

Chapter 2

Diffusion and Transport of Molecules In Living Cells

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2.1 Introduction

Diffusion, derived from the Latin word *diffundere* meaning *to spread out*, is a mass transport phenomenon in both fluids (without requiring bulk fluid motion) and solids. Both macroscopic or phenomenological and microscopic or atomistic and molecular approaches are employed to introduce the concept of *diffusion*. According to the former approach, the diffusion transport goes from regions of high concentration to regions of low concentration, whereas according to the latter diffusion is a result of the random walk of the particles. In molecular diffusion, moving molecules are self-propelled by thermal energy.

In this chapter we discuss the historical developments, diffusion in cells and the current status of research, basic mathematical models of diffusion, and osmosis and its importance for living systems.

2.1.1 Historical Perspective

The history of diffusion goes back to several centuries B.C. Mechanisms of many technical processes in use over centuries are in fact controlled by diffusion, for example cementation used in gold or silver refining, carbon diffusion in elemental iron for steel making by the cementation process since medieval times or earlier, diffusion soldering of gold artefacts, colouring of glasses, earthenware, or chinaware, all happened long before the development of any theory of diffusion. In

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the seventeenth century, Robert Boyle demonstrated diffusion of zinc into a copper coin. The well-known Brownian motion, never-ending movement of particles in suspension in a fluid, discovered in 1827 by Robert Brown, a botanist, is a manifestation of the random walk of microscopic particles suspended in a fluid. This motion has been described on one hand as the wanderings of a drunken sailor and on the other hand as the zoom image of molecular movements. Interestingly, Brownian motion is a mathematical object treated in many text books as well as a physical one allowing us to rationalize natural facts as varied as the flight of birds or mosquitoes, the spread of diseases, dissemination of pollutants, the properties of biological membranes, the brain imaging by nuclear magnetic resonance (NMR) spectroscopy, etc. In his theory of Brownian motion, Albert Einstein developed the microscopic theory of diffusion of particles at sufficiently low concentration in a liquid in 1905. Significant contributions towards this approach were also made by Marian Smoluchowski and Jean-Baptiste Perrin. However, long before in 1858, James Clerk Maxwell developed the first microscopic theory of transport in gases based on gas kinetics; the concept of mean free path was introduced by Rudolf Clausius in the same year. Ludwig Boltzmann developed the atomistic backgrounds of the macroscopic transport processes and introduced the Boltzmann transport equation in 1872. The equation has been serving mathematics and physics with a source of transport process ideas and concerns over the last 140 years [1, 2].

The phenomenological approach was introduced by Adolf Fick as a 26-year-old assistant in anatomy and physiology, in his famous papers in 1855 establishing the now classical Fick's equations, governing the mass transport through diffusive means. It is worth mentioning that later as a chair professor of physiology he authored the first treatise on medical physics, the first book of this kind. He remains a well-known name in the history of cardiology. Fick's approach was inspired by Thomas Graham's famous experimentation on diffusion of salts in water for investigating and comparing the diffusibility of different salts in 1850 and his earlier work on diffusion in gases in 1833. Fick used the law of conservation of matter and the deep analogy between diffusion and hydraulic flow (Darcy's law), heat conduction (Fourier's law), or charge transport (Ohm's law), to develop his fundamental laws for diffusion. He used Graham's method to design his experiments on the measurements of concentrations and fluxes of salts diffusing between two reservoirs through tubes of water. Fick's work although originally concerned with diffusion in fluids, his laws later also became the core of understanding diffusion in solids. Today, Fick's laws are the most popularly used laws for diffusion in gases, liquids, and solids [1, 2].

The successful use of Fick's laws to solid state diffusion was demonstrated first in 1896 by William Chardler Roberts-Austen, a longtime associate of Thomas Graham, while extending Graham's work to diffusion of gold in lead. George de Hevesy studied and measured self-diffusion of radioactive isotopes of lead in liquid and solid lead in 1920–1921. In 1926, Yakov Frenkel introduced the idea of diffusion in crystals through local defects (vacancies and interstitial atoms) and concluded that the diffusion in process in condensed matter is an ensemble of elementary jumps and quasi-chemical interactions of particles and defects. He proposed several mechanisms of diffusion and found rate constants from experimental data.

Sometime later, Carl Wagner and Walter H. Schottky developed Frenkel's ideas about mechanisms of diffusion further. It is now universally recognized that atomic defects are necessary to mediate diffusion in crystals. In 1922, Saul Dushman and Irving Langmuir applied Arrhenius' law to determine the coefficient of diffusion of thorium through tungsten and found satisfactory results. Henry Eyring and his coworkers applied his theory of absolute reaction rates to Frenkel's quasi-chemical model of diffusion in 1935. The analogy between reaction kinetics and diffusion leads to various nonlinear versions of Fick's law. Nonlinear models are also required for diffusion on catalyst surfaces [3, 4].

Diffusion is a widely applicable concept. It applies to any field involving random walks in the ensembles of individuals. In fact, the concept of diffusion is used across diverse fields stretching from physics, chemistry and biology to sociology, economics, and even finance.

2.1.2 Diffusion In Living Cells

The efficient delivery of proteins, drugs, and other products to their correct locations within a cell (transport) is of prime importance to the normal cellular function and development [5]. On the other hand, cytoplasm and other aqueous intracellular organelles such as mitochondria, nucleus, etc. are crowded with solutes, soluble macromolecules, skeletal proteins, and membranes inside the cell. In order to maintain homeostasis and cellular functions in the cell, most of the physiological processes depend on selective exchanges of metabolites between the cell and its exterior [6]. Substances such as liquids, nutrients, hormones and other signaling molecules, and waste products are routinely transported (received and delivered) across the cell plasma membranes.

Transportation of materials inside and outside of cells can be described in two ways: passive transport and active transport. In passive transportation, movement of substances does not require energy (adenosine triphosphate, ATP). Types of passive transportation include simple diffusion, facilitated diffusion, osmosis, and filtration. The diffusion process can continue until the concentration of solute in the extracellular and intracellular spaces is attaining the equilibrium. In facilitated diffusion, solute particles move from higher to lower concentration via cell surface channels. Diffusion and facilitated diffusion involve transport of solutes, while osmosis involves movement of water (or solvents) through a membrane. The movement of some transported proteins and glucose inside the cell membrane is highly selective so that movement across the cell membrane occurs only when assisted by the concentration gradient, a type of carrier-assisted transport known as facilitated diffusion. Both simple diffusion and facilitated diffusion are driven by the potential energy differences of a concentration gradient. Simple diffusion is a nonselective process by which any molecule capable of dissolution in the phospholipid bilayer is able to cross the plasma membrane and equilibrate between inside and outside of the cell. Thus, only small hydrophobic molecules are able to diffuse across a phospholipid bilayer at significant rates.

The gases such as oxygen and carbon monoxide, hydrophobic molecules like benzene, and small polar but uncharged molecules hydrogen and ethanol, are able to transport across the plasma membrane by simple diffusion. Other larger uncharged polar molecules, such as glucose, are unable to cross the plasma membrane by passive diffusion. Facilitated diffusion involves the movement of molecules in the direction determined by their relative concentrations inside and outside of the cell without any external energy. However, facilitated diffusion differs from simple diffusion in that the transported molecules do not dissolve in the phospholipid bilayer. Therefore, facilitated diffusion allows only polar and charged molecules, such as nucleosides, carbohydrates, amino acids, and ions to cross the plasma membrane.

Facilitated diffusion is mediated by two classes of proteins such as carrier proteins and channel proteins. Carrier proteins attach with specific molecules for transportation to the other side of the membrane and undergo conformational changes, allowing the molecule to pass through the membrane. Carrier proteins are responsible for the facilitated diffusion of sugars, amino acids, and nucleosides across the plasma membranes of most cells. Channel proteins create open pores through the membrane and allow free diffusion of any molecule of the appropriate size and charge.

Active transport is the movement of a substance across a cell membrane against its concentration gradient. There are three main types of active transport. Active transport in a cell requires energy, usually in the form of ATP. It includes transportation of large molecules (non-lipid soluble) and the sodium–potassium pump. In the case of active transport, the proteins and other molecules move against the concentration gradient. Primary active transport directly uses ATP. Secondary active transport does not directly use ATP. It takes advantage of a previously existing concentration gradient (via carriers). In a sodium–potassium pump, Na^+ is maintained at low concentrations inside the cell and K^+ is found at higher concentrations in nerve cells. When a nerve message is propagated, the ions are transported across the membrane, and a new message is generated. The ions must be actively transported back to their starting positions across the membrane using ATP as the carrier energy.

Active transports are classified as: uniport transport, cotransport, and vesicle-mediated transport. In uniport transport, only one solute movement takes place at a time. It is a facilitated low resistance diffusion and thermodynamically favoured process. It is a reversible process and accelerates the reaction by low concentration gradient. It takes place in glucose transportation, impulse transmission in neurons, primary insulin regulated glucose transportation in muscle, and adipose tissue. In cotransport, movement of one substrate down the gradient is coupled with the movement of another substrate against the gradient at the same time. In 1960, Robert K. Crane introduced the term cotransport in his discovery of the sodium–glucose cotransport as the mechanism for intestinal glucose absorption for the first time [7]. It can transport different numbers of molecules in different directions at the same time. It is also known as secondary active transport or coupled transport. It is divided into two types: (i) symporter—both the substrate (the solute and a cotransported solute) go in the same direction against its electrochemical gradient. It is found in glucose symporter SGLT1, which cotransports one glucose

(or galactose) molecule into the cell for every two sodium ions it imports into the cell. This symporter is located in the small intestine, trachea, heart, brain, testis, and prostate, and S3 segment of the proximal tubule in each nephron in the kidneys [8], and (ii) antiporter—the molecules of the solute go in (or out) and the cotransported solute go in the opposite direction across the membrane. It is found in the sodium–calcium exchanger, in which three sodium ions allowed into the cell to transport one calcium ion out [9].

In vesicle-mediated transport, vesicles and vacuoles fused with the cell membrane is utilized to transport or release chemicals out of the cell. It is also categorized as: (i) exocytosis, in which transport is out of the cell, and (ii) endocytosis, in which a molecule causes the cell membrane to bulge inward, forming a vesicle.

Diffusion also plays a fundamental role in every biochemical process in living cells. Characterizing and distinguishing the cytoskeletal migration, which includes all motor protein-mediated transport within a cell, is critical to understanding cellular function and is regulated by the diffusion process [10]. The rate of diffusion in the cell depends on several factors, such as concentration gradient, thickness of the exchange surface, and the surface area. The most well-known example of diffusion is gas exchange in living organisms. Oxygen gas is transferred from lungs to red blood cells and vice versa via diffusion. Carbon dioxide is produced by all cells as a result of cellular metabolic processes. Since the source is inside the cell, the concentration gradient is constantly being replenished/re-elevated, thus the net flow of CO_2 is out of the cell. In photosynthesis, the gas exchange process (carbon dioxide from air to leaf and oxygen from leaf to air) follows diffusion process. Acetylcholine neurotransmitter is transported from presynaptic to postsynaptic membrane at a synapse via diffusion. In alveolus, macrophages eating viruses swim and tumble but can be modelled as diffusion. Cellular Ca^{2+} dynamics involves the exchange of Ca^{2+} ions between intracellular stores and the cytosol, the interior and exterior of a cell or between cells, as well as transport by diffusion and buffering due to the binding of Ca^{2+} to proteins.

There are two ways in which substances can enter or leave a cell. According to this, diffusion may be classified as: (i) *intracellular diffusion or self-diffusion*, (ii) *interdiffusion*. The process of spontaneous mixing of molecules taking place in the absence of concentration (or chemical potential) gradient is known as self-diffusion. The self-diffusion is diffusion in one-component material, when all atoms that exchange positions are of the same type. In the absence of external forces, the displacements of the particles result from their thermal agitation. This is an incoherent process leading to random motions of the particles in any state of aggregation. Nowadays, this process is usually denoted as self-diffusion [11]. Some authors denote self-diffusion in liquid mixtures as intra-diffusion [12], retaining the term self-diffusion only for diffusive processes in pure liquids. Unkel and others described variety in intracellular diffusion during the cell cycle [13].

The self-diffusion coefficient of neat water is: $2.299 \times 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$ at 25°C and $1.261 \times 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$ at 4°C [14]. Topgaard and others demonstrated a new method for the characterization of water-swollen biological porous structures using NMR to determine the amount and self-diffusion of water within the porous objects [15].

The method shows slower diffusion of water in starch granules in comparison to cellulose fibres and it is attributed to the smaller amount of freezable water and the pore geometry.

Drugs diffuse through various barriers for metabolism and excretion when administered to the body. Some drugs diffuse through the skin, gastric mucosa. Parenteral drugs must diffuse through muscle, connective tissue, and so on, to get to the site of action; even intravenous drugs must diffuse from the blood to the site of action. Considering all the diffusion processes that occur in the body (passive, active, and facilitated), it is not surprising that the laws governing diffusion are important to drug delivery systems. In the dissolution of the particles of drug, the dissolved molecules diffuse away from the individual particle body.

2.1.3 Current Status of Research: Diffusion In Cell

Over the last three decades, the accelerating growth of publications in the area of ion transport has witnessed the interest in this area of research in current science [16–18]. The ion exchange process intensifies, increasing research interest among chemists, chemical engineers, and biologists in understanding the transport processes occurring across the natural and artificial membranes [19]. As artificial ligand models, several types of macrocyclic molecules have been prepared specifically to transport alkali, alkaline earth, and organic ammonium ions with high selectivities, useful in active transport process [20, 21]. Carrier-mediated transport (pertraction) of metal ions by soluble macromolecules has so far been investigated using the neutral or functionalized polymers and the effectiveness of such macro-ionophores has been demonstrated [22, 23]. For the maintenance of homeostasis in the cell, newly synthesized products from the nucleus are transported to other intracellular medium or the cell membrane via a microtubular network from centrosomes. Various animal viruses including HIV were described as taking advantage of microtubule-based transport in order to reach the nucleus from the cell surface and releasing their genomic material through the nuclear pores [24].

The challenges of cellular transport are particularly great for neurons (brain cells), which are amongst the largest and most complex cells in biology with regard to the efficient transport of newly synthesized proteins from the cell body. In microrheology, the transport and motion of probes especially fluorescent molecules is tracked and recorded over a time period; local mechanical properties in the vicinity of the probes are deduced depending upon the driving mechanisms. Cells respond to the external conditions through internal structural, compositional, and functional modifications; their transport and mechanical properties get altered. Thus, the measurements of changing particle-transport properties indicate an evolution of the internal structure of the cell after administering nocodazole as expected during microtubule dissociation [25]. Extensive theoretical and experimental studies based on the carrier-mediated transport through liquid membranes have been reviewed in literature [26, 27].

Verkman demonstrated diffusion of solutes and macromolecules in aqueous cellular compartments. This is required for numerous cellular processes including metabolism, second messenger signaling, and protein–protein interactions [28]. Recently, Videcoq and others described the diffusion of two pectin methylsterases enzyme (PMEs) with different origins and modes of action and characterized with a multi-scale approach in different media consisting of pectin macromolecular solutions and physical gels [29]. Another useful method for quantitative measurement of the translational diffusion of fluorophores and fluorescently labelled macromolecules is fluorescence recovery after photo bleaching. It is more sensitive than diffusion-weighted imaging (DWI) and permits cell-level spatial resolution. In this method, fluorescently labelled molecules are introduced inside the cells by microinjection or incubation, or by targeted expression of green fluorescent protein (GFP) chimeras. In spot photo bleaching, fluorophores in a defined volume of a fluorescent sample are irreversibly bleached by a short intense light pulse. Using an attenuated probe beam, the diffusion of unbleached fluorophores into the bleached volume is measured as a quantitative index of fluorophore translational diffusion. A variety of optical configurations, detection strategies, and analysis methods have been used to quantify diffusive phenomena in photo bleaching measurements [30].

To measure diffusion, modulated gradient spin-echo method (MGSE) is used, in which pulsed gradients are not necessarily applied [31]. It gives information about diffusion in the frequency domain. By using a periodically oscillating phase factor, the MGSE experiment results in signal attenuation, which is proportional to the spectrum of the velocity autocorrelation function (VAF) of the spin-bearing particles. The diffusion spectrum probed by MGSE is related to the mean square displacement, and analogously to the time-dependent diffusion coefficient, and contains information about the morphology [32]. The MGSE technique, which enables spectral characterization of diffusion with chemical-shift resolution, has been introduced. The use of spin echoes instead of gradient echoes [33] is advantageous in reducing the effects of field inhomogeneity and susceptibility artefacts. The technique is particularly suitable for *in vitro* studies of samples, where diffusion of several compounds with different chemical shifts is of interest. Whereas, optical tweezers (optical tweezer is a device that allows for manipulation of nano- and microscopic particles by a focused laser beam) are capable of studying diffusion at short timescales, optical particle tracking is typically used for studying diffusion and transport processes at larger timescales (greater than 0.01 s); a combination of these methods yields quite a large frequency range [34].

2.2 Basic Models of Diffusion

The following is an outline of the basic models of linear diffusion put forward by Fick, Einstein, Teorell, and Onsagar.

2.2.1 Fick's Law

The first prominent equation of diffusion is Fick's first law which expresses the diffusion flux, J in $\text{mol.m}^{-2}.\text{s}^{-1}$ as proportional to the anti-gradient of the local concentration, c (in mol. m^{-3}) at a position vector \mathbf{r} at time t :

$$\mathbf{J} = -D\nabla c(\mathbf{r}, t) \quad (2.1)$$

where D symbolizes diffusion coefficient (in $\text{m}^2. \text{s}^{-1}$) and ∇ is the del operator. Equation 2.1 applies to ideal mixtures and postulates that the flux goes from regions of higher concentration to regions of lower concentration. In one dimension, Eq. 2.1 reduces to:

$$J_i = -D \frac{\partial c}{\partial x_i} \quad (2.2)$$

where the subscript i denotes the i -th position (in m). For systems other than ideal solutions or mixtures, the concentration gradient ($\partial c / \partial x_i$) in one dimension is replaced by $(a / RT) (\partial \mu / \partial x_i)$, where μ is the chemical potential of the species (in Jmol^{-1}), a is the activity of the species (in mol. m^{-3}), R is the universal gas constant (in $\text{J.K}^{-1}. \text{mol}^{-1}$), and T is the temperature (in Kelvin). It may be noted that the anti-gradient of chemical potential, $-\nabla \mu$, the driving force of diffusion is not necessarily a truly real force. It represents the spontaneous tendency of the molecules to disperse as a consequence of the second law of thermodynamics and the hunt for maximum entropy. For ideal or near-ideal solutions and mixtures, a becomes c . The form of Fick's law in one dimension becomes:

$$J_i = -D \frac{c}{RT} \frac{\partial \mu}{\partial x_i} \quad (2.3)$$

The corresponding diffusion equation predicting how diffusion changes concentration with time is Fick's second law, according to which the time derivative of the concentration is the negative divergence of the flux, J . Using Eq. 2.1, we have:

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = -\nabla \cdot \mathbf{J} = D \nabla^2 c(\mathbf{r}, t) \quad (2.4)$$

where ∇^2 is the Laplacian operator. In one dimension, Eq. 2.4 becomes:

$$\frac{\partial c(x, t)}{\partial t} = D \frac{\partial^2 c(x, t)}{\partial x^2} \quad (2.5)$$

In all these expressions, D has been assumed constant, independent of concentration, position, and direction. The linear diffusion equation (Eq. 2.4 or 2.5) applies

to isotropic diffusion only and is in fact a special case of the generalized diffusion equation:

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = -\nabla \cdot [D(c, \mathbf{r}) \nabla c(\mathbf{r}, t)] \quad (2.6)$$

where $D(c, \mathbf{r})$ is the collective diffusion coefficient for the concentration c at the location \mathbf{r} . The expression for Fick's first law, Eq. 2.1 would be written as:

$$\mathbf{J} = -D(c, \mathbf{r}) \nabla c(\mathbf{r}, t) \quad (2.7)$$

More generally, when D is a symmetric positive definite matrix, Eq. 2.6 describes anisotropic diffusion which is written as:

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = \sum_{i=1}^3 \sum_{j=1}^3 \frac{\partial}{\partial x_i} \left[D_{ij}(c, \mathbf{r}) \frac{\partial c(\mathbf{r}, t)}{\partial x_j} \right] \quad (2.8)$$

The nonlinear equation (Eq. 2.6) would obviously reduce to the linear form (Eq. 2.4), when D becomes a constant independent of $c(\mathbf{r})$. The generalized equation (Eq. 2.6 or Eq. 2.8) applies to inhomogeneous media, where D varies in space; anisotropic media, where D depends on the direction or inhomogeneous anisotropic media, where D depends upon both position and direction.

The linear diffusion equation (Eq. 2.4) can be solved using Fourier transformation with the initial condition $c(\mathbf{r}, 0) = c_0 \delta(\mathbf{r})$, c_0 is $c(0, 0)$; that is, all the solute molecules are at the origin initially. The solution is:

$$c(\mathbf{r}, t) = c_0 \left(\frac{1}{4\pi Dt} \right)^{3/2} e^{-r^2/(4Dt)} \quad (2.9)$$

At any time, the distribution is three-dimensional Gaussian function. Clearly, as the time passes the mixture becomes uniform. Using Eq. 2.9, the mean square displacement from the origin at time t is calculated as:

$$\langle r(t)^2 \rangle = 6Dt = 2dDt \quad (2.10)$$

where d is the spatial dimension.

The square-root-of-time dependence of the distance travelled is characteristic of diffusive motion and Eq. 2.10 may be considered as a practical definition of the diffusion coefficient. The length $\sqrt{2dDt}$ is defined as the diffusion length. This is the diffusion law derived by Albert Einstein [1, 35–38].

Diffusion results from Brownian motion, the random battering of solute molecules by the solvent molecules. Application of the one-dimensional random walk

model leads, interestingly, to the same expression for $\langle x(t)^2 \rangle$ in one dimension, that is:

$$\langle x(t)^2 \rangle = \frac{l^2 t}{\tau} \quad (2.11)$$

where l is the step length and τ is the time interval between two successive displacements with the identification of $l^2 / \tau = 2D$. The solutions of diffusion and random walk problems thus become identical. Equation 2.10 is, in fact, a connector between a macroscopic entity D and the microscopic one $\langle r^2 \rangle$ [1, 38].

2.2.2 Einstein's Mobility

While developing the theory of Brownian motion, Albert Einstein compared the motion of particles at sufficiently low concentration in a liquid under a constant force \mathbf{F} with diffusion. For a given \mathbf{F} (in N), each particle has the average velocity $u\mathbf{F}$ (in m.s^{-1}), where u is the mobility (the ratio of the particle's terminal drift velocity to the applied force) of the particle (in $\text{m.s}^{-1}.\text{N}^{-1}$) and obtained the connection

$$D = uk_B T \quad (2.12)$$

known as the Einstein–Smoluchowski relation, the relation being revealed independently by Marian Smoluchowski, where k_B is the Boltzmann constant (in $\text{JK}^{-1}\text{molecule}^{-1}$). The mobility u is referred as the *Einstein mobility* [1, 38]. This is an early example of the famous fluctuation–dissipation theorem, which bridges microscopic fluctuations with macroscopic transport coefficients. A special case of the Einstein–Smoluchowski relation is the Einstein–Stokes equation for diffusion of spherical particles through a liquid in the limit of low Reynolds number:

$$D = \frac{k_B T}{6\pi\eta\rho} \quad (2.13)$$

where η is the viscosity coefficient of the liquid (in Nm^{-2}s), ρ is radius of the particle (in m), and $6\pi\eta\rho$ is the Stokes' frictional coefficient. In the case of rotational diffusion, Eq. 2.12 becomes:

$$D_{\text{rot}} = \frac{k_B T}{8\pi\eta\rho} \quad (2.14)$$

Using Eq. 2.13, one can estimate the diffusion coefficient (D) of spherical particles from measurements of the viscosity coefficient (η) of a liquid [1, 38]. However, for real solutions at sufficiently high concentrations, the expression for D in terms of u (Eq. 2.12) is modified to:

$$D = u(RT + 2Bc + 3Mc^2 + \dots) \quad (2.15)$$

where B , M , ... are the second, third, and higher order Virial coefficients [38].

2.2.3 Teorell Formula

In 1935, Torsten Teorell used the mobility-based approach for studying diffusion of ions through a membrane and formulated the essence of his approach as:

$$\text{Flux} = \text{mobility} \times \text{concentration} \times \text{force per gram ion} \quad (2.16)$$

This formula called Teorell formula [4, 39] ignores heat effects, special membrane effects, and chemical reactions. The force under isothermal conditions has two components:

- Diffusion force caused by concentration gradient: $-\nabla\mu = -RT\nabla\ln(c/c^{\text{eq}})$, where c^{eq} is the equilibrium concentration.
- Electrostatic potential gradient: $q\nabla\phi$, where q is the charge and ϕ is the electric potential.

The Teorell formula for flux J is thus:

$$\mathbf{J} = uc \left(-\frac{RT}{c} \nabla c + q \nabla \phi \right) \quad (2.17)$$

This expression allows us to find the concentration jumps and the electric potential across the membrane caused by the combined action of diffusion and the electric field, when mobilities of various components are different. For nonideal systems under isothermal conditions, Teorell equation becomes:

$$\mathbf{J} = ua(-\nabla\mu + \text{external force per gram particle}) \quad (2.18)$$

where a , the activity measures the effective concentration of a species in a nonideal mixture and $a = c/c^0 + o(c/c^0)$, where c^0 is the standard state concentration; the second term is a small correction, the activity coefficient. Equation 2.18 is the main analogue of Fick's law for monomolecular diffusion in non-perfect media.

The time derivative of a or c (as normalized dimensionless quantity) in the Einstein–Teorell approach, for small value of c becomes:

$$\frac{\partial(c/c^0)}{\partial t} = \nabla \cdot [ua(\nabla\mu - \text{external force per gram particle})] \quad (2.19)$$

2.2.4 Onsager's Linear Phenomenology and Equations for Multicomponent Diffusion

In 1931, Lars Onsager included multicomponent diffusion in the general context of the linear nonequilibrium thermodynamics:

$$\mathbf{J}_i = \sum_j L_{ij} \mathbf{X}_j \quad (2.20)$$

where \mathbf{J}_i is the flux of the i -th component and \mathbf{X}_j is the j -th thermodynamic force (for pure diffusion, it is the space anti-gradient of the j -th chemical potential, μ_j divided by T , that is $-\nabla(\mu_j / T)$). After linearization near equilibrium, this approach gives for perfect systems (where deviations of c_j from c_j^{eq} are assumed small) under isothermal conditions:

$$\mathbf{X}_j = -\frac{1}{T} \nabla \mu_j \quad (j > 0) \quad (2.21)$$

$$\mathbf{X}_j = -\frac{R}{c_j^{\text{eq}}} \nabla c_j \quad (j > 0) \quad (2.22)$$

$$\mathbf{J}_i = -\sum_j L_{ij} \frac{R}{c_j^{\text{eq}}} \nabla c_j \quad (i, j > 0) \quad (2.23)$$

$$\frac{\partial c_i}{\partial t} = R \sum_j L_{ij} \frac{\nabla^2 c_j}{c_j^{\text{eq}}} \quad (i, j > 0) \quad (2.24)$$

The matrix of kinetic coefficients L_{ij} are symmetric, $L_{ij} = L_{ji}$: Onsager reciprocal relations and their symmetry follow from microscopic reversibility and statistical mechanics of fluctuations and their decay.

The Onsager form of diffusion equations (Eqs. 2.22–2.24) is correct near the equilibrium but violates the obvious physical requirement: \mathbf{J}_i is zero if c_i has zero value. The Teorell approach (Eqs. 2.17–2.19) satisfies this requirement. Fick's laws (Eqs. 2.1–2.5) also satisfy this requirement in the sense: if for nonnegative smooth $c(x)$, the concentration vanishes at some points, then at these points the flux vanishes too (because these points are minimizers of concentration and the gradient vanishes there).

For isotropic non-perfect systems, the thermodynamic driving forces in Onsager's form for isothermal diffusion in the linear approximation near the equilibrium (using Eq. 2.21) are:

$$\mathbf{X}_j = -\frac{1}{T} \sum_k \left(\frac{\partial \mu_j}{\partial c_k} \right)_{c=c^{\text{eq}}} \nabla c_k, \quad (j, k > 0) \quad (2.25)$$

and the diffusion equations become:

$$\mathbf{J}_i = \sum_j L_{ij} \mathbf{X}_j = -\frac{1}{T} \sum_j L_{ij} \left[\sum_k \left(\frac{\partial \mu_j}{\partial c_k} \right)_{c=c^{\text{eq}}} \nabla c_k \right], \quad (j, k > 0) \quad (2.26)$$

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \mathbf{J}_i = \frac{1}{T} \sum_k \left[\left(\sum_j L_{ij} \frac{\partial \mu_j}{\partial c_k} \right)_{c=c^{\text{eq}}} \right] \nabla^2 c_k, \quad (i, j, k > 0) \quad (2.27)$$

The matrix of diffusion coefficients, D_{ik} becomes:

$$D_{ik} = \frac{1}{T} \sum_j L_{ij} \left(\frac{\partial \mu_j}{\partial c_k} \right)_{c=c^{\text{eq}}} \quad (i, j, k > 0) \quad (2.28)$$

The intrinsic arbitrariness in the definitions of \mathbf{X}_j and L_{ij} is to be noted. These are not measurable separately and only their combinations $\sum_j L_{ij} X_j$ can be measured. Thus, the Onsager's formalism of linear irreversible thermodynamics gives the system of linear diffusion equations in the form:

$$\frac{\partial c_i}{\partial t} = \sum_j D_{ij} \nabla^2 c_j \quad (i, j > 0) \quad (2.29)$$

If the matrix D_{ij} is diagonal, this system of equations is simply a collection of decoupled Fick's equations for various components [4, 40–42].

Non-diagonal diffusion must be nonlinear. Diffusion preserves the positivity of concentrations. If the diffusion is non-diagonal and linear, e.g. $D_{12} \neq 0$, for a state where $c_2 = \dots = c_n = 0$, the diffusion equation would be:

$$\frac{\partial c_2}{\partial t} = D_{12} \nabla^2 c_1(x) \quad (2.30)$$

If $D_{12} \nabla^2 c_1(x) < 0$ at some points, $c_2(x)$ becomes negative at these points in a short time. Therefore, linear non-diagonal diffusion does not preserve the positivity of concentrations and consequently, non-diagonal equations of multicomponent diffusion are nonlinear [4].

2.2.5 Teorell Formula For Multicomponent Diffusion

The Teorell formula with combination of Onsager's definition of the diffusion force gives:

$$\mathbf{J}_i = u_i a_i \sum_j L_{ij} \mathbf{X}_j \quad (2.31)$$

For isothermal perfect systems:

$$\mathbf{J}_i = -u_i c_i R \sum_j L_{ij} \frac{1}{c_j} \nabla c_j \quad (2.32)$$

Thus, the Einstein–Teorell approach gives the following generalization of the Fick’s law for multicomponent diffusion:

$$\frac{\partial c_i}{\partial t} = \sum_j \nabla \cdot \left(D_{ij} \frac{c_i}{c_j} \nabla c_j \right) \quad (2.33)$$

where D_{ij} is the matrix of coefficients [4]. It should be stressed that these physical models of diffusion are different from the toy models (Eq. 2.29), which are valid for very small deviations from uniform equilibration.

For anisotropic multicomponent diffusion coefficients (for example, in crystals) one needs 4-index quantities, for example, $D_{ij\alpha\beta}$, where i, j are related to the components and $\alpha, \beta = 1, 2, 3$ correspond to the space coordinates.

2.3 Nonlinear Diffusion

As discussed earlier, the linear diffusion equation has limitations. There are many nonlinear diffusion models. We discuss a few of these below.

2.3.1 Diffusion of Reagents on the Surface of a Catalyst: Jumps on the Surface

Alexander N. Gorban and his coauthors proposed a model of diffusion in monolayers of reagents on the surface, which is based on the jumps of the reagents on the nearest free places. This model has been used for oxidation of CO on platinum under low gas pressure.

The system includes several reagents A_1, A_2, \dots, A_n on the surface. Their surface concentrations are c_1, c_2, \dots, c_n , respectively. The surface is a lattice of the adsorption sites. Each reagent molecule fills a place on the surface. Some of the places are free. A_0 symbolizes a free place and its concentration is $c_0 (=z)$. It follows that $\sum_{i=0}^{i=n} c_i = b$, a constant representing the density of adsorption places. According to the jump model, the diffusion flux of A_i ($i = 1, 2, \dots, n$) is:

$$\mathbf{J}_i = -D_i (z \nabla c_i - c_i \nabla z) \quad (2.34)$$

and the corresponding diffusion equation is:

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \mathbf{J}_i = D_i (z \nabla^2 c_i - c_i \nabla^2 z) \quad (2.35)$$

Due to conservation of the places on the surface $z = b - \sum_{i=1}^{i=n} c_i$ we have a system of n diffusion equations:

$$\mathbf{J}_i = -D_i \left[\left(b - \sum_{i=1}^n c_i \right) \nabla c_i + c_i \nabla \sum_{i=1}^n c_i \right] \quad (2.36)$$

$$\frac{\partial c_i}{\partial t} = D_i \left[\left(b - \sum_{i=1}^n c_i \right) \nabla^2 c_i + c_i \nabla^2 \sum_{i=1}^n c_i \right] \quad (2.37)$$

It may be noted that for one component:

$$(b - c) \nabla c + c \nabla c = b \nabla c \quad (2.38)$$

$$(b - c) \nabla^2 c + c \nabla^2 c = b \nabla^2 c, \quad (2.39)$$

and the diffusion equation becomes linear, the Fick's law (Eq. 2.29). Obviously, for two or more components, the equations are nonlinear. When $c_i \geq 0$ for all x , $(\partial c_i / \partial t) \geq 0$ for all $c_i = 0$, which is necessary for the preservation of positivity.

If all particles can exchange their positions with their closest neighbours, a simple generalized equation follows:

$$\mathbf{J}_i = - \sum_j D_{ij} (c_j \nabla c_i - c_i \nabla c_j) \quad (2.40)$$

$$\frac{\partial c_i}{\partial t} = \sum_j D_{ij} (c_j \nabla^2 c_i - c_i \nabla^2 c_j) \quad (2.41)$$

where $D_{ij} = D_{ji} \geq 0$ is a symmetric matrix of coefficients which characterize the extent of jumps [4].

2.3.2 Diffusion In a Porous Medium

The basic equation describing diffusion in porous media, porous medium equation (PME), is a nonlinear parabolic-type evolution equation:

$$\frac{\partial c}{\partial t} = \nabla^2 c^m = \nabla \cdot [D(c) \nabla c] \quad (2.42)$$

where $c = c(r, t) > 0$, $m > 1$, and $D(c)$, the concentration-dependent diffusivity is given as $D(c) = mc^{m-1}$. PME applies to a number of processes such as the flow of an isentropic gas through a porous medium ($m \geq 2$), infiltration of ground water ($m=2$), heat radiation in plasmas ($m \geq 4$) [43].

2.3.3 Phase Separation: Cahn–Hilliard Equation

The process by which the two components of a binary fluid spontaneously separate and form domains pure in each component is a problem of nonlinear diffusion and is described by the Cahn–Hilliard equation:

$$\frac{\partial c}{\partial t} = D \nabla^2 (c^3 - c - \gamma \nabla^2 c) \quad (2.43)$$

where c is the concentration of the fluid, $c = \pm 1$ indicates domains, D is the diffusion coefficient, and γ is the square of the of the length of the transition regions between the domains. The quantity $(c^3 - c - \gamma \nabla^2 c)$ is identified as a chemical potential μ . The term $-\gamma \nabla^2 c$ is derived from a component of the free energy modelling the interface energy and it regularizes the solutions of the equation [4, 44]. In the phase separation problem, the components are definitely non-perfect and necessary corrections by the activity coefficients can be incorporated.

2.3.4 Diffusion In Solids: Eyring’s Quasi-Chemical Model

Diffusion in solids takes place through the movement of defects, for example point defects (vacancies, interstitial atoms) are responsible for lattice diffusion. Diffusion occurs when an atom jumps from a normal lattice site into an adjacent vacant one or from an interstitial site to one of the neighbouring interstitial ones. The interstitial mechanism which involves significant lattice distortion is, however, favoured when interstitial atoms are sufficiently small as compared to normal lattice atoms, for example light atoms like H, C, N, O interstitially dissolved in metals. When lattice distortion becomes too large for the interstitial mechanism to be probable, the interstitialcy mechanism (where an interstitial atom pushes one of its nearest neighbours on a normal lattice site into another interstitial position and itself occupies the lattice site of the displaced atom) is favoured.

The quasi-chemical theory of diffusion in solids was initially developed by Yakov Frenkel and later improved by F. C. Frank and D. Turnbull [1, 4, 45]. This was further developed by Henry Eyring and coauthors who applied their famous activated complex theory (ACT) for chemical reactions to diffusion in solids. The diffusion in the treatment is represented by an ensemble of elementary events, each of which is represented by the creation or destruction of an activated complex (transition state). The rate of the elementary process is given by the concentration of the activated complex multiplied by the rate of its decomposition. It is hypothesized that the complex is in quasi-equilibrium with the stable components and the concentration of the complex can be calculated using equilibrium statistical thermodynamics [3].

Eyring’s approach to diffusion problems is illustrated here for vacancy diffusion in cubic lattice of an elemental solid. The coefficient for such diffusion may be expressed as:

$$D = \alpha a_0^2 w N_d \quad (2.44)$$

where α is a geometrical factor ($=1$ for *bcc* and *fcc* lattices), a_0 is the lattice parameter, w is the frequency of a jump to an adjacent site, and N_d is the fraction of vacancies in the lattice.

To obtain an expression for the temperature dependence of D (Eq. 2.44), it needs considering how N_d and w change with temperature. The diffusing atoms may make a jump, only when a neighbouring lattice site is vacant. If ΔG_d is the Gibbs free energy of vacancy formation, N_d may be expressed as:

$$N_d = e^{-\Delta G_d / (RT)} = e^{-(\Delta H_d / RT)} e^{\Delta S_d / R} \quad (2.45)$$

where ΔH_d and ΔS_d are the corresponding enthalpy and entropy terms.

ΔH_d is generally positive and N_d increases with temperature. The rate at which an atom jumps between neighbouring sites in a lattice may be written following ACT as:

$$\omega = \nu e^{-\Delta G_m / RT} = \nu e^{\Delta S_m / R} e^{-\Delta H_m / RT} \quad (2.46)$$

where ΔG_m , ΔH_m , and ΔS_m are the free energy, enthalpy, and entropy changes associated with the movement of the atom from the initial equilibrium condition to the activated complex at the top of the potential energy barrier, which the atom has to surmount during the jump to another equilibrium site. ν in Eq. 2.46 represents the vibration frequency and is of the order of 10^{13} Hertz. ΔS_m is generally small $\sim 10 \text{ JK}^{-1} \text{ mol}^{-1}$.

The temperature dependence of D for vacancy diffusion in a cubic lattice of an elemental solid may now be expressed as [3, 45]:

$$D = \alpha a_0^2 \nu e^{(\Delta S_d + \Delta S_m) / R} e^{-(\Delta H_d + \Delta H_m) / (RT)} \quad (2.47)$$

The experimental D versus T data leads to the following equation:

$$D = D_0 e^{-Q / RT} \quad (2.48)$$

where Q is the activation energy.

On comparing Eq. 2.48 with Eq. 2.47, the activation energy consists of:

$$Q = \Delta H_d + \Delta H_m \quad (2.49)$$

and the corresponding D_0 is given by:

$$D_0 = \alpha a_0^2 \nu e^{(\Delta S_d + \Delta S_m) / R} \quad (2.50)$$

2.4 Osmosis

Transport processes occurring via artificial membranes separating different salt solutions are of great interest to chemists, chemical engineers, and biologists. To understand the mechanism of transport is a thrust area of research for chemists and chemical engineers; they are interested in fabricating membranes of any desired properties. However, biologists would like to use them as simple models for understanding the properties of complex cell membranes [46]. The transport of solvent molecules through semipermeable membranes is known as osmosis. If two solutions of different concentrations are separated by a semipermeable membrane, the solvent tends to transport across the membrane from the less concentrated to the more concentrated side. Osmosis is a selective diffusion process driven by the internal energy of the solvent molecules. It is convenient to express the available energy per unit volume in terms of osmotic pressure.

The movement of a pure solvent is driven for reducing the free energy of the system by equalizing solute concentrations on each side of a membrane, generating osmotic pressure. Osmosis is driven by the imbalance in water concentration. Osmosis is vital to life, because of its function in maintaining equilibrium inside and outside of a cell. In the human body, osmosis is used by the kidneys to cleanse the blood. Osmosis is of great importance in biological processes where the solvent is water. The transport of water and other molecules across biological membranes is essential to many processes in living organisms. The cell membrane functions as a semipermeable barrier; it allows selective passage of molecules through it. Osmosis depends upon concentration of solute particles, ionization of solute particles, hydration of solute particles, and temperature.

Both plant and animal living cells are enclosed by semipermeable membranes, called the cell membranes that regulate the flow of liquids and of dissolved solids and gases into and out of the cell. The cell membrane forms a selective barrier between the cell and its environment so that not all substances can pass through the membrane easily. Without this selectivity, toxic materials from the surroundings would enter the cell. If blood or other cells are placed in contact with an isotonic solution, they will neither shrink nor swell. If the cell is placed in a hypertonic solution, it will lose water and shrink (plasmolysis) and shows exosmosis. If a cell is placed in a hypotonic solution (or if a pure solvent is used), the cells swell and show endosmosis. Hence, the osmotic pressure so developed inside the cell may even be great enough to rupture the cell membrane. In plants, osmosis is at least partially responsible for the absorption of soil water by root hairs and for the up pull of the liquid to the leaves of the plants. However, plants wilt when watered with saltwater or treated with too much fertilizer, since the soil around their roots becomes hypertonic.

The phenomenon of osmosis takes place in the absorption of water by plant roots, reabsorption of water by the proximal and distal convoluted tubules of the nephron, reabsorption of tissue fluid into the venule ends of the blood capillaries, and the absorption of water by the alimentary canal, stomach, small intestine, and colon.

Purification or desalination of water is also carried out by osmosis. Currently, two types of osmosis are used in the purification of water: forward osmosis (FO), reverse osmosis (RO). FO is a manipulated osmosis or engineered osmosis. It involves low-cost energy processes and is one of the emerging membrane technologies, as it has the ability to desalinate seawater or brackish water naturally [47]. RO is currently the most commonly used water purification technology because of its merits over other conventional thermal desalination technologies. In RO, an applied pressure is used to overcome osmotic pressure, a colligative property that is driven by chemical potential, a thermodynamic parameter [48].

In osmotic drug delivery system, the osmotic pressure of drug or other solutes (osmogens or osmagents) is used for the controlled delivery of drugs. In drug delivery, the two most critical properties considered for the selection of osmogen are osmotic activity and aqueous solubility. Osmotic agents or osmogens for drug delivery are classified as: (i) *inorganic water soluble osmogens*: magnesium sulphate, sodium chloride, sodium sulphate, potassium chloride, sodium bicarbonate, etc. (ii) *organic polymeric osmogens*: sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), etc. and (iii) *organic water soluble osmogens*: sorbitol, mannitol, etc.

Cellulose acetate is a commonly used semipermeable membrane for the preparation of osmotic pumps in biological systems. Some other examples of polymers used in semipermeable membrane are agar acetate, amylose triacetate, beta-glucan acetate, poly (vinylmethyl) ether copolymers, poly (orthoesters), polyacetals, poly (glycolic acid), and poly (lactic acid) derivatives.

Osmosis has several implications in medical science. If blood cells were stored in water, osmosis would cause them to swell and eventually burst. Osmosis is closely related to dialysis, which is critical to the survival of many victims of kidney diseases. Dialysis is the process by which an artificial kidney machine removes waste products from the patients' blood, performing the role of a healthy, normally functioning kidney.

Osmosis is classified based on the solution in which the cell is placed: endosmosis, exosmosis. When a cell is placed in hypotonic solution, water enters into the cell from the outer (hypotonic) solution. This process of diffusion of water into a cell from the outside is called endosmosis. When a cell is immersed in a hypertonic solution, water diffuses out of the cell because the concentration of water molecules in the cell is more than the outer solution. This is known as exosmosis.

2.4.1 Historical Perspective

In 1748, osmosis phenomenon through semipermeable membranes was first observed by Cleric Jean-Antoine Nollet [49]. The term “osmosis” descends from the Greek words meaning “endosmose” and “exosmose”, which were coined by the French physician René Joachim Henri Dutrochet. The general term osmose (now osmosis) was introduced in 1854 by a British chemist, Thomas Graham [50]. Experimental work was conducted primarily with membranes of animals and plants.

In 1867, the first artificial semipermeable membrane of inorganic compound copper ferrocyanide was prepared by Traube [51]. Osmosis was first thoroughly studied in 1877 by a German plant physiologist Wilhelm Pfeffer by successful quantitative measurement of osmotic effect. Pfeffer measured the effect by utilizing a membrane, which is selectively permeable to water but impermeable to sugar. The membrane separated sugar solution from pure water. Pfeffer observed flow of water into the sugar solution, which stopped when a pressure p was applied to the sugar solution. Pfeffer postulated that this pressure, the osmotic pressure π of the sugar solution is proportional to the solution concentration and absolute temperature. Van't Hoff established an expression that is analogous to the Pfeffer results and the ideal gas laws [52] in 1886 as $\pi = n_2 RT$, where n_2 represents the molar concentration of sugar (or other solute) in the solution, R is the gas constant and T is the absolute temperature.

The most carefully documented use of pressure as a driving force for membrane filtration was published in 1907 by Bechold [53]. Osmotic drug delivery uses the osmotic pressure of drug or other solutes (osmogens or osmagents) for controlled delivery of drugs. Osmotic drug delivery has come a long way since the Australian physiologists Rose and Nelson developed an implantable pump in 1955 [54]. Drug itself may act as an osmogen showing good aqueous solubility (e.g. potassium chloride pumps). If the drug does not possess an osmogenic property, osmogenic salt and other sugars can be incorporated in the formulation.

2.4.2 *Current Status of Research*

New therapeutically active molecules for the treatment and prevention of diseases are currently being developed. It is a primary requirement for the therapeutically active molecules to reach its site of action, hence novel drug delivery systems (NDDS) have been recognized as an attraction for the pharmaceutical and health industry [55]. Many conventional drug delivery systems have been designed by various scientists to modulate the release and transport of drugs over an extended period of time. The rate and extent of drug absorption and release may depend on the factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, and pH of the gastrointestinal tract (GI) [56]. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis and this is known as the osmotic drug delivery process. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called osmagents) for controlled delivery of drugs. Drug delivery systems are independent of the different physiological factors of gastrointestinal tract; the release characteristics can be predicted easily from the known properties of the drug and the dosage form [57]. It is a cost-effective method for the drug delivery. The major advantage of osmotic drug delivery are: (i) the delivery rate of zero order (which is most desirable) is achievable with osmotic systems, (ii) desired drug delivery may be delayed or pulsed, (iii) for oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions, which is mainly attributed to the unique properties of semipermeable membrane employed in coating of osmotic formulations.

2.5 Summary

Diffusion is a widely applicable concept. It applies to any field involving random walks in ensembles of individuals. In fact, the concept of diffusion is used across diverse fields stretching from physics, chemistry, and biology to sociology, economics, and finance even. The diffusion behaviour in many of the cases follows linear Fick's laws. However, there are a good number of instances where diffusive flows become non-Fickian. For diffusion on catalyst surfaces, in crystal lattices, porous media, phase-segregation, etc., a more general nonlinear approach is required.

The biological cells use different mechanisms for transportation of substrates, products, waste, etc. to maintain homeostasis. Diffusion and osmosis are involved in active metabolism in living cells. The implications of restricted molecular diffusion for cell function remain a major unresolved issue. Diffusion has played a key role in extending the applicability of MRI technique and given rise to new MRI techniques. One such technique, diffusion-weighted imaging MR (DW-MRI) relies on the determination of random microscopic motion of free water molecules in tissues with clinical applications to a wide range of pathological conditions. Another technique, diffusion tensor imaging MRI (DT-MRI) is based on the fact that mobilities of water molecules in directionally ordered cellular structures such as cell membranes and myelin become directionally dependent. DT-MRI characterizes this directional nature of water motion and thereby provides structural information that cannot be obtained by standard anatomical imaging. On the other hand, osmosis has also several implications in medical care, particularly for the storage of red blood cells. For drug delivery in the living systems, scientists are pursuing development of osmosis that has better absorptive and pharmacokinetic properties. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called osmagents) for controlled delivery of drugs in biological systems.

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