Steady-State Sieving across Membranes

Abstract. *The constraint of steady-state operation for sieving or ultrafiltration across membranes greatly restricts possible theoretical mechanisms. Effective sieving in the steady state requires the coexistence of a removal mechanism with the rejection mechanism. These points are illustrated without elaborate mathematics by a model of membranes in a series array with intervening compartments. This model also shows that in certain regimes the structure of the first membrane alone determines the overall sieving characteristics of the array.*

An important characteristic of many membranes is their ability to act as molecular sieves when a convective flow is generated across them. There have been a number of attempts to develop theoretical descriptions of the sieving process (*1*).

We point out here that the condition of steady-state flow, which is the usual situation in practice, imposes a severe constraint on the detailed description of the sieving properties of membranes, and that it is necessary to take this condition into account in developing any theoretical approach. We argue that under this condition all effective sieving occurs at a surface layer (or membrane-solution interface) where the rejected material is removed and that this constraint holds regardless of the details or mechanisms of local transport within the membrane, or of the rate of solute or convective flow. Thus, although the magnitude of the sieving may ultimately depend on the internal structure of the membrane, the effect can be manifested only at the membrane surface, and the concept of "internal sieving" suggested in some detailed theories may be misleading.

In order to illustrate the foregoing remarks without resorting to an elaborate mathematical treatment and to make clear the importance of a removal mechanism as well as a rejection mechanism to achieve effective steady-state sieving, we consider the schema of a series array of three membranes shown in Fig. 1. The intervening solution compartments are denoted as I and II, the feed solution (filtrand) on the upstream side as A, and the filtrate solution on the downstream side as B. For simplicity, we consider all solutions to be well stirred; the stirrer at the upstream interface keeps boundary conditions constant and removes solute into an infinite sump held at concentration C_s^A. It is convenient to describe sieving in terms of a rejection coefficient R, defined as (*2*):

$$R = 1 - \frac{\text{filtrate concentration}}{\text{filtrand concentration}} \qquad (1)$$

for which (i) when $R = 0$, no rejection occurs; (ii) when $R = 1$, complete separation of solute from solvent occurs; and (iii) when $0 < R < 1$, partial rejection or separation occurs. The value of R may depend somewhat on the boundary conditions at the membrane surfaces, but, if we regard all solutions as dilute, take the pressure difference across each membrane element to be large as compared with the osmotic pressure (that is, $\Delta P \gg \Delta\pi$), and suppose the convective flow through the membranes to be of sufficient magnitude that diffusion is negligible, then R can be regarded as having a value determined by the structure of the membrane alone. Under these conditions the steady-state constraint leads to the surprising result that the sieving characteristics of the system as a whole are determined by the rejection coefficient of the first membrane only.

We ascribe the rejection coefficients R_1, R_2, and R_3 to the three membrane elements. After the steady state is attained, the solute flux J_s will be the same everywhere:

$$J_s = J_v C_s^A (1 - R_1) = J_v C_s^I (1 - R_2) = J_v C_s^{II} (1 - R_3) = J_v C_s^B \qquad (2)$$

where J_v is the volume flux and C_s^A, C_s^I, C_s^{II}, and C_s^B are the concentrations of solute in the four regions. Since J_v is also everywhere constant at the steady state, the composition of the filtrate is seen to be

$$C_s^B = C_s^A (1 - R_1) \qquad (3)$$

As far as filtrate composition is concerned, the result in the steady state would be the same regardless of how many membrane elements were added on after the first one, and regardless of the rejection coefficients of the added elements. The only effect of varying the properties of the membrane elements after the first element would be to change the steady-state concentrations in the intervening compartments, as can be seen if we solve for C_s^I and C_s^{II}:

$$C_s^I = \left(\frac{1 - R_1}{1 - R_2}\right) C_s^A$$

$$C_s^{II} = \left(\frac{1 - R_1}{1 - R_3}\right) C_s^A \qquad (4)$$

Thus C_s^I and C_s^{II} can be arbitrarily adjusted by the adjustment of R_2 and R_3, without this adjustment having any effect on the filtrate concentration C_s^B.

If we relax our simplifying assumptions, then R is no longer a property of each membrane element alone, but may depend on the properties of the other membranes through their influence on boundary conditions. In this way the sieving of the system as a whole may come to depend on the properties of the membrane elements after the first. Nevertheless, at the steady state each membrane element has a definite value for its rejection coefficient, the foregoing results still hold in a formal mathematical sense, and all effective sieving still occurs at the first membrane, where the rejected solute is removed.

Parenthetically, we note that an arrangement of series membranes having different rejection coefficients permits accumulation or depletion of solute between membranes, as pointed out previously by Kedem and Katchalsky (*3*). This arrangement provides a means, in a dynamic open system such as in living organisms, for achieving stable and precise concentrations of specific molecules in sharply localized regions.

The important point we wish to

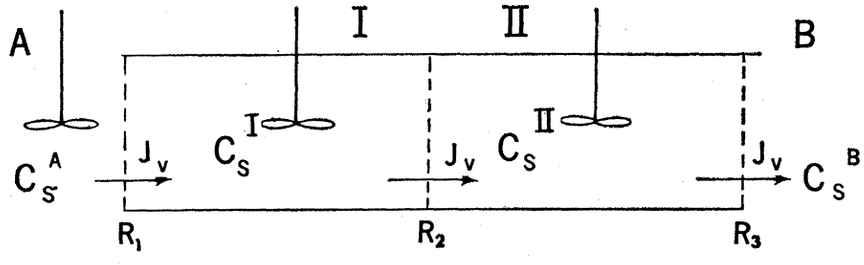

Fig. 1. Three membrane elements in series with rejection coefficients R_1, R_2, and R_3. In the steady state the solute and solvent fluxes must be the same across each membrane, and the filtrate concentration C_s^B is independent of R_2 and R_3.

stress is that effective steady-state sieving can occur only when a removal mechanism coexists with the rejection mechanism. Thus no effective sieving can occur within the body of a real membrane unless some removal mechanism for the rejected solute is provided; otherwise solute would continue to accumulate within the membrane, which is impossible at steady state. In the case of ultrafiltration the removal mechanism usually consists of stirring or rapid flow parallel to the upstream face of the membrane, so that effective sieving occurs only at this interface where both a means of sieving and a removal mechanism coexist. It is commonly accepted that an ultrafiltration membrane will cease to sieve effectively in the absence of stirring because of what is termed concentration polarization (*4*).

Finally, on the basis of the foregoing considerations we can conclude that separation processes such as those operative in chromatography, which depend on differences of interaction between each species and the matrix throughout the column, will be effective only in the transient mode and will become inoperative in the steady state. Thus models of sieving based on interactions analogous to those observed in chromatography are unlikely to provide a basis for physical insight into the mechanism of steady-state sieving.

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Susceptibility of Mink to Sheep Scrapie

Abstract. *A progressive, fatal spongiform polioencephalopathy was induced in mink intracerebrally inoculated with a suspension of brain from a Suffolk sheep with naturally acquired scrapie. The clinical signs and pathological lesions of the experimental disease were indistinguishable from transmissible mink encephalopathy, a disease of undetermined origin that occurs in mink.*

Transmissible mink encephalopathy (TME) is an infection of ranch mink characterized by a long incubation period (minimum of 4 months on intracerebral inoculation) followed by a clinical course of progressive neurologic illness ending in severe debilitation and death. The principal histopathologic lesion seen in affected animals is a spongiform degeneration of the gray matter of the brain.

Epizootiologic evidence suggests that the rare natural occurrence of TME in mink herds results from the introduction of the disease agent through some item in the animal's diet. Clinically and pathologically, TME is very similar to scrapie of sheep. Studies on the physical and chemical properties of the TME agent have failed to differentiate it from the transmissible agent producing scrapie (*1*). However, since neither scrapie (*2*) nor TME (*3*) have been found to elicit a detectable immune response from their hosts, it has not been possible to relate the two diseases by means of immunologic procedures. Studies in experimental transmission between species have indicated that the etiologic agent of TME may in fact differ from scrapie in host range. Mink encephalopathy, in contrast to scrapie, has not as yet been demonstrated to be directly transmissible to Swiss white mice (*4, 5*) and, conversely, intraperitoneal inoculation of mink with mouse-adapted scrapie has failed to produce disease after 20 months (*5*). The TME agent has been transmitted to three species of subhuman primates (*6*) as well as to the raccoon and striped skunk (*7*). Various primates inoculated with mouse-adopted scrapie have failed to develop disease (*8*), while carnivore susceptibility to the scrapie agent is untested.

An experiment was designed to determine the susceptibility of mink exposed to the unadapted scrapie agent in tissues of infected sheep. Part of the continuing experiment is reported here. Brain homogenates were made from a purebred Cheviot and a purebred Suffolk sheep, respectively, each killed in an advanced stage of the naturally occurring disease. The diagnosis of scrapie was confirmed by pathologic examination and by mouse inoculation.

The inocula were prepared at Purdue University by trituration of frozen portions of brain tissue with the addition of enough physiological salt solution to produce a 10 percent suspension by weight. Five mink were inoculated (0.1 ml each) intracerebrally with the Suffolk homogenate and five with the Cheviot homogenate; the homogenates were also concurrently tested by intracerebral inoculation of mice. Mink used in the experiment were obtained in Wisconsin from ranch stock with no past history of TME and no known exposure to sheep tissues in their diet. At no time prior to transport to Purdue were the animals housed in facilities where research had ever been conducted on mink encephalopathy. The design of mink pens and holding shed, and the procedures for care and feeding, followed standards accepted by the mink industry. Inoculated animals were observed daily for signs of abnormal behavior.

The response of the mink inoculated with the Suffolk brain was uniform with the earliest signs of disease recorded 12 months after inoculation, and all five animals were affected after 14 months. The clinical signs consisted of behavioral changes, slowing of the animal's normal movements, postural ataxia, incoordination beginning in the hindquarters, and periods of somnolence with the mink apparently alert during the interim. The signs of disease were indistinguishable from those seen in natural (*9*) and experimental (*10*) mink encephalopathy. Mink inoculated with Cheviot brain remained normal 20 months after inoculation. Disease has never been produced in mink by the inoculation of normal mink brain nor have any uninoculated animals housed in the same sheds ever developed spontaneous disease. Both inocula induced scrapie in mice after incubation periods of 15 months for the Suffolk homogenate and 16 months for the Cheviot homogenate.

There were no gross pathological alterations in the central nervous sys-