest. Even in those cases where diffusion is not the basis of some underlying biological process, these random motions are a part of the backdrop faced by the macromolecules of the cell as they perform their tasks. The mathematical description of such processes has been one of the centerpieces of mathematical physics for nearly two centuries and permits the construction of simple rules of thumb for evaluating the characteristic time scales of diffusive processes. The concentration of some diffusing species as a function of both position and time is captured mathematically using the so-called diffusion equation. One of the key results that emerges from the mathematical analysis of diffusion problems is that the time scale  $\tau$  for a particle to travel a distance  $x$  is given by  $\tau = x^2/6D$ , where  $D$  is the diffusion constant for the particle of interest.

How long does it take macromolecules to traverse a given cell? The characteristic diffusion constant of for a protein in water is  $\sim 100 \mu\text{m}^2/\text{s}$  but drops to  $\sim 10 \mu\text{m}^2/\text{s}$  inside a cell with large variation based on the cellular context (Table 1). Using the simple rule of thumb introduced above, we find that it takes roughly 0.01 seconds for a protein to traverse the 1 micron diameter of an *E. coli* cell (BNID 103801). A similar calculation results in about 10 seconds for a protein to traverse a HeLa cell (BNID 103788, HeLa cell radius  $\sim 10 \mu\text{m}$ ). An axon 1 mm long is about 100 times longer still and from the diffusion time scaling as the square of the distance it would take  $10^5$  seconds or  $\sim 2$  days for a molecule to travel this distance by diffusion. This enormous increase in diffusive time scales as cells approach macroscopic sizes demonstrates the necessity of mechanisms other than diffusion for molecules to travel these long distances. Using a molecular motor moving at a rate of  $\sim 1 \mu\text{m}/\text{s}$  (BNID 105241, Time axis) it will take a “reasonable”  $\sim 15$  minutes to traverse this same distance.

Table 1: A compilation of empirical diffusion constants showing the dependence on size and cellular context

Molecule (BNID)	Cell context	Diffusion rate ( $\mu\text{m}^2/\text{s}$ )	BNID/Ref/ comments
H <sub>2</sub> O	In water	<u>2100</u>	104087, Stein 1990
H <sub>2</sub> O	Nucleus of chicken erythrocyte	230	104645, García-Pérez 1999
CO <sub>2</sub>	In water	1880	<u>102625</u> , Fridlyand 1996 (Maxarei 1980)
Protein (GFP)	In water	87	100301, Elowitz 1999 (Swaminathan 1997)
Protein (GFP)	In eukaryotic cell (CHO) cytoplasm	27	101997, Elowitz 1997 (Swaminathan 1997)
Protein (GFP)	Rat liver mitochondria	25 (20-30)	100300, Elowitz 1999 (Partikian 1998)
Protein (GFP)	<i>E. coli</i> cytoplasm	<u>7.7±2.5</u>	100193, Elowitz 1999
Fluorescent dye (Carboxy-fluorescein)	Aqueous solution	487±22	105032, Kramer 2007
Fluorescent dye (Carboxy-fluorescein)	<i>A. thaliana</i> cell wall	32±14	<u>105033</u> , Kramer 2007
Fluorescent dye (Carboxy-fluorescein)	<i>A. thaliana</i> mature root epidermis	<u>2.5±0.7</u>	105034, Kramer 2007
Transcription factor (LacI)	One dimensional movement along DNA <i>in vitro</i>	0.04	102036, Elf 2007. Equivalent to $4 \times 10^5 \text{ bp}^2\text{s}^{-1}$ . In vivo apparent 1D diffusion coefficient is an order of magnitude higher due to 3D diffusion
Morphogen (Bicoid)	Cytoplasm of <i>Drosophila</i> embryo	0.3±0.1	<u>103811</u> , Gregor 2007
Morphogen (Wingless)	Wing imaginal disk of <i>Drosophila</i>	0.05 (0.02-0.08)	<u>101072</u> , Kicheva 2007