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Fields, Forces, and Flows in Biological Systems

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With the technical and editorial assistance of Dr. Eliot H. Frank

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Preface

SCOPE AND PURPOSE

This textbook describes the fundamental driving forces for mass transport, electric current, and fluid flow as they apply to the biology and biophysics of molecules, cells, tissues, and organs. Basic mathematical and engineering tools are presented in the context of biology and physiology. The chapters are structured in a framework that moves across length scales from molecules to membranes to tissues. Examples throughout the text deal with applications involving specific biological tissues, cells, and macromolecules. In addition, a variety of applications focus on sensors, actuators, diagnostics, and microphysical measurement devices (e.g., bioMEMS/NEMS microfluidic devices) in which transport and electrokinetic interactions are critical.

The book is written for beginning graduate students and advanced undergraduates and is aimed at an audience that has seen basic freshman physics (mechanics, electricity, and magnetism) as well as undergraduate exposure to differential operators and differential equations. In addition, it is hoped that the textbook will be a valuable resource for interdisciplinary researchers, including biophysicists, physical chemists, materials scientists, and chemical, electrical, and mechanical engineers seeking a common language for the subject.

PHILOSOPHY OF THE TEXTBOOK

A primary objective of this text is to integrate the fundamental principles of transductive coupling between chemical, electrical, and mechanical forces and flows that are intrinsic to transport within biological tissues, membranes, macromolecules, and biomaterials. These principles are applied and interpreted in the context of state-of-the-art discoveries and challenges in biology, physiology, and macromolecular science. Thus, a balanced presentation of selected, basic principles from chemical, electrical, mechanical, and materials engineering and science is intended, in order to establish a common language for biological and biomedical engineering students, rather than the disparate languages often used by chemical, electrical, or mechanical engineers alone. However, this text is not intended as simply a compilation of examples in which traditional engineering techniques are applied to problems in physiology. Rather, current problems in biology and biophysics are used to motivate quantitative engineering approaches applicable from the nanometer length scale of biomacromolecules up through the complex structural organization of tissues and organs.

While the global aim of bioengineering curricula is to integrate engineering fundamentals with modern biological and medical science, the underlying interdisciplinary nature of the engineering components themselves can be a blessing and a curse. Some specialized texts by necessity are focused on one or two engineering disciplines connected to physiology. However, there is also a need for foundational bioengineering courses and texts that are cross-disciplinary even within the

engineering fundamentals. The topic of transport is an ideal medium in which to achieve this objective.

At the same time, this text is not focused on transport alone. Rather, our objective is to describe more broadly the intra- and intermolecular *fields* and *forces* that affect the biology, physiology, and biophysics of molecules, cells, tissues, and organs. Most biological tissues and macromolecules (e.g., proteins, polysaccharides, and nucleic acids) are electrically charged under physiological conditions. Therefore, it is necessary to describe electrical forces and interactions from first principles, just as fundamentals laws are needed to describe fluid velocity fields and chemical transport. In this way, electrical interactions at multiple length scales can be addressed on an equal footing with forces that derive from local chemical and mechanical gradients. Thus, electrical forces at the nanoscale are fundamental components underlying the integration of molecular structure and biochemistry with tissue-level mechanics, transport, biophysics, and biology.

ORGANIZATION OF THE TEXTBOOK

The organization of the book derives from the order of major topics covered in the MIT Biological Engineering core curriculum subject: chemical transport in electrolyte media (Chapter 1); electrical fields and electrochemically mediated transport (selected sections from Chapters 2 and 3), the concepts of stress and the stress tensor (the early sections of Chapter 4); fluid mechanics and convective transport (Chapter 5); and integrative case studies involving physicochemical interactions at the macromolecular and cellular levels (examples in Chapter 4) and electrokinetic examples fundamental to MEMS and physical chemistry (Chapter 6). At the same time, many sections in Chapters 1, 4, and 7 are also essential components of MIT's undergraduate and graduate courses in molecular, cellular, and tissue biomechanics, including the rheological and deformational behavior of tissues and gels. Thus, the coverage of the textbook is broader than that used solely in a one-term course, and is intended to allow flexibility in choosing the order and content to adapt to the breadth of topics and courses of interest to biological and biomedical engineering students and instructors.

The course at MIT has evolved over many years, and is now typically taken each term by students in biological engineering, mechanical, chemical, and electrical engineering, materials science and engineering, and other departments. Thus, while each student has seen aspects of some of the material, none has seen the breadth of topics covered, and therefore no assumptions are made concerning the students' background, except for exposure to undergraduate-level mathematics and physics. Pedagogically, starting with chemical transport enables the mathematical treatment to focus initially on diffusion of a scalar (solute concentration) before the added complexities of dealing with vector fields (fluid velocity and electric fields). The spirit of the course is such that the instructor focuses each lecture using a current problem from the biological or medical literature, and then uses the text material as the fundamental basis for discussing, modeling, and critically analyzing and interpreting the results. The numerous examples and homework problems in the book are used by the students to gain additional experience and further insight. A solutions manual and figures from the book are available to qualified adopters of the text, and additional homework problems will be available to students on the book web site.

Acknowledgments

It is extremely difficult in a short space to acknowledge the tremendous debt of gratitude that I owe to the many people who have made this book possible. Dr Eliot Frank is the person who is mainly responsible for this book seeing light of day. Eliot is a long-time colleague and member of our research group whose intellectual strengths and technical talents are immeasurable. In addition to all of the figures he has drawn for each chapter and his LaTeX'ing of the text, he has been the go-to person to ask, "what do you think about" this section or that approach to the field.

The inspiration for this book all along has been my own teacher, mentor, and thesis advisor at MIT, Professor James R. Melcher, who tragically passed away at an early age 20 years ago. Jim contributed invaluable insights and sections to the early versions of this book when it was initially organized as a set of course notes for the first graduate subject I taught. In addition, he and the late Professor Hermann Haus, another giant in Electrical Engineering and Computer Science at MIT, taught me how to teach, how to organize a blackboard, and how to best tie together ideas in a logical fashion for presentation in a lecture to students ranging from freshman to advanced graduates.

I have also learned a tremendous amount from faculty who have co-taught this material with me more recently, including Professors William Deen, Doug Lauffenburger, Roger Kamm, and Mark Bathe. Doug has also been instrumental in the gestation and organization of the curriculum in Biological Engineering at MIT, where this material continues within the core. Perhaps the most influential people in my continued education and ongoing efforts for the course are the many students I've had the pleasure to have in class. Some of these extraordinarily gifted students have gone on to be instrumental as teaching assistants for the course before embarking on their own careers. Dr Rachel Miller additionally went on to contribute her invaluable skills in the editing of the final page proofs. Dr Paul Kopesky provided cover art from his own research (marrow-derived progenitor cells in a peptide hydrogel scaffold).

Over the years, many close colleagues have used sections of this book in their own teaching and research, and have thereby contributed invaluable insights and suggestions on the presentation, including Professors Larry Bonassar (Cornell University), Michael Buschmann (École Polytechnique de Montréal), Solomon Eisenberg (Boston University), Moonsoo Jin (Cornell University), Young-Jo Kim (Harvard Medical School), John Kisiday (Colorado State University), Marc Levenston (Stanford University), Tom Quinn (McGill University), Bob Sah (University of California San Diego), Joonil Seog (University of Maryland), Ronald Siegel (University of Minnesota), David Smith and his colleagues (University of Western Australia), and Aryeh Weiss (Jerusalem College of Technology); and Drs Peter Basser (National Institutes of Health), Jonathan Fitzgerald (Merrimack Pharmaceuticals), Jenny Lee (Gates Foundation), Michael DiMicco (Genzyme Corp.), Parth Patwari (Harvard Medical School), and Jeff Sachs (Merck and Co., Inc.).

I would also like to thank the reviewers of this textbook for their excellent suggestions: Michael Buschmann (École Polytechnique

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Contents in Brief

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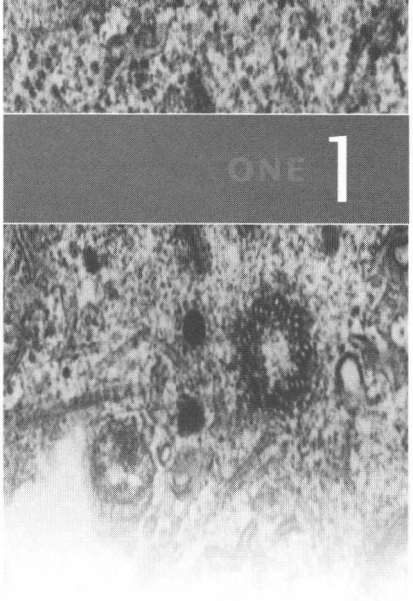

ONE 1

Chemical Transport in Electrolyte Media

1.1 INTRODUCTION

We first consider the diffusive motion of solutes in a fluid electrolyte medium. Low- and high-molecular-weight solutes are of interest, from mobile ions and small electrically neutral solutes to proteins, nucleic acids, glycoproteins, proteoglycans, and biological and chemical pharmaceutical compounds. Concentration gradients of such solutes will cause diffusive solute flow within and across biological tissues, cell membranes, and intracellular and extracellular spaces, and through hydrogels and other porous biomaterials. Fundamentally, diffusion is the transfer of a chemical species from regions of higher concentration to those of lower concentration by the mechanism of random Brownian motion of individual molecules within an ensemble [1–3]. Diffusive processes have also been thoroughly treated regarding carrier motions in semiconductor and solid state materials, gaseous media, and the general description of transport provided by nonequilibrium thermodynamics [4–6].

In this chapter, solute flux results solely from the presence of solute concentration gradients within the electrolyte medium. For the case of charged solutes, the additional electrical migration flux caused by the direct action of an applied electric field will be treated in Chapter 3. Since biological tissues and biomaterials contain fixed-charge groups that induce local, built-in electric fields ("self-fields"), solute migration fluxes will also need to be included in that discussion. The motion of solutes associated with convection of the fluid solvent are introduced in Chapter 5 after a more detailed treatment of Newtonian fluid mechanics.

After considering both a continuum and a molecular view of diffusive motions along with conservation of species (Sections 1.2 and 1.3), the concepts of boundary conditions and the solution of boundary value problems defined by the diffusion equation are introduced (Section 1.5). The importance of solute binding to cell surface receptors, extracellular matrix, and biopolymers in general is included in the context of specific examples in Section 1.4, leading to a discussion of diffusion–reaction rate processes and kinetics in Section 1.6. The ionization of biomolecular charge groups associated with acid–base reactions provides another important set of examples of diffusion–reaction in biological systems. This provides the opportunity to introduce key macromolecular constituents of the extracellular matrix (Section 1.4).

1.2 DIFFUSIVE FLUX AND CONTINUITY

Within an electrolyte medium, empirical evidence has shown that the diffusive flux $\boldsymbol{N}_i$ of solute species i with respect to the solvent is often linearly related to the local gradient in the concentration of

that species, c_i, by

$$\boldsymbol{N}_i = -D_i \nabla c_i \tag{1.1}$$

where D_i is the diffusivity and the parameters in (1.1) have the SI units:
$\boldsymbol{N}_i \equiv$ molar flux (mol m^{-2} s^{-1})
$c_i \equiv$ molar concentration (mol m^{-3})
$D_i \equiv$ diffusivity (m^2 s^{-1})
In cartesian coordinates, $\nabla \equiv \boldsymbol{i}_x \partial/\partial x + \boldsymbol{i}_y \partial/\partial y + \boldsymbol{i}_z \partial/\partial z$ ($\boldsymbol{i}_j$ being the unit vector in the jth direction; see Appendix B for definitions of ∇ in other coordinate systems). The flux equation (1.1) can be regarded as a phenomenological constitutive law, often referred to as Fick's first law of diffusion (1855). The linear form of (1.1) corresponds to the case of a dilute solution in an isotropic medium, D_i being independent of concentration. A tensor form of the diffusivity would apply for anisotropic media [3]. We will see in later chapters that additional flux terms are added to (1.1) to account for solute motion caused by convection of the solvent as well as the motion of charged solutes in the presence of an electric field (the electrical migration flux).

1.2.1 Continuity of Solutes with Respect to a Stationary Fluid

Having established the basic point-by-point constitutive relation between the solute flux and the local solute concentration gradient, (1.1), we now use the integral form of continuity (conservation) to describe the global relation between *solute accumulation* in a region of space, the *net flux of solute entering the region*, and the rate at which solutes are *generated or lost by chemical reaction* within that region. The stationary control volume of Figure 1.1 is enclosed by the surface S, and the outward flux of solute species i is denoted by the vector $\boldsymbol{N}_i$. The continuity law then takes the form

$$\frac{d}{dt}\int_V c_i \, dV = -\oint_S \boldsymbol{N}_i \cdot \boldsymbol{n} \, da + \int_V R_i \, dV \tag{1.2}$$

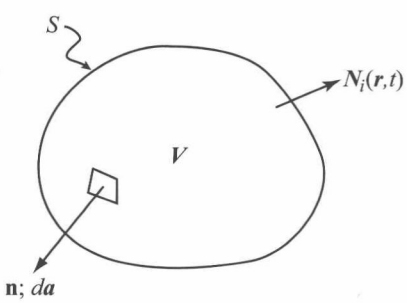

Figure 1.1 A control volume V is enclosed by a surface S. An area element on the surface has unit normal $\boldsymbol{n}$, so that a differential area vector can be defined as $d\boldsymbol{a} = \boldsymbol{n}\, da$. $\boldsymbol{N}_i(\boldsymbol{r}, t)$ is the outward flux across the surface.

where the left-hand term is the net accumulation of solute in V, and the minus sign in front of the surface integral on the right corresponds to net flux crossing into the control volume. R_i (mol m^{-3} s^{-1}) is the net volume rate of formation of species i by chemical reaction. The volume V and surface S are assumed to be fixed in space.

"Flux" versus "flux density", a word on nomenclature: The "net flux" of species through the surface S in (1.2) corresponds to the closed surface integral of $\boldsymbol{N} \cdot d\boldsymbol{a}$. Therefore, N is strictly the "flux density" of the solute, as used in [7]. However, in much of the literature on mass transport and electrochemical systems, $\boldsymbol{N}$ is simply referred to as the "flux," and we will therefore use that nomenclature throughout. We note this to anticipate any confusion on this point in other subsystems. For example, we will see in Chapter 2 that Gauss' law in the electric field subsystem involves the integral of $\epsilon \boldsymbol{E} \cdot d\boldsymbol{a}$ around a closed surface, which is called the "net electric flux," and $\epsilon \boldsymbol{E}$ is then called the (electric displacement) "flux density."

From (1.2), we can then derive the point-by-point differential form of continuity by using Gauss' theorem,

$$\oint_S \mathbf{N}_i \cdot \boldsymbol{n} \, da = \int_V \nabla \cdot \mathbf{N}_i \, dV \tag{1.3}$$

and noting that the time derivative of the left hand term of (1.2) can be brought inside the volume integral since V and S are stationary:

$$\int_V \left(\frac{\partial c_i}{\partial t} + \nabla \cdot \boldsymbol{N}_i - R_i \right) dV = 0 \tag{1.4}$$

Since the volume element dV is arbitrary, we can set the sum of the integrands in (1.4) to be zero, giving the differential form of continuity in the absence of convective or electrical forces:

$$\boxed{\frac{\partial c_i}{\partial t} = -\nabla \cdot \boldsymbol{N}_i + R_i} \tag{1.5}$$

Combining the flux constitutive law (1.1) with the continuity law (1.5) in the absence of chemical reactions gives

$$\frac{\partial c_i}{\partial t} = \nabla \cdot (D_i \nabla c_i) \tag{1.6}$$

For cases in which D_i is a constant independent of position, (1.6) gives the classic form of the diffusion equation (Fick's second law):

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 c_i \tag{1.7}$$

where the Laplacian operator in Cartesian coordinates is $\nabla^2 c \equiv \partial^2 c/\partial x^2 + \partial^2 c/\partial y^2 + \partial^2 c/\partial z^2$, and thus the one-dimensional form of the diffusion equation is

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial x^2} \tag{1.8}$$

1.2.2 Continuity of Solutes with Respect to a Moving Deforming Fluid

We will often have occasion to consider the coupling of electrical, mechanical, and chemical processes occurring in a multicomponent system consisting of a fluid and several distinct chemical species. In formulating the governing laws or equations of change, it is often convenient to focus on a volume of fixed identity that may be moving and deforming. A continuity law must be written for each chemical species that, along with the relevant laws of motion and electromagnetism, serves to uniquely characterize the system of interest. For example, we might be interested in characterizing a small volume of fluid moving in the extracellular space of a deforming tissue and then modeling the diffusion of proteins out of the volume. A simpler case is pictured in Figure 1.2, which depicts a volume of water containing a dilute ionic solution. We wish to write a continuity law relating the time rate of change of electrolyte ions in V to the flux of ions through the surface S.

Defining a volume of fixed identity can be subtle. In a mixture such as that in Figure 1.2, each species has a different velocity—a situation not encountered in viscous fluid flow or heat conduction problems. One must first choose a relevant *local material* velocity for the mixture, a velocity with respect to which the motion of the volume V and surface S can be defined. Typical choices that are used in the membrane filtration literature [8], as well as that of general mixture theory in the study

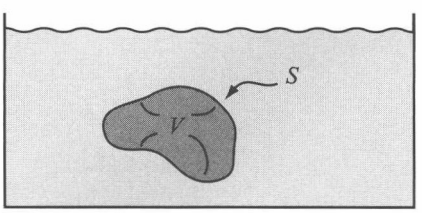

Figure 1.2 A moving, deforming volume of fluid V, with the associated closed surface S.

of transport phenomena [9], are the *mass-averaged velocity* $\boldsymbol{v}$ or the *molar-averaged* velocity $\boldsymbol{v}$:

$$\boldsymbol{v} \equiv \frac{\sum_i \rho_i \boldsymbol{v}_i}{\sum_i \rho_i} \tag{1.9}$$

$$\boldsymbol{v} \equiv \frac{\sum_i c_i \boldsymbol{v}_i}{\sum_i c_i} \tag{1.10}$$

where ρ_i is the density ($\mathrm{kg\,m^{-3}}$ in SI units) and c_i is the molar concentration ($\mathrm{mol\,m^{-3}}$) of the ith species.

In aqueous electrolyte media, the velocities (1.9) and (1.10) can be well-approximated by that of the solvent, water. For example, $\boldsymbol{v}$ for a 0.15 M NaCl solution becomes

$$\boldsymbol{v} = \frac{c_{\mathrm{Na}}\boldsymbol{v}_{\mathrm{Na}} + c_{\mathrm{Cl}}\boldsymbol{v}_{\mathrm{Cl}} + c_{\mathrm{H_2O}}\boldsymbol{v}_{\mathrm{H_2O}}}{c_{\mathrm{Na}} + c_{\mathrm{Cl}} + c_{\mathrm{H_2O}}} \tag{1.11}$$

With $c_{\mathrm{H_2O}} \simeq 55\,\mathrm{M}$ $(= 1000\,\mathrm{g\,L^{-1}}/18\,\mathrm{g\,mol^{-1}}) \gg 0.15\,\mathrm{M}$, and considering relevant velocity magnitudes, $\boldsymbol{v} \simeq (c_{\mathrm{H_2O}}\boldsymbol{v}_{\mathrm{H_2O}})/c_{\mathrm{H_2O}} = \boldsymbol{v}_{\mathrm{H_2O}}$ in (1.11) if there is any reasonable fluid convection at all. (In mixtures of gases, the average velocities do not reduce to such a simplified result, and the choice of reference frame (local velocity) is usually one of convenience.)

With the results of (1.11), we can return to Figure 1.2 and define the volume of fixed identity, V. The convecting fluid provides the best reference frame, and V is therefore delineated by always following the same water molecules in the ensemble. If the molecules of interest were labeled, we would always be sure of following the given volume. In actuality, the statistical fluctuation of the water molecules results in a continual exchange of molecules back and forth across S, so that the volume of "fixed" identity must be defined within a statistical context. With this in mind, we write the *continuity* law relating the time rate of change of solute in V to the flux of solute through S using the integral form

$$\frac{d}{dt}\int_{V(t)} c_i\, dV = -\oint_{S(t)} \boldsymbol{N}_i' \cdot \boldsymbol{n}\, da + \int_{V(t)} R_i\, dV \tag{1.12}$$

where $\boldsymbol{N}_i'$ is the flux of the ith species across S and R ($\mathrm{mol\,m^{-3}\,s^{-1}}$) is the volume rate of its formation due to chemical reactions. The volume and surface are both time-dependent, as indicated in (1.12); thus, $\boldsymbol{N}_i'$ with respect to the moving, deforming surface S is given by

$$\boldsymbol{N}_i' = -D_i \nabla c_i \tag{1.13}$$

We now use the result of an integral theorem (see Appendix A) that prescribes mathematically how to evaluate the time rate of change of a volume integral when the volume is a function of time. From (A.9) of Appendix A with $\zeta = c_i$,

$$\frac{d}{dt}\int_{V(t)} c_i\, dV = \int_{V(t)} \frac{\partial c_i}{\partial t}\, dV + \oint_{S(t)} c_i \boldsymbol{v} \cdot \boldsymbol{n}\, da \tag{1.14}$$

where $\boldsymbol{v}$ is the fluid velocity, i.e., the velocity of the deforming surface. Equations (1.12) and (1.14) can be combined, Gauss' theorem being used to convert the closed surface integrals to volume integrals, resulting in a differential statement of continuity for the ith species,

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \boldsymbol{N}_i' - \nabla \cdot c_i \boldsymbol{v} + R_i \tag{1.15}$$

Expansion of the second right-hand term of (1.15) gives

$$\nabla \cdot (c_i \boldsymbol{v}) = \boldsymbol{v} \cdot \nabla c_i + c_i \nabla \cdot \boldsymbol{v} \tag{1.16}$$

For the most part, we will be dealing with incompressible liquids, for which a physical statement of conservation of mass is (see Chapter 5)

$$\nabla \cdot \boldsymbol{v} = 0 \tag{1.17}$$

Equations (1.15)–(1.17) taken together give

$$\frac{\partial c_i}{\partial t} + \boldsymbol{v} \cdot \nabla c_i = -\nabla \cdot \boldsymbol{N}_i' + R_i \tag{1.18}$$

The physical significance of the two terms on the left-hand side of (1.18) can be understood by asking how we might express the time rate of change of $c_i(x, y, z, t)$ for an observer *moving with the fluid.* In general, Taylor expansion of Δc_i gives

$$\Delta c_i = \frac{\partial c_i}{\partial t}\Delta t + \frac{\partial c_i}{\partial x}\Delta x + \frac{\partial c_i}{\partial y}\Delta y + \frac{\partial c_i}{\partial z}\Delta z \tag{1.19}$$

The last three terms arise since a moving observer would measure a Δc_i if c_i varied in space—even if c_i were independent of time. Dividing by Δt and taking the limit as $\Delta t \to 0$,

$$\lim_{\Delta t \to 0} \frac{\Delta c_i}{\Delta t} \equiv \frac{\mathrm{D}c_i}{\mathrm{D}t} = \frac{\partial c_i}{\partial t} + \frac{\partial c_i}{\partial x} v_x + \frac{\partial c_i}{\partial y} v_y + \frac{\partial c_i}{\partial z} v_z \tag{1.20}$$

where $\mathrm{D}c_i/\mathrm{D}t$ is the material or *convective derivative.* Equation (1.20) may be written conveniently in vector notation by noting that the last three terms on the right-hand side take the form $\boldsymbol{v} \cdot \nabla c_i$. Thus,

$$\frac{\mathrm{D}c_i}{\mathrm{D}t} = \frac{\partial c_i}{\partial t} + \boldsymbol{v} \cdot \nabla c_i \tag{1.21}$$

But the right-hand side of (1.21) is identical to the left-hand side of (1.18), giving

$$\boxed{\frac{\mathrm{D}c_i}{\mathrm{D}t} = -\nabla \cdot \boldsymbol{N}_i' + R_i} \tag{1.22}$$

which equates the total time rate of change of c_i for an observer moving with the fluid to the divergence of the flux of the ith species with respect to the moving fluid, accounting for chemical reactions that lead to the generation or recombination of species. This is precisely the continuity law that we were looking for, now written in differential form.

1.3 A MOLECULAR VIEW OF DIFFUSION

We first summarize several key aspects of solute flow by diffusion that have been emphasized in general treatments of this subject. First, there is no net force on any particular solute molecule in the direction of flow. Rather, solute flux is completely determined by random thermal motion in which it is more likely that there is a net flux of solutes flowing from regions of high to low concentration. Second, especially in the limit of dilute solutions, the solute molecules are assumed to undergo collisions primarily with solvent molecules and not with each other.