Wolf R. Vieth

Membrane Systems: Analysis and Design

Applications in Biotechnology, Biomedicine and Polymer Science

with 146 Figures and 37 Tables

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Author:
Prof. Wolf R. Vieth
College of Engineering, Rutgers University, Piscataway NJ 08854

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DEDICATION

This book is dedicated to my beloved wife, Peggy, and to my family, the well-springs of my inspiration and encouragement. Along with her love and support, this project could not have succeeded without Peggy's excellent word-processing, editing and sketching efforts.

PREFACE

The science and engineering of membrane systems are rapidly becoming of major interest as applications arise in such diverse fields as Biotechnology, Biomedicine and Polymer Science. There is a definite need to pull together the seemingly disparate threads of knowledge which are appearing in the several disciplines.

The writing of this book arose out of these convictions, as well as from the perspective of more than twenty five years of research and teaching in these areas. Quite naturally, in attempting such a synthesis of ideas, I rely rather strongly on work carried out in our own laboratory in pursuit of the goal of unification. The purpose of this book, then, is to unify the principles of diffusion and reaction which are applying at the molecular level in synthetic and biological membrane systems. This is an ambitious task and the writer freely acknowledges that this work is just a beginning; it makes no pretense of setting out to be all-encompassing. But it is a necessary and worthwhile beginning, I believe.

While it is true that the subjects of molecular kinetics, diffusion and thermodynamics are in relatively good shape (Sherwood et al., 1975), their interrelation with membrane (polymeric) microstructure adds a new and exciting dimension. By the same token, chemical and physical phenomena are displayed in a particularly simple, often unidimensional domain, where their analysis is tractable and revealing.

It is especially rewarding to explore the interactive control systems encountered in biology. The inherited wisdom of evolution is on display whereby efficient use of relatively few elements; i.e., simple chemical messengers interacting with complex biopolymers in membrane structures is revealed. And yet, the function of these highly sophisticated systems is reflected in the behavior of simpler synthetic membrane systems, as well as in the design of artificial ones; for example, asymmetric enzyme membranes, as biosensors. The common theme is the *response of a membrane system to penetrant-induced conformational changes* ; frequently, this response is multimodal, as we shall see.

At this point, it is of interest to define more precisely what is meant by some of the terms I am employing. By system, I mean "a regularly interacting or interdependent group of items forming a unified whole." The lac operon is a good example of a system, albeit as

part of a still larger one (the synthetic machinery for ß- galactosidase). I will employ a process approach; that is, "a series of actions or operations conducing to an end," literally taking a system apart (analysis) to see "what makes it tick," prior to recomposing it (synthesis or design).

The approach just outlined is readily identified as one which originated in Cartesian thinking. To Dean Elmer Easton I owe another debt, for his definition of Engineering which is, "The humane art and science of employing knowledge of the materials and energy of nature for the creation of utility and beauty." In this spirit, I liken the approach I share with kindred research colleagues to a kind of mental sculpture; that is, the shaping of ideas into the images of phenomena and processes. Thanks to many such efforts, some of these images have been polished to a certain smoothness and lustre; for instance, dual sorption theory. Others might still have a few rough spots; for example, transport regulation of anaerobic processes. Lastly, the reader will recognize that all the foregoing is rooted in the continuing intellectual traditions which began in the Renaissance, a modern chapter of which I believe is being written even now in our profession.

ACKNOWLEDGEMENTS

A man's character is shaped through his experiences; two periods which had considerable influence for me were those spent as Director of the MIT School of Chemical Engineering Practice in the 1960s and as a Department Chairman during the formative years for Rutgers Biochemical Engineering in the 1970s. Prior to those days, I was fortunate to acquire a firm foundation in Chemical Engineering and Applied Chemistry under the tutelage of such Professors as C.E. Dryden, T.K. Sherwood and A.S. Michaels. To them and to my close colleagues, Drs. K. Venkat, G.K. Chotani, S. Hirose, S. Gondo, T. Matsuura and K. Sladek, I owe a special debt of thanks.

I am grateful to the administrative officers at Rutgers, especially Drs. E.J. Bloustein, T.A. Pond and E.H. Dill, for their support and for approving my application for Sabbatical leave to write this book. Likewise, I appreciate the contributions and/or constructive criticism of my faculty colleagues at Rutgers: Profs. Alkis Constantinides, Henrik Pedersen, John Sauer, Darrell Morrow, Seymour Gilbert, Kan-Ichi Hayakawa, Shaw Wang and Burton Davidson. I have learned much, too, from my professional colleagues: Drs. Shuichi Suzuki, Isao Karube, Walter Marconi, Tarun Ghose, T.M.S. Chang, Csaba Horvath and Don Paul, Harry Gregor, Vivian Stannett, Harold Hopfenberg, Norman Li, Alex Stern, Jim Barrie, Enrico Drioli, Bill Koros and Harry Frisch, John Petropoulos, Joop Roels, Jay Bailey, Mike Shuler, Bob Tanner, Bill Weigand, Don Kirwan, Bob Coughlin, Henry Lester and many others. All of these individuals helped me to gradually acquire sharper tools.

It is a distinct pleasure to acknowledge the work of my students and postdoctoral fellows; their contributions, marked by reference citations, illuminate the pages of this book. I wish to thank especially Kwang Nho who prepared the graphs which appear in each chapter and Nick Bosko, a true friend in need in the laboratory and outside. I am grateful to Dr. E. Immergut and his colleagues at Hanser Publishers for their assistance and unfailing courtesy.

All in all, the experiences leading up to this book as well as its actual preparation were for me a voyage of discovery, full of wonders and marvels; I would not have traded it for anything. Perhaps I can express this feeling more eloquently through the idiom of folk music,

another passion of mine, by introducing each main chapter with a few phrases from pieces which have special meaning for me.

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Wolf Vieth

Cape May Point, New Jersey
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1

INTRODUCTION

1.0 GENERAL

The diffusive transport of matter across a membrane in response to an activity gradient is a unifying thread in the fabric of the chapters which are to follow, so a brief "primer," so to speak, is in order. In the simplest case, molecular transport occurs via a random walk mechanism which concludes with desorption of the penetrant from the surface at the lower concentration. The total permeation process consists then of sorption, diffusion and desorption.

With a time-invariant concentration difference across the membrane (see Figure 1.1) the steady state, unidirectional flux of gas can be described by Fick's first law of diffusion:

$$J = -D \frac{\partial c}{\partial x} \qquad [1.1]$$

where J is the flux and $\partial c/\partial x$ the concentration gradient. (When a counterposing gradient involving another chemical component exists, one is dealing with the process of *counterdiffusion*.)

To consider a simple standard case, the sorption of gas in rubbery polymeric membranes is so low that gas-gas interactions are negligible and D is independent of concentration.

$$\text{Thus with } D \neq f(c) \qquad [1.2]$$

$$J = D [c_1 - c_2] / l \qquad [1.3]$$

where c_1 and c_2 are the concentrations at the upstream and downstream surfaces of the membrane, respectively, and l is the thickness of the membrane.

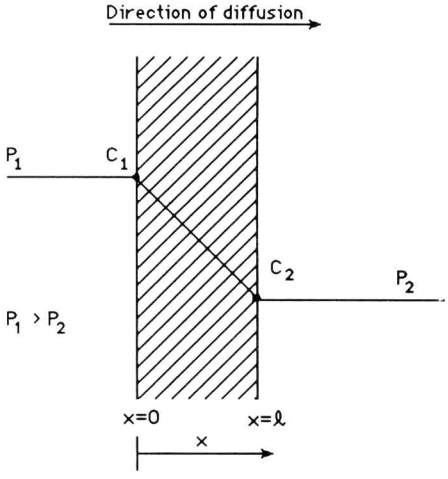

Figure 1.1 Molecular diffusion across a polymer membrane.

Accumulated evidence has demonstrated that sorption of gases in rubbery polymers is often well-described by Henry's Law, so that the concentration of the gas, c, at either surface of the membrane can be related to its partial pressure there:

$$c = kp \qquad [1.4]$$

Thus,

$$J = Dk \frac{[p_1 - p_2]}{\ell} \qquad [1.5]$$

where k is the Henry's Law solubility constant, and p_1 and p_2 refer to the pressures at the film surfaces.

By definition, the product of D and k is $\overline{P}$, the permeability constant,

$$\overline{P} \equiv kD \qquad [1.6]$$

and,

$$\overline{P} = \frac{J l}{[p_1 - p_2]} = \frac{\Delta Q}{\Delta t} \frac{l}{A [p_1 - p_2]} \qquad [1.7]$$

where ΔQ is the amount of gas transmitted in the given interval of time, Δt, and A is the area of the membrane exposed to the diffusing gas.

1.1 TRANSIENT STUDIES

Much progress has been made by focusing attention on separate measurement of the diffusion and solubility constants and correlating the data obtained according to molecular models of the permeation process. An important step was taken by Barrer (1939) who adapted the dynamic method of Daynes (1920), called the time lag method, to the measurement of diffusion constants. The mathematical basis for this procedure is an integration of Fick's second law,

$$D \frac{\partial^2 c}{\partial x^2} = \frac{\partial c}{\partial t} \qquad [1.8]$$

applying to unsteady state, unidirectional diffusion. The necessary boundary conditions are an initially gas free film, attainment of equilibrium at the inlet gas-polymer interface, and zero concentration of gas held at the polymer outflow face. The first condition is assured by evacuation of the film prior to introduction of the permeant, the second has been experimentally found to apply for many polymer-gas systems, through sorption isotherms, and the third condition is automatically satisfied because of the extremely slow rates of permeation encountered experimentally. These conditions being satisfied, extrapolation to zero pressure of the steady state portion of a plot of pressure downstream of the polymer membrane versus time yields a value θ, called the time lag. This extrapolation may be accurately accomplished because the pressure-time plot is linear after steady state has been attained. The time lag is simply related to the diffusion constant.

$$D = \frac{l^2}{6\theta} \qquad [1.9]$$

Permeabilities can be calculated from the amount of gas which has passed through the polymer in the course of an experiment. The gas is collected and application of the perfect gas law allows a calculation of $\overline{P}$. From the ratio of $\overline{P}$/ D, the solubility constant k is determined.

1.2 MICROHETEROGENEITY IN MEMBRANES

In contrast to the "ideal" case of the rubbery polymer membrane, synthetic polymer membranes and biological membranes frequently display various kinds and degrees of microheterogeneity. In the case of synthetic glassy polymers, this effect arises out of the "freezing-in" of unrelaxed excess free volume as the polymer passes through the glass transition temperature, below which segmental translations and rotations do not readily occur. The resulting structure contains penetrant-entrapping microvoids, as well as regions which are rich in amorphous chain segments of more normal density. For biological membranes, the coexistence of lipids and proteins in the structure produces the effect. In both cases, the presence of microheterogeneity confers a multi-fold transport character on the structure. For penetrants in glassy polymers, duality of transport modes often suffices to explain the results. For biological membrane systems, various hierarchies are possible, including the duality of passive and active transport.

The interactions of the penetrant with the polymer microstructure are conveniently described with equilibrium thermodynamic models; Langmuir and Henry's law relations for synthetic systems and ligand binding relations such as the Monod allosteric model for biological membrane systems. In the latter case, the model can be described as a Langmuir relation with a variable site saturation coefficient.

In all these instances, the influences of the penetrant binding reactions on the diffusional process can be profound, particularly in the transient regime. Reversible site-binding reactions almost invariably prolong the time lag which is a measure of the time required to reach the stationary state for a membrane system. These delays are offset in biological systems through the agency of essentially irreversible forward reaction processes which produce sharper gradients.

In order to comprehend these diverse phenomena it is perhaps best to cut one's teeth (as did the author) on the synthetic membrane

penetrant. Next, one can move on to a structure which is a hybrid synthetic polymer-biopolymer membrane system; i.e., an enzyme membrane or biosensor. Then, membrane enclosure of active biological entities such as enzymes or whole cells leads logically to a consideration of biocatalysts and bioreactors. These chapters provide a bridge between the purely synthetic membrane systems treated near the beginning of this book and the purely biological membrane systems treated near its conclusion.

1.3 BIOSENSORS AND ENZYME CATALYSIS

It is helpful to begin a discussion of biological membrane systems with the consideration of enzyme biosensors. Now, to the elementary transport steps of sorption and diffusion for a penetrant, we must add the elementary reaction steps which consume the penetrant or produce it from another species, the "substrate."

KINETIC BEHAVIOR OF IMMOBILIZED ENZYMES

The simplest model of conversion of substrate (S) to product (P) catalyzed by unsupported enzyme (E) is,

$$E + S \underset{k_{-1}}{\overset{k_1}{\Leftrightarrow}} ES \overset{k_2}{\Rightarrow} P + E$$

where k_1, k_{-1} and k_2 are kinetic constants. If one assumes that a steady state exists in which the concentration of intermediate (ES) does not vary with time, the Michaelis-Menten relationship can be developed:

$$V = \frac{k_2 E_O S}{K_m + S} \qquad [1.10]$$

where V = velocity of the enzyme reaction; K_m = Michaelis-Menten constant; E_O = total enzyme concentration; and S = substrate concentration.

If the concentration of substrate is large relative to K_m, then $V = k_2 E_O = V_m$ and the rate of reaction is at its maximum.

When an enzyme is attached to a solid support, the kinetic pattern of reaction changes considerably, leading to changes in the values of the kinetic parameters K_m and V_m. The kinetics of such