Chapter 2
Diffusion and Kinetics

Everything changes and nothing stands still.

Heraclitus of Ephesus (544-483 BC)

The principles of physical and chemical laws are essential for the understanding of drug kinetics in mammalian species. This also applies to pharmacodynamics since the interaction of drug with the receptor(s) relies on the physicochemical principles of the law of mass action. In reality one can consider the entire course of drug in the body as consecutive and/or concurrent processes of diffusion and convection. For example, the oral administration of a drug may include, among many others, the following processes:

- dissolution in the gastrointestinal fluids (diffusion),
- transport in the chyme by intestinal peristalsis (convection),
- transcellular uptake (diffusion),
- transport with the blood to organs (convection),
- transfer from the bloodstream into the interstitial and intracellular spaces (diffusion),
- interaction with receptors at the effect site (diffusion),
- transfer from tissues back into blood (diffusion),
- glomerular filtration (convection),
- transport with the urine into the efferent urinary tract (convection),
- reabsorption from the tubular lumen to the peritubular capillary (diffusion).

The above convection processes are the result of the movement of a liquid in bulk, i.e., the flow of the biological fluid. Consequently, convection processes are particularly dependent on physiology. For example, the glomerular filtration of a drug is extremely important from a therapeutic point of view, but it is solely determined by the physiological condition of the patient, e.g., the glomerular filtration rate. This is so, since a common translational velocity is superposed on the thermal motions of all drug molecules in any element of volume. On the other hand, convection processes for the dissolved and undissolved drug in the gastrointestinal tract are much more complicated. Here, physiology still plays a major role but dietary conditions and the type of formulation are important too. The picture becomes even more complicated

P. Macheras, A. Iliadis, *Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics*, Interdisciplinary Applied Mathematics 30,
DOI 10.1007/978-3-319-27598-7_2

if one takes into account the oscillatory nature of intestinal motility, which is related to the food intake. Despite the complexity involved, the term convection implies that both dissolved drug molecules and undissolved drug particles along with the gastrointestinal fluid molecules are transported together without separation of individual components of the solution/suspension.

On the other hand, diffusion is the random migration of molecules or small particles arising from motion due to thermal energy. Here, drug diffusive fluxes are produced by differences in drug concentrations in different regions. Thus, diffusion is one of the most significant process in all fields of pharmaceutical research either in vitro or in vivo. This is justified by the fact that everything is subject to thermal fluctuations, and drug molecules or particles immersed in aqueous environments are in continuous riotous motion. Therefore, understanding of these random motions is crucial for a sound interpretation of drug processes.

2.1 Random Walks and Regular Diffusion

Particles under the microscope exhibiting Brownian motion demonstrate clearly that they possess kinetic energy. We are also familiar with the diffusional spreading of molecules from the classical experiment in which a drop of dye is carefully placed in an aqueous solution. Fick's laws of diffusion describe the spatial and temporal variation of the dye molecules in the aqueous solution. However, before presenting Fick's differential equation, attention will be given to a proper answer for the fundamental question: How much do the molecules move on average during diffusional spreading?

The correct answer to the above question is a law of physics: "the mean square displacement is proportional to time." We can intuitively reach this conclusion with particles executing an imaginary one-dimensional random walk. A simple model is presented in Figure 2.1, ignoring the detailed structure of the liquid and temperature effects and assuming no interaction between particles. The particles are placed at $z = 0$ and start their random walk at $t = 0$ moving at a distance δ either to the right or to the left once every $t_\circ$ units of time; thus, the particles execute i steps in time $t = it_\circ$. Equal probabilities $(1/2)$ are assigned for each movement of the particles (either to the right or to the left). This means that the successive jumps of particles are statistically independent and therefore the walk is unbiased. We say that the particles are blind since they have no "memory" of their previous movement(s).

Fig. 2.1 A one-dimensional random walk of particles placed at $z = 0$ at $t = 0$. The particles occupy only the positions 0, $\pm\delta$, $\pm 2\delta$, $\pm 3\delta$, $\pm 4\delta$

The question arises: How far will a particle travel in a given time interval? The average distance a particle travels is given by mean square displacement evaluated as follows: The position of a particle along the z-axis after i steps z_i is

$$z_i = z_{i-1} \pm \delta, \tag{2.1}$$

where z_{i-1} is the position of the particle at the previous $(i-1)$-th step. Taking the square of (2.1) we get the square displacement

$$z_i^2 = z_{i-1}^2 \pm 2\delta z_{i-1} + \delta^2,$$

which if averaged for the total number of particles, provides their mean square displacement $\langle z_i^2 \rangle$:

$$\langle z_i^2 \rangle = \langle z_{i-1}^2 \rangle \pm 2\delta \langle z_{i-1} \rangle + \delta^2 = \langle z_{i-1}^2 \rangle + \delta^2. \tag{2.2}$$

The second term in the brackets vanishes since the plus sign corresponds to half of the particles and the minus sign to the other half. Given that $z_0 = 0$ and applying (2.2) for the successive steps $1, 2, \ldots, i$, we get

$$\langle z_1^2 \rangle = \delta^2, \langle z_2^2 \rangle = 2\delta^2, \ldots, \langle z_i^2 \rangle = i\delta^2. \tag{2.3}$$

Since as previously mentioned the number of steps is proportional to time ($i = t/t_\circ$), we can express the positioning of particles as a function of time t using (2.3):

$$\langle z^2(t) \rangle = \left(\delta^2 / 2t_\circ \right) t. \tag{2.4}$$

The use of 2 in the denominator of the previous equation will be explained in Section 2.4. The last expression shows that the mean square displacement of the particles is proportional to time, t:

$$\langle z^2(t) \rangle \propto t. \tag{2.5}$$

The same result is obtained if one considers a simple random walk in two dimensions, i.e., the walk is performed on a two-dimensional lattice. Here, the walker (particle) moves either vertically or horizontally at each time step ($t_\circ$ units of time) with equal probabilities. Two configurations for eight-time-step random walks are shown in Figure 2.2A, along with the trail of a random walk of 10,000 steps, Figure 2.2B. In the general case and assuming that the lattice spacing is δ, the position of the walker on the plane after i steps z_i is

$$z_i = \delta \sum_{j=1}^{i} u_j,$$

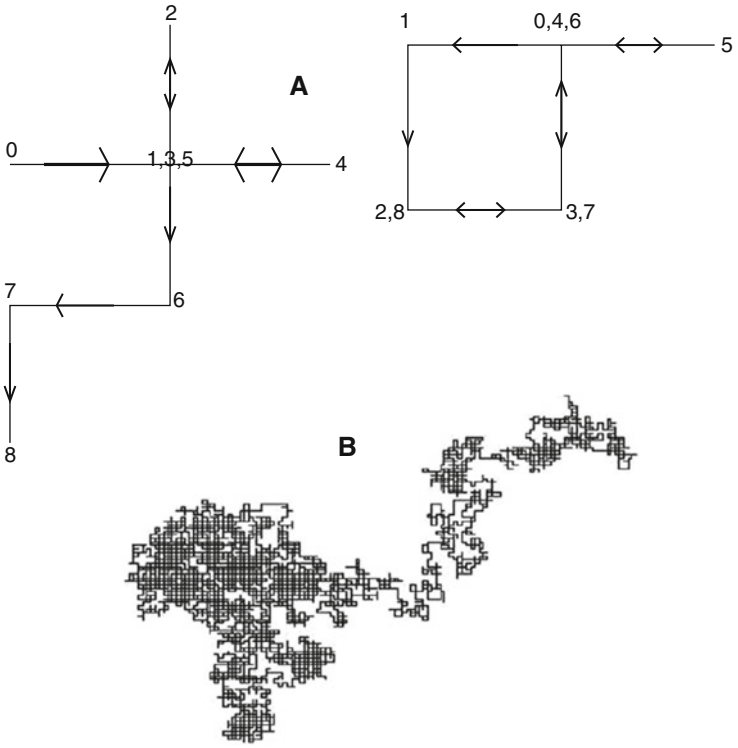

Fig. 2.2 (**A**) Two configurations of eight-step random walks in two dimensions. The numbers correspond to the successive eight steps and the arrows indicate the direction of movement. (**B**) A random walk of 10, 000 steps

where u_j is a (unit) vector pointing to a nearest-neighbor site; it represents the j-th step of the walk on the two-dimensional lattice. The mean displacement $\langle z_i \rangle$ of the walker can be obtained if z_i is averaged for the total number of walkers, $\langle z_i \rangle = 0$. This equation is obtained from the previous one since $\langle u_j \rangle = 0$. Moreover, the mean square displacement can be obtained from the previous equation if one takes into account that $\langle u_j u_j \rangle = 1$, and $\langle u_j u_k \rangle = 0$:

$$\begin{aligned} \langle z_i^2 \rangle &= \left\langle \left[\delta \sum_{j=1}^{i} u_j \right]^2 \right\rangle \\ &= \delta^2 \left\langle (u_1 + u_2 + \ldots + u_i)(u_1 + u_2 + \ldots + u_i) \right\rangle \\ &= \delta^2 \sum_{j=1}^{i} \langle u_j u_j \rangle + \delta^2 \sum_{\substack{j=1 \\ k \neq j}}^{i} \langle u_j u_k \rangle = i\delta^2. \end{aligned} \tag{2.6}$$

Substituting $i = t/t_\circ$ in the last equation, (2.4) is recovered using the factor $\frac{1}{2}$ for the derivation once again.

The theory for motion in three dimensions results in the same law if the same assumptions are applied and motions in the three directions are statistically independent. The important result for regular diffusion is that its time dependence is universal regardless of the dimension of the medium. This square root relation (2.5) has striking consequences for the distance covered by diffusing molecules. It takes *four* times as long to get *twice* as far while a particle can cover *half* the distance in a *quarter* of the time. Thus, transport by diffusion is very slow if there is far to go, but very rapid over very short distances. For example, the exchange and transport of solutes within cells and between cells and capillaries can be effectively maintained by diffusion due to the small size and close spacing of cells and capillaries in the body of mammals. On the contrary, the slowness of diffusion over large distances points to the necessity for a circulatory system to bring oxygen, for example, from the lungs to the brain or glucose from the liver to the muscles of the arms. To permit these exchanges, the bulk flow of blood carries a large number of solutes around the body in the vascular system by convection.

Equation (2.4) will help us to define and understand the meaning of the diffusion coefficient $\mathcal{D}$. This term corresponds to the proportionality constant of (2.4),

$$\mathcal{D} \triangleq \frac{\delta^2}{2t_\circ}, \tag{2.7}$$

has dimensions of area×time^{-1} and takes different values for different solutes in a given medium at a given temperature. Hence, the value of $\mathcal{D}$ is characteristic for a given solvent (or better, medium structure) at a given temperature of the diffusing tendency of the solute. For example, a small drug molecule in water at 25 °C has $\mathcal{D} \approx 10^{-5}\,\mathrm{cm}^2/\,\mathrm{s}$, while a protein molecule like insulin has $\mathcal{D} \approx 10^{-7}\,\mathrm{cm}^2/\,\mathrm{s}$. Using these values one can roughly calculate the time required for the drug and protein molecules to travel a distance of 1 mm; it takes $(0.1)^2/10^{-5} \approx 1000\,\mathrm{s} \approx 16.6\,\mathrm{min}$ for the drug and 1666.6 min for insulin. Hence, the value of $\mathcal{D}$ is heavily dependent on the size of the solute molecules. These numerical calculations are very useful in obtaining insight into the rapidity or slowness of a solute migration, e.g., drug release from controlled release formulations when regular diffusion is the operating mechanism.

2.2 Anomalous Diffusion

In the previous section we analyzed the random walk of molecules in Euclidean space and found that their mean square displacement is proportional to time (2.5). Interestingly, this important finding is not true when diffusion is studied in fractals and disordered media. The difference arises from the fact that the nearest-neighbor

sites visited by the walker are equivalent in spaces with integer dimensions but are not equivalent in fractals and disordered media. In these media the mean correlations between different steps $\langle u_j u_k \rangle$ are not equal to zero, in contrast to what happens in Euclidean space; cf. derivation of (2.6). In reality, the anisotropic structure of fractals and disordered media makes the value of each of the correlations $u_j u_k$ structurally and temporally dependent. In other words, the value of each pair $u_j u_k$ depends on where the walker is at the successive times j and k, and the Brownian path on a fractal may be a "fractal of a fractal" [9]. Since the correlations $u_j u_k$ do not average out, the final important result is $\langle u_j u_k \rangle \neq 0$, which is the underlying cause of anomalous diffusion. In reality, the mean square displacement does not increase linearly with time in anomalous diffusion and (2.5) is no longer exact.

To characterize the dynamic movement of particles on a fractal object, one needs two additional parameters: the spectral or fracton dimension d_s and the random-walk dimension d_w. Both terms are quite important when diffusion phenomena are studied in disordered systems. This is so since the path of a particle or a molecule undergoing Brownian motion is a random fractal. A typical example of a random fractal is the percolation cluster shown in Figure 1.5.

The definition of spectral dimension d_s refers to the probability $p(t)$ of a random walker returning to its origin after time t:

$$p(t) \propto t^{-d_s/2}. \tag{2.8}$$

According to (2.8), the value of d_s governs the decrease of the probability $p(t)$ with time. When diffusion is considered in Euclidean spaces the various dimensionality terms become identical: $d_t = d_s = d_f$. However, in fractal spaces the following inequalities hold: $d_t < d_s < d_f < d_e$, where d_e is the embedding dimension. For example, we found for the Sierpinski gasket (Figure 1.2A) $d_f = 1.5815$, while $d_s = 1.3652$ and the embedding dimension in this case is $d_e = 2$. The meaning of d_s can be understood if one considers a walker executing a random walk on a ramified system, like the Sierpinski gasket with $d_f = 1.5815$, Figure 1.2A. Due to the system's ramification, the walker has many alternatives of movement in the branched system, and therefore the probability of the walker being back at the origin is small. Hence, the value of d_s goes up in accord with (2.8) and is higher than one ($d_s > 1$), i.e., the topological dimension of a curve. In actual practice, the calculation of d_s is accomplished numerically. Analytical solutions for d_s are available when the recursion algorithm of the system is known, e.g., Sierpinski gasket.

Finally, a stochastic viewpoint may be associated with the relation (2.8) since the spectral dimension also characterizes the number $n(t)$ of distinct sites visited by the random walker up to time t:

$$n(t) \propto t^{d_s/2}. \tag{2.9}$$

The random-walk dimension d_w is useful whenever one has a specific interest in the fractal dimension of the trajectory of the random walk. The value of d_w is exclusively dependent on the values of d_f and d_s:

$$d_w = \min\left[2\frac{d_f}{d_s}, d_f\right].$$

The type of the random walk (recurrent or nonrecurrent) determines the minimum value of the two terms in the brackets of the previous equation. If the walker does not visit the same sites (nonrecurrent), then $d_w = 2d_f/d_s$. If the walk is of recurrent type, then the walker visits the same sites again and again and therefore the walker covers the available space (space-filling walk). Consequently, the meaning of d_w coincides with d_f ($d_w = d_f$). The mean square displacement in anomalous diffusion follows the pattern

$$\left\langle z^2(t)\right\rangle \propto t^{2/d_w}, \tag{2.10}$$

where d_w is the fractal dimension of the walk and its value is usually $d_w > 2$. The exponent d_w arises from the obstacles of the structure such as holes, bottlenecks, and dangling ends, i.e., the diffusional propagation is hindered by geometric heterogeneity. The previous equation is the fundamental relation linking the propagation of the diffusion front to the structure of the medium, and it recovers also the classical law of regular diffusion when $d_w = 2$.

In conclusion, the dynamic movement of particles on a fractal object may be described by functional characteristics such as the spectral dimension d_s and the random-walk dimension d_w. This anomalous movement of the molecules induces heterogeneous transport and heterogeneous reactions. Such phenomena present a challenge to several branches of science: chemical kinetics, surface and solid state physics, etc. Consequently, one may argue that all mechanisms involved in drug absorption, metabolism, enzymatic reactions, and cell microscopic reactions can be analyzed in the new heterogeneous context since these processes are taking place under topological constraints.

2.3 Fick's Laws of Diffusion

Apart from the above considerations of diffusion in terms of the distance traveled in time, the amount of substance transported per unit time is useful too. This approach brings us to the concept of the rate of diffusion. The two considerations are complementary to each other since the diffusion of molecules at the microscopic level results in the observed "flux" at the macroscopic level. Fick's laws of diffusion describe the flux of solutes undergoing classical diffusion.

The simplest system to consider is a solution of a solute with two regions of different concentrations c_l and c_r to the left and right, respectively, of a boundary separating the two regions, Figure 2.3. In reality, the rate of diffusion is the net flux, i.e., the difference between the two opposite unidirectional fluxes. There will be a net movement of solute molecules to the right if $c_l > c_r$ or to the left if $c_l < c_r$. When $c_l = c_r$, the unidirectional fluxes are equal and the net flux is zero. Since the

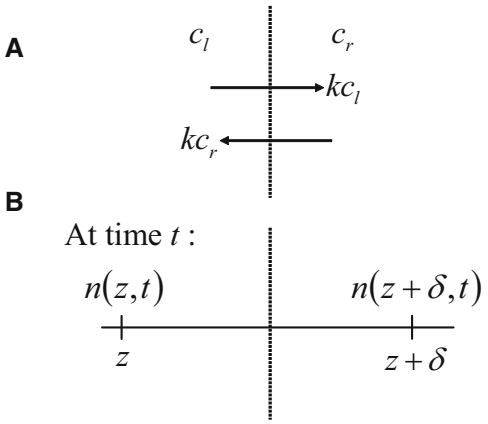

Fig. 2.3 A solute diffuses across a plane. (**A**) Solute diffusion from two regions of different concentrations c_l and c_r; the plane indicates the boundary of the regions. The transfer rate of material is proportional to concentrations c_l and c_r. (**B**) At a given time t there are $n(z,t)$ and $n(z+\delta,t)$ molecules at positions z and $z+\delta$, respectively

two fluxes across the boundary from left to right and vice versa are proportional to c_l and c_r, respectively, the net flux is proportional to the concentration difference across the boundary.

The derivation of Fick's first law of diffusion requires a reconsideration of Figure 2.3A in terms of the one-dimensional random walk as shown in Figure 2.3B. Let us suppose that at time t, there are $n(z,t)$ molecules at the left position z and $n(z+\delta,t)$ molecules at the right position $z+\delta$, Figure 2.3B. Since equal probabilities $(1/2)$ are assigned for the movement of the molecules (either to the right or to the left), half of the $n(z,t)$ and $n(z+\delta,t)$ molecules will cross the plane at the next instant of time $t+t_\circ$, moving in opposing directions. The net number of molecules crossing the plane to the right is $-\frac{1}{2}\left[n\left(z+\delta,t\right)-n\left(z,t\right)\right]$ and the corresponding net flux J of the diffusate is

$$J\left(z,t\right)=-\frac{1}{2\mathcal{A}t_\circ}\left[n\left(z+\delta,t\right)-n\left(z,t\right)\right],$$

where $\mathcal{A}$ is the area of the plane and $t_\circ$ is the time interval. Multiplying and dividing the right part by δ^2 and rearranging, we get

$$J\left(z,t\right)=-\frac{\delta^2}{2t_\circ}\frac{1}{\delta}\left[\frac{n\left(z+\delta,t\right)}{\mathcal{A}\delta}-\frac{n\left(z,t\right)}{\mathcal{A}\delta}\right].$$

The terms in the brackets express the concentration of molecules per unit volume $\mathcal{A}\delta$, i.e., $c(z+\delta,t)\equiv c_r\left(t\right)$ and $c(z,t)\equiv c_l\left(t\right)$ at positions $z+\delta$ and z, respectively, while the term $\delta^2/2t_\circ$ is the diffusion coefficient $\mathcal{D}$; the presence of 2 in the denominator explains its use in (2.4). We thus obtain

$$J\left(z,t\right)=-\mathcal{D}\frac{c\left(z+\delta,t\right)-c\left(z,t\right)}{\delta}.$$

Since the term in the brackets in the limit $\delta \to 0$ is the partial derivative of $c(z,t)$ with respect to z, one can write

$$J(z,t) = -\mathcal{D}\frac{\partial c(z,t)}{\partial z}. \tag{2.11}$$

The minus sign indicates that the flow occurs from the concentrated to the dilute region of the solution. Equation (2.11) is Fick's first law, which states that the net flux is proportional to the gradient of the concentration function (at z and t). Flux has dimensions of mass×area^{-1}×time^{-1}.

Since the flux J is the flow of material $\dot{q}(z,t)$ from the left to the right through the surface $\mathcal{A}$, (2.11) is rewritten as follows:

$$\dot{q}(z,t) = -\mathcal{D}\mathcal{A}\frac{\partial c(z,t)}{\partial z}. \tag{2.12}$$

From this relationship it is clear that the force acting to diffuse the material q through the surface is the concentration gradient $\partial c/\partial z$. This gradient may be approximated by differences

$$\frac{\partial c(z,t)}{\partial z} \approx \frac{\Delta c(z,t)}{\Delta z} = \frac{c(z+\delta,t) - c(z,t)}{\delta} = \frac{c_r(t) - c_l(t)}{\delta}, \tag{2.13}$$

and the previous expression becomes

$$\dot{q}(t) \triangleq R_{lr} = -\frac{\mathcal{D}\mathcal{A}}{\delta}\left[c_r(t) - c_l(t)\right], \tag{2.14}$$

where R_{lr} is the transfer rate of material. This equation usually takes one of two similar forms:

$$\dot{q}(t) = -CL_{lr}\left[c_r(t) - c_l(t)\right] \qquad \text{or} \qquad \dot{q}(t) = -P\mathcal{A}\left[c_r(t) - c_l(t)\right]. \tag{2.15}$$

The new introduced parameter $CL_{lr} \triangleq \mathcal{D}\mathcal{A}/\delta$ is called *clearance*, and it has dimensions of flow, volume×time^{-1}. The clearance has a bidirectional use and indicates the volume of the solution that is cleared from drug per unit of time because of the drug movement across the plane. For an isotropic membrane, structural and functional characteristics are identical at both sides of the membrane, $CL_{lr} = CL_{rl}$. In practice, the term "clearance" is rarely used except for the irreversible removal of a material from a compartment by unidirectional pathways of metabolism, storage, or excretion. The other new parameter $P \triangleq \mathcal{D}/\delta$ characterizes the diffusing ability of a given solute for a given membrane, and it is called *permeability*. Permeability has dimensions of length×time^{-1}.

We now write a general mass conservation equation stating that the rate of change of the amount of material in a region of space is equal to the rate of flow across the

boundary plus any that is created within the boundary. If the region is $z_1 < z < z_2$ and no material is created

$$\frac{\partial}{\partial t}\int_{z_1}^{z_2} \mathrm{d}q\,(z,t) = \frac{\partial}{\partial t}\int_{z_1}^{z_2} c\,(z,t)\,\mathrm{d}z = J\,(z_1,t) - J\,(z_2,t)\,.$$

Here, if we assume $\mathcal{D}$ constant in (2.11) and $z_2 = z_1 + \Delta z$, at the limit $\Delta z \to 0$, this relation leads to

$$\frac{\partial c\,(z,t)}{\partial t} = \mathcal{D}\frac{\partial^2 c\,(z,t)}{\partial z^2}. \tag{2.16}$$

This is the second Fick's law stating that the time rate of change in concentration (at z and t) is proportional to the curvature of the concentration function (at z and t). There is a clear link between the two laws (2.11) and (2.16).

In order to examine the relevance of the two laws, let us consider that the layer separating the two regions in Figure 2.3A is not thin but has an appreciable thickness δ, while z is the spatial coordinate along it. According to (2.11), if $\partial c/\partial z$ is constant, then the flux J is constant. This happens when c is a linear function of z. Consequently, $\partial^2 c/\partial z^2 = 0$ in (2.16) and this implies the steady-state condition $\partial c\,(z,t)\,/\partial t = 0$, where the concentration is stationary in time. Under these conditions, as many drug molecules diffuse in from the side of higher concentration as diffuse out to the side of lower concentration. This can be accomplished experimentally if the concentrations c_l and c_r in the two regions of Figure 2.3A are maintained constant. With boundary conditions $c(0,t) = c_l$ and $c(\delta,t) = c_r$, and initial condition $c(z,0) = 0$, the solution of (2.16) is given by [10]

$$\begin{aligned} c\,(z,t) = {} & c_l - (c_l - c_r)\,\frac{z}{\delta} \\ & - \frac{4c_l}{\pi}\sum_{i=1}^{\infty}\frac{1}{2i-1}\sin\left[(2i-1)\,\pi\,\frac{z}{\delta}\right]\exp\left[-\frac{(2i-1)^2\,\pi^2}{\delta^2}\mathcal{D}t\right] \\ & + \frac{2\,(c_l - c_r)}{\pi}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{i}\sin\left(i\pi\,\frac{z}{\delta}\right)\exp\left(-\frac{i^2\pi^2}{\delta^2}\mathcal{D}t\right). \end{aligned} \tag{2.17}$$

By using the above relationship, Figure 2.4 simulates the distance–concentration profiles $c\,(z,t)$ at times $t = 15$ min, 1 and 5 h with $\mathcal{D} = 0.1$ cm^2/ h, $\delta = 1$ cm, $c_l = 10$ and $c_r = 2$ g/ l. Since there is no solute inside the layer initially ($c(z,0) = 0$), for early times (e.g., $t = 15$ min) the solute molecules undergo diffusion with two opposite directions, from the boundaries to the interior of the layer ($\partial c/\partial z < 0$ and $J\,(z,t) > 0$ for $0 \le z < z^{\bullet}$; $\partial c/\partial z > 0$ and $J\,(z,t) < 0$ for $z^{\bullet} \le z < 1$ cm with $z^{\bullet} \approx 0.6$ cm according to Figure 2.4). As time grows, the diffusion becomes unidirectional with $\partial c/\partial z < 0$ and $J\,(z,t) > 0$ because $c_l > c_r$. As time goes by

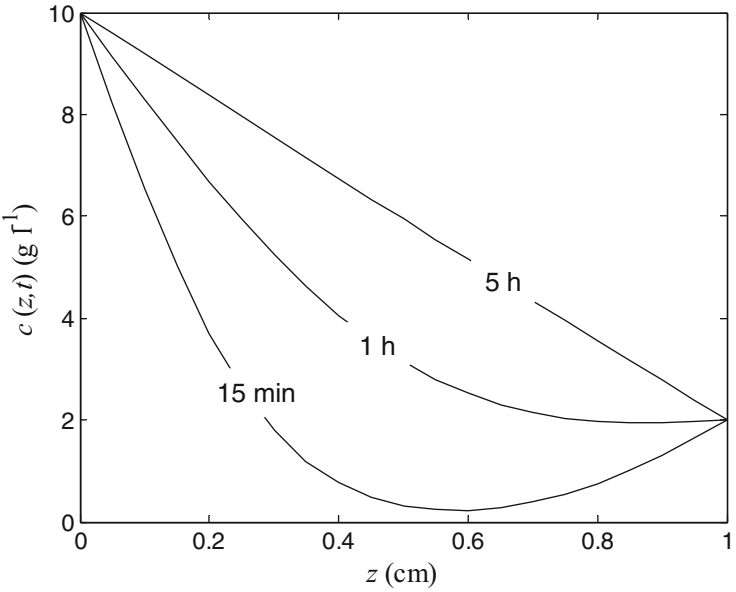

Fig. 2.4 Simulation of distance–concentration profiles $c\,(z,t)$ at times $t = 15$ min, 1 and 5 h with $\mathcal{D} = 0.1$ cm^2/ h, $\delta = 1$ cm, $c_l = 10$ and $c_r = 2$ g/ l

(e.g., $t = 5$ h), the steady state is reached, the solution of the partial differential equation 2.16 is $c\,(z,.) = c_l - (c_l - c_r)\,\frac{z}{\delta}$ and according to the definition 2.11 the net flux

$$J\,(.,.) = \frac{\mathcal{D}}{\delta}\,(c_l - c_r)$$

is constant.

If we postulate that molecules move independently, the concentration $c\,(z,t)$ at some point z is proportional to the probability density $p\,(z,t)$ of finding a molecule there. Thus, the diffusion partial differential equation (2.16) holds when probability densities are substituted for concentrations:

$$\frac{\partial p\,(z,t)}{\partial t} = \mathcal{D}\frac{\partial^2 p\,(z,t)}{\partial z^2}. \tag{2.18}$$

If a molecule is initially placed at $z = 0$, then the solution of the previous equation is

$$p\,(z,t) = (4\pi\mathcal{D}t)^{-1/2}\exp\left(-\frac{z^2}{4\mathcal{D}t}\right).$$

For $t \gg 1$ at any z, we obtain $p\,(z,t) \propto t^{-1/2}$. This behavior in a homogeneous medium corresponds to (2.8), giving the probability density in a fractal medium with spectral dimension d_s.

2.4 Classical Kinetics

Pharmacy, like biology and physiology, is wet and dynamic. Drug molecules immersed in the aqueous environment of intravascular, extravascular, and intracellular fluids participate in reactions, such as reversible binding to membrane or plasma proteins; biotransformation or transport processes, e.g., drug release from a sustained release formulation; drug uptake from the gastrointestinal membrane; and drug permeation through the blood–brain barrier. This classification is very rough since some of these processes are more complex. For example, drug release is basically a mass transport phenomenon but may involve reaction(s) too, e.g., polymer dissolution and/or polymer transition from the rubbery to the glassy state. However, irrespective of the detailed characteristics, the common and principal component of the underlying mechanism of numerous drug processes is diffusion. This is the case for the ubiquitous passive transport processes that rely on diffusion exclusively. The value of $\mathcal{D}$ depends on the nature of the environment of the diffusing species. If the environment changes from one point to another, the value of $\mathcal{D}$ may depend on position. Usually, we deal with systems in which the environment of the diffusing species is the same everywhere, so that $\mathcal{D}$ is a constant. The diffusion coefficient is constant for diffusion of dilute solute in a uniform solvent. This case takes in a large number of important situations, and if the dilute solute is chemically the same as the solvent but is isotopically tagged, then the diffusion is termed self-diffusion. In contrast, chemical reactions can be either reaction-limited or diffusion-limited. In the following sections we will discuss them separately.

2.4.1 Passive Transport Processes

There appear to be two main ways for solutes to pass through cell membranes, namely, transcellular and paracellular. The most important is the transcellular route, whereby compounds cross the cells by traversing the cell membrane following either passive diffusion or carrier-mediated transport. Undoubtedly, the transcellular passive diffusion is the basic mechanism of solute permeation through cell membranes. According to this mechanism the solute leaves the fluid bathing the membrane, dissolves in the substance of the membrane, diffuses across in solution, and then emerges into the intracellular fluid. Accordingly, the mathematical treatment of drug diffusion across a membrane can be based on (2.12), which is a very useful expression of Fick's first law of diffusion. This equation is used extensively in the pharmaceutical sciences. It describes the mass (number of molecules, or moles, or amount) transported per unit time, $\dot{q}$, across an area $\mathcal{A}$ with a concentration gradient $\partial c/\partial z$ at right angles to the area. According to this definition, the numerical value of the diffusion coefficient $\mathcal{D}$, expressed in mass units, corresponds to the amount of solute that diffuses per unit time across a unit area under the influence of a unit concentration gradient.

For a passive transport process, the concentration gradient across the membrane can be considered constant and therefore the gradient can be approximated by differences as in (2.13) to obtain

$$\dot{q}(t) = \frac{\mathcal{D}'\mathcal{A}}{\delta}\left[c_l(t) - c_r(t)\right],$$

where $\mathcal{D}'$ is a modified diffusion coefficient, for restricted diffusion inside the membrane. The value of $\mathcal{D}'$ is much smaller than the diffusion coefficient $\mathcal{D}$ in free solution. The minus sign is not used in the previous equation since the rate of transport corresponds to the solute transfer from the external to the internal site ($c_l > c_r$). Furthermore, if sink conditions prevail ($c_l \gg c_r$), the previous equation can be simplified to

$$\dot{q}(t) = CLc(t) = P\mathcal{A}c(t). \tag{2.19}$$

The last equation reveals that estimates for P can be obtained in an experimental setup if the permeation rate $\dot{q}(t)$ and the total membrane area $\mathcal{A}$ available for transport are measured and the drug concentration $c(t)$ in the donor compartment remains practically constant. What is implicit from all the above is that the diffusion coefficient $\mathcal{D}'$ is at the origin of the definition of the clearance CL and permeability P, and these parameters are incorporated into the global rate constant of the rate equations used in pharmacokinetics. For example, the first-order absorption rate constant k_a in the following equation is proportional to the diffusion coefficient $\mathcal{D}'$ of drug in the gastrointestinal membrane:

$$\dot{c}_b(t) = k_a c_{GI}(t),$$

where $c_b(t)$ and $c_{GI}(t)$ denote drug concentration (amount absorbed/volume of distribution) in blood and in the gastrointestinal lumen (amount dissolved in the gastrointestinal fluids/volume of gastrointestinal fluids), respectively. In other words, $\mathcal{D}'$ controls the rate of drug absorption from the gastrointestinal tract.

2.4.2 *Reaction Processes: Diffusion- or Reaction-Limited?*

Pharmacokinetics has been based on the concepts of classical chemical kinetics. However, the applicability of the rate equations used in chemical kinetics presupposes that the reactions are really reaction-limited. In other words, the typical time for the two chemical species to react when placed in close proximity (reaction time t_{reac}) is larger than the typical time needed for the two species to reach each other (diffusion time t_{diff}) in the reaction space. When the condition $t_{\text{reac}} > t_{\text{diff}}$ is met, then one can use the global concentrations of the reactant species in the medium to obtain the classical rate equations of chemical kinetics. This is so since the rate of

the reaction is proportional to the global concentrations of the reactant species (law of mass action). The inequality $t_{\text{reac}} > t_{\text{diff}}$ underlines the fact that the two reactant species have encountered each other more than one time previously in order to react effectively.

The opposite case, $t_{\text{reac}} < t_{\text{diff}}$, indicates that the two reactant species actually react upon their first encounter. The diffusion characteristics of the species control the rate of the reaction, and therefore these reactions are called *diffusion limited*. Consider, for example, a system consisting of species A and B with n_A and n_B molecules of A and B, respectively. The problem of the reaction rate between A and B is in essence reduced to the rate at which A and B molecules will encounter one another. The principal parameters governing the reaction rate are the diffusion coefficients $\mathcal{D}_A$ and $\mathcal{D}_B$ of the reactant species since they determine the diffusing tendency of the species. Focusing on B molecules, it can be proven that the rate of B molecules diffusing to an A molecule is proportional to the diffusion coefficient of B, the number of B molecules, and the distance between A and B, namely, $4\pi\mathcal{D}_B(\rho_A + \rho_B)n_B$, where $\rho_A + \rho_B$ is the distance between the centers of A and B molecules; accordingly, the total rate of A and B encounters is $4\pi\mathcal{D}_B(\rho_A + \rho_B)n_Bn_A$. In an analogous manner the total rate of A and B encounters, viewed in terms of the A molecules, is $4\pi\mathcal{D}_A(\rho_A + \rho_B)n_Bn_A$. The mean of these separate rates provides a reasonable expression for the rate per unit volume for A and B molecules separately:

$$\text{Rate of } A \text{ and } B \text{ encounters} = 2\pi(\mathcal{D}_A + \mathcal{D}_B)(\rho_A + \rho_B)n_An_B.$$

Although the previous equation signifies the importance of the diffusion characteristics of the reactant species, it cannot be used to describe adequately the rate of the reaction. The reason is that the concept of global concentrations for the n_A and n_B molecules is meaningless, since a unit volume cannot be conceived due to the local fluctuations of concentrations. Hence, the local concentrations of the reactants determine the rate of the reaction for diffusion-limited reactions. Accordingly, local density functions with different diffusion coefficients for the reactant species are used to describe the diffusion component of reaction–diffusion equations describing the kinetics of diffusion-limited reactions.

2.4.3 Carrier-Mediated Transport

The transport of some solutes across membranes does not resemble diffusion and suggests a temporary, specific interaction of the solute with some component (protein) of the membrane characterized as "carrier," e.g., the small-peptide carrier of the intestinal epithelium. The rate of transport increases in proportion to concentration only when this is small, and it attains a maximal rate that cannot be exceeded even with a large further increase in concentration. The kinetics of carrier-mediated transport is theoretically treated by considering carrier–solute complexes in the same manner as enzyme–substrate complexes following the principles of enzyme-

catalyzed reactions in Michaelis–Menten kinetics. In both biotransformation and carrier-mediated transport, unrestricted diffusion is considered for the reactant species. Due to the analogous formulation of the two processes, the equations describing the rates of biotransformation,

$$\dot{c}(t) = \frac{V_{\max} c(t)}{k_M + c(t)}, \tag{2.20}$$

and carrier-mediated transport,

$$\dot{c}(t) = \frac{R_{\max} c(t)}{k_M + c(t)}, \tag{2.21}$$

are similar. In these expressions, $c(t)$ is the solute (substrate) concentration, k_M is the Michaelis constant, $V_{\max}$ is the maximum biotransformation rate, and $R_{\max}$ is the maximum transport rate. Both equations indicate that the rate of biotransformation or carrier-mediated transport becomes independent of substrate (solute) concentration when this is large. In this case, the rate of biotransformation or carrier-mediated transport is said to exhibit *saturation kinetics*. The graphical representation of the previous equations is shown in Figure 2.5.

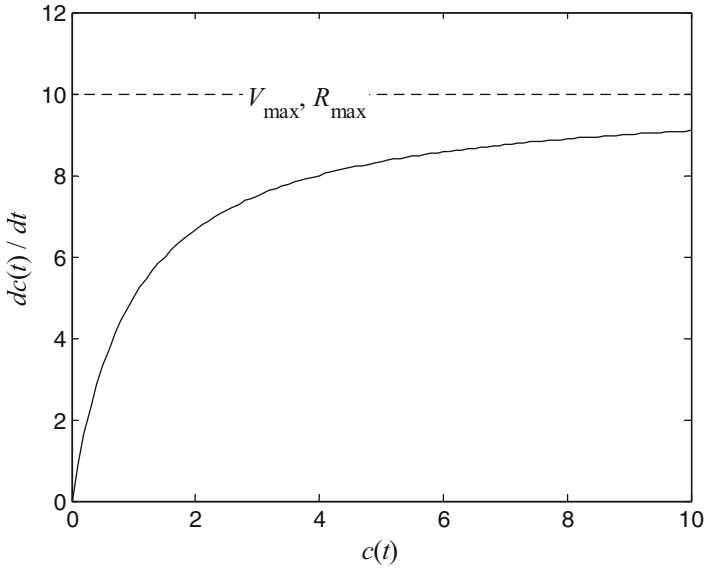

Fig. 2.5 The rate of biotranformation or carrier-mediated transport vs. solute concentration. The plateau value corresponds to $V_{\max}$ or $R_{\max}$. k_M and $V_{\max}$ were set to 1 and 10, respectively, with arbitrary units

2.5 Fractal-like Kinetics

The undisputable dogma of chemistry whether in chemical synthesis or classical chemical kinetics is to "stir well the system." The external stirring re-randomizes the positioning of the reactant species, and therefore the rate of the reaction follows the classical pattern imposed by the order of the reaction. However, many reactions and processes take place under dimensional or topological constraints that introduce spatial heterogeneity. A diffusion process under such conditions is highly influenced, drastically changing its properties. A general well-known result is that in such constrained spaces, diffusion is slowed down and diffusion follows an anomalous pattern. Obviously, the kinetics of the diffusion-limited reactions (processes) are then sensitive to the peculiarities of the diffusion process. In other words, the transport properties of the diffusing species or the reactants largely determine the kinetics of the diffusion-limited processes. Under these circumstances one can no longer rely on classical rate equations and a different approach is necessary. The drastic and unexpected consequences of nonclassical kinetics of diffusion-limited reactions are called *fractal-like kinetics*. An extensive review on the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences has been published recently [11]; the essentials for this "understirred" type of kinetics are delineated below.

2.5.1 Segregation of Reactants

Classical homogeneous kinetics assumes that the reactants are located in a three-dimensional vessel, and that during the reaction process the system is constantly stirred, thus causing the positions (locations) of the reactants to be constantly re-randomized as a function of time. However, there are important chemical reactions, which are called "heterogeneous," in which the reactants are spatially constrained by either walls or phase boundaries, e.g., liquid–solid boundaries. This is the case for in vivo drug dissolution as well as for many bioenzymatic and membrane reactions. Due to dimensional or topological constraints these heterogeneous reactions take place under understirred conditions. The most dramatic manifestation of such highly inefficient stirring is the spontaneous segregation of reactants in $A + B$ reactions [12–14]. This means that correlations begin to develop between the reactants' positions, which subsequently have a profound effect on the rate of a diffusion-controlled reaction. The build-up of such correlations is strongly dependent on the dimensionality, being more pronounced the further one goes below three-dimensional spaces. This is so because quantitatively the parameter values in the diffusion laws are very different in different dimensions. In addition, if the space where the reaction takes place is not smooth, but highly irregular, this has an added

effect on the building of such correlations. This happens if the space is a fractal structure characterized by its own dimensionality, which as discussed in Chapter 1 could be different from the integer 1, 2, or 3.

An important segregation effect is related to the violation of Wenzel's old law for heterogeneous reactions; this law states that the larger the interface, the higher the reaction rate [15]. Thus, the most classical way to speed up a heterogeneous process, e.g., drug dissolution, is to grind the material in order to increase the surface area. At the macroscopic level, this law has been verified in numerous physicochemical studies [16] as well as in in vitro drug dissolution studies and in vivo bioavailability studies using micro instead of macro drug particles. However, violation of Wenzel's law has been observed in simulation studies [17, 18] at the microscopic level. Simulations for the catalytic reaction $A + B \rightarrow AB \uparrow$, which takes place only on the rims of surfaces, indicate that the steady-state rate per unit surface area is not constant but rather depends on the size of the sample. In reality, lower reaction rates were observed for a connected catalyst compared to a disjointed one despite the fact that equal lengths for both designs were used. This is due to the lower segregation of the reactants on the rims of the disjointed catalyst, which results in a higher rate coefficient for the catalytic reaction. The clear message taken from these results is that shredding a sample not only increases the surface area but can also increase the reactivity per unit area. The latter observation violates Wenzel's law.

2.5.2 Time-Dependent Rate Coefficients

The spatial reactant correlations result in building a depletion zone around each reactant, which grows steadily with time. This means that in the close neighborhood of each reactant there is a void, a space that is empty of reactants. The net result is that the reactant distribution for the two-reactant case ($A + B \rightarrow C$) shows clear segregation of unlike species (A from B) and aggregation of like species (either A or B). Naturally, the diffusion-controlled reaction slows down, since as reactants get further apart, they must travel longer distances to find another reactant to react with (cf. equation 2.9). A curious effect now is that the rate constant k of the reaction is no longer "constant," but depends on the growth of this depletion zone and consequently is time-dependent:

$$k(t) = k_{\circ} t^{-\lambda} \qquad (t > t_{\circ}),$$

where $k(t)$ is the instantaneous rate coefficient since it depends on time t, and λ is the fractal kinetics exponent with $0 \leq \lambda < 1$. In fact, $k(t)$ crosses over from a constant regime at short times, $t < t_{\circ}$, to a power-law decrease at longer times, $t > t_{\circ}$. The switching time $t_{\circ}$ depends on the experimental conditions. This behavior is the hallmark of fractal kinetics [17].

Under homogeneous conditions (e.g., vigorous stirring), $\lambda = 0$ and therefore $k(t)$ is a constant giving back the classical kinetics result. The previous equation

has been applied to the study of various reactions in fractals as well as in many other nonclassical situations. For instance, theory, simulations, and experiments have shown that the value of λ for $A+A$ reactions is related to the spectral dimension d_s of the walker (species) as follows [9, 19]:

$$\lambda = 1 - \frac{d_s}{2}.$$

From this relationship, we obtain $\lambda = 1/3$ since the value of d_s is $\approx 4/3$ for $A + A$ reactions taking place in random fractals in all embedded Euclidean dimensions [9, 20]. It is also interesting to note that $\lambda = 1/2$ for an $A + B$ reaction in a square lattice for very long times [13]. Thus, it is now clear from theory, computer simulation, and experiment that elementary chemical kinetics are quite different when reactions are diffusion limited, dimensionally restricted, or occur on fractal surfaces [9, 12, 21–23].

We emphasize that the fractal-like kinetic characteristics are not observed only under "bing-bang" type conditions (also called batch) as discussed above but also under quasi-steady-state conditions (cf. Section 8.5.1). Consider, for example, the homodimeric reaction with two molecules of a single substrate reacting to form product ($A + A \rightarrow C$). Under homogeneous conditions the rate at quasi-steady state will be proportional to substrate concentration squared, $c^2(t)$, i.e., it is time-independent (by definition). However, the rate for the bimolecular $A + A$ diffusion-limited reaction under topological or dimensional constraints will be proportional to $c^{\gamma}(t)$. Surprisingly, the effective reaction order γ is higher than 2 and is related to the spectral dimension d_s and in turn to the fractal kinetics exponent λ [9]:

$$\gamma = 1 + \frac{2}{d_s} = 1 + (1 - \lambda)^{-1},$$

with $d_s \leq 2$. Typical values for the Sierpinski gasket and the percolation cluster are $\gamma = 2.46$ and $\gamma = 2.5$, respectively. If $d_s = 1$, so that diffusion is compact, then $\gamma = 3$ for the bimolecular $A + A$ reaction. In all these cases, the mechanism of diffusion is bimolecular. However, the increase in the effective reaction order arises from the distribution of the species, which as time goes by becomes "less random," i.e., it is actually more ordered.

Before we close this section some major, unique kinetic features and conclusions for diffusion-limited reactions that are confined to low dimensions or fractal dimensions or both can now be derived from our previous discussion. First, a reaction medium does not have to be a geometric fractal in order to exhibit fractal kinetics. Second, the fundamental linear proportionality $k \propto \mathcal{D}$ of classical kinetics between the rate constant k and the diffusion coefficient $\mathcal{D}$ does not hold in fractal kinetics simply because both parameters are time-dependent. Third, diffusion is compact in low dimensions and therefore fractal kinetics is also called *compact kinetics* [24, 25] since the particles (species) sweep the available volume compactly. For dimensions $d_s > 2$, the volume swept by the diffusing species is no longer

compact and species are constantly exploring mostly new territory. Finally, the initial conditions have no importance in classical kinetics due to the continuous re-randomization of species but they may be very important in fractal kinetics [17].

2.5.3 *Effective Rate Equations*

The dependence of kinetics on dimensionality is due to the physics of diffusion. This modifies the kinetic differential equations for diffusion-limited reactions, dimensionally restricted reactions, and reactions on fractal surfaces. All these chemical kinetic patterns may be described by power-law equations with time-invariant parameters like

$$\dot{c}(t) = -\kappa c^{\gamma}(t), \quad c(t_0) = c_0, \tag{2.22}$$

with $\gamma \geq 2$. Under these conditions, the traditional rate law for the $A + A$ reaction with concentration squared exhibits a characteristic reduction of the rate constant with time:

$$\dot{c}(t) = -k(t)\, c^2(t), \quad c(t_0) = c_0, \tag{2.23}$$

where $k(t) = k_\circ t^{-\lambda}$. Conversely, (2.23) is equivalent to a time-invariant rate law (2.22) with an increased kinetic order γ. New parameters λ and $k_\circ$ are given by

$$\lambda = (\gamma - 2)/(\gamma - 1) \text{ and } k_\circ = \kappa^{1/(\gamma-1)} (\gamma - 1)^{(2-\gamma)/(\gamma-1)}$$

with $0 \leq \lambda < 1$.

In traditional chemical kinetics $\lambda = 0$, the rate constant is time-invariant, and the effective kinetic order γ equals molecularity 2. As the reaction becomes increasingly diffusion-limited or dimensionally restricted, λ increases, the rate constant decreases more quickly with time, and the kinetic order in the time-invariant rate law increases beyond the molecularity of the reaction. When the reaction is confined to a one-dimensional channel, $\gamma = 3.0$, or it can be as large as 50 when isolated on finely dispersed clusters or islands [9, 22]. The kinetic order is no longer equivalent to the molecularity of the reaction. The increase in kinetic order results in behavior with a higher effective cooperativity. The kinetic orders in some cases reflect the fractal dimension of the physical surface on which the reaction occurs.

This anomaly stems from the nonrandomness of the reactant distributions in low dimensions. Although in a classical reaction system the distribution of the reactants stays uniformly random, in a fractal-like reaction system the distribution tends to become "less random." Similar changes take place in other reactions and other spaces. Such findings are well established today, and they have been observed

experimentally and theoretically. Also, results from Monte Carlo simulations (a powerful tool in this field) are in very good agreement with these findings.

The solution of the differential equations above is a power function of time, namely $c(t) = \beta t^{\alpha}$ with parameters β and α satisfying the initial condition $c(t_0) = c_0$. Usually β and α are estimated by curve fitting on experimental data, and the parameters of (2.22) and (2.23) are obtained by

$$\kappa = -\alpha\beta^{1/\alpha} \text{ and } \gamma = 1 - 1/\alpha$$

and

$$k_{\circ} = -\alpha/\beta \text{ and } \lambda = 1 + \alpha,$$

respectively. Since we have assumed $\gamma \geq 2$ or $0 \leq \lambda < 1$, the parameter α satisfies $-1 \leq \alpha < 0$.

2.5.4 *Enzyme-Catalyzed Reactions*

In the same vein and under dimensionally restricted conditions, the description of the Michaelis–Menten mechanism can be governed by power-law kinetics with kinetic orders with respect to substrate and enzyme given by noninteger powers. Under quasi-steady-state conditions, Savageau [26] defined a fractal Michaelis constant and introduced the fractal rate law. The behavior of this fractal rate law is decidedly different from the traditional Michaelis–Menten rate law:

- the effective k_M decreases as the concentration of enzyme increases, and
- the kinetic order of the overall reaction with respect to total enzyme is greater than unity.

These properties are likely to have an important influence on the behavior of intact biochemical systems, e.g., within the living cell, enzymes do not function in dilute homogeneous conditions isolated from one another. The postulates of the Michaelis–Menten formalism are violated in these processes and other formalisms must be considered for the analysis of kinetics in situ. The intracellular environment is very heterogeneous indeed. Many enzymes are now known to be localized within two-dimensional membranes or quasi-one-dimensional channels, and studies of enzyme organization in situ [27] have shown that essentially all enzymes are found in highly organized states. The mechanisms are more complex, but they are still composed of elementary steps governed by fractal kinetics.

Power-law formalism was used by Savageau [28] to examine the implications of fractal kinetics in a simple pathway of reversible reactions. Starting with elementary chemical kinetics, that author proceeded to characterize the equilibrium behavior of a simple bimolecular reaction, then derived a generalized set of conditions for microscopic reversibility, and finally developed the fractal kinetic rate law

for a reversible Michaelis–Menten mechanism. By means of this fractal kinetic framework, the results showed that the equilibrium ratio is a function of the amount of material in a closed system, and that the principle of microscopic reversibility has a more general manifestation that imposes new constraints on the set of fractal kinetic orders. So, Savageau concluded that fractal kinetics provide a novel means to achieve important features of pathway design.

2.5.5 *Importance of the Power-Law Expressions*

Power-law expressions are found at all hierarchical levels of organization from the molecular level of elementary chemical reactions to the organismal level of growth and allometric morphogenesis. This recurrence of the power law at different levels of organization is reminiscent of fractal phenomena. In the case of fractal phenomena, it has been shown that this self-similar property is intimately associated with the power-law expression [29]. The reverse is also true; if a power function of time describes the observed kinetic data or if a reaction rate higher than 2 is revealed, the reaction takes place in fractal physical support.

The power-law formalism is a mathematical language or representation with a structure consisting of ordinary nonlinear differential equations whose elements are products of power-law functions. Power-law formalism meets two of the most important criteria for judging the appropriateness of a kinetic representation for complex biological systems: the degree to which the formalism is systematically structured, which is related to the issue of mathematical tractability, and the degree to which actual systems in nature conform to the formalism, which is related to the issue of accuracy.

2.6 Fractional Diffusion Equations

Before closing this chapter we would like to mention briefly a novel consideration of diffusion based on the recently developed concepts of fractional kinetics [30]. From our previous discussion it is apparent that if $d_s \leq 2$, diffusion is recurrent. This means that diffusion follows an anomalous pattern described by (2.10); the mean squared displacement grows as $\left\langle z^2(t)\right\rangle \propto t^{\gamma}$ with the exponent $\gamma \neq 1$. To deal with this, a consistent generalization of the diffusion equation (2.18) could have a fractional order temporal derivative such as

$$\frac{\partial^{\gamma} p(z,t)}{\partial t^{\gamma}} = \mathcal{D}_{\gamma} \frac{\partial^2 p(z,t)}{\partial z^2},$$

where $\mathcal{D}_{\gamma}$ is the fractional diffusion coefficient and the fractional order γ depends on d_w, the fractal dimension of the walk. The previous fractional diffusion equation

generalizes Fick's second law, and therefore it allows scientists to describe complex systems with anomalous behavior in much the same way as simpler systems [30].

Also, in order to appreciate the extent of spatial heterogeneity, Berding [31] introduced a heterogeneity function for reaction–diffusion systems evolving to spatially inhomogeneous steady-state conditions. The same author discusses particular applications and compares specific reaction–diffusion mechanisms with regard to their potential for heterogeneity.