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SCALING LAWS AND THE EFFECTS OF CONCENTRATION POLARIZATION ON THE PERMEABILITY OF HYALURONIC ACID

MARK JOHNSON[1], ROGER KAMM[1], C ROSS ETHIER[2], and TIM PEDLEY[3]

[1]Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
[2]University of Toronto, Toronto, Canada
[3]Cambridge University, Cambridge, England

Abstract

Investigators [1,2] have modeled the hydraulic permeability of hyaluronic acid using a fiber matrix model such as developed by Happel [3]. However, Ethier [4] found that the concentration dependence of the sedimentation rate of hyaluronic acid is inconsistent with the predictions of the fiber matrix model and with perfusion measurements of the hydraulic permeability [1]. These discrepancies are investigated and a tentative explanation provided.

Using the pearl necklace model introduced by Kirkwood and Riseman [5] and scaling laws described by deGennes [6], we have found that the permeability of hyaluronic acid can be described in terms of three separate concentration regimes: a dilute regime, a semi-dilute regime and a homogeneous regime. The sedimentation data considered by Ethier were in the semi-dilute concentration regime where the fiber matrix model is not expected to apply: our results indicate that only for concentrations in the homogeneous regime is the fiber matrix model appropriate.

The discrepancy found between the predictions of the fiber matrix model and the results of perfusion studies may be due to concentration polarization. This process was modeled and examined experimentally. The experimental results are in qualitative agreement with the theory.

1. Introduction. Hyaluronic acid is a long chain, linear polyelectrolyte that is ubiquitous in the extracellular matrix of vertebrates. It is one of a group of anionic polysaccharides known as glycosaminoglycans. The repeat unit of hyaluronic acid is a disaccharide comprised of D-glucuronic acid and N-acetyl-D-glucosamine. This dimer has a length of 0.95 nm and a radius

of approximately 0.5 nm [7], carries a single negative charge and has a molecular weight of 400 (including the sodium ion that is carried in the Debye sheath). In physiological situations, the molecular weight of the hyaluronic acid polymer varies between 10^5 and 10^7 and thus the end-to-end length of the polymer can be many microns.

We investigate here the permeability of hyaluronic acid solutions. This has application to many physiologic situations including the permeability of the arterial wall [8], the transport of nutrients through connective tissue [9] and the flow resistance of the aqueous humor outflow system in the eye [2]. In the latter context, many investigations have been conducted into the relevance of hyaluronic acid to the pathogenesis of glaucoma [e.g. 10].

The fiber matrix model. When determining the permeability of a polymer solution, it is convenient to idealize the polymer to consist of long, randomly oriented molecular fibers over which the solvent flows. In this description, bound solvent, polymer-polymer interactions and kinetic polymer motions are neglected. This description is in fact identical to that of flow through a fibrous porous medium.

Viscous flow through such a system (with macroscopic dimensions) has been modeled by several investigators [3,11,12]. In each of these approaches, the porous medium is described as a homogeneous material composed of 'average' fibers. In the Happel [3] and Kuwabara [11] approach, a cell model is constructed in which each fiber (radius a) is placed in a fluid cell of radius b such that the solid fraction (Φ) of this cell ($\pi a^2/\pi b^2$) is equal to the average solid fraction in the porous medium. Then, a no-slip boundary condition is applied at the surface of the fiber, and a zero-shear (Happel) or zero-vorticity (Kuwabara) boundary condition is applied at the cell boundary (r=b). The Stokes equations are then solved for various orientations of the fiber relative to the superficial fluid velocity and the permeability (K) of the system is determined.

In the Spielman and Goren [12] approach, a single representative fiber is placed in an otherwise homogeneous porous medium, composed of similar fibers. The flow resistance of the neighboring fibers are accounted for through the use of the Debye-Brinkman equation in which a body force term is added to the Stokes equation.

Ethier [4] has reviewed the above work and found that, to a good approximation, the permeability can be described by:

$$K = 0.31\, a^2\, \Phi^{-1.17} \qquad (1)$$

This expression is accurate to within 5% of the Spielman and Goren model for $6\times10^{-5} < \Phi < 1.3\times10^{-2}$.

Ethier [4] also reviewed the literature concerning measurements of the permeability of hyaluronic acid and found relevant data from perfusion and sedimentation studies that allowed the permeability to be determined as a function of concentration (Figure 1; note that hyaluronic acid has a density of 1.5 g/ml [13]). He discovered that the data resulting from perfusion studies differed from those resulting from sedimentation studies:

while the values were generally similar, the permeabilities determined in the perfusion study varied as $\Phi^{-1.02}$ while those from sedimentation studies varied as $\Phi^{-1.47}$. Furthermore, both of these results differed from the predictions of the fiber matrix model ($K \sim \Phi^{-1.17}$). It is the purpose of this paper to investigate these discrepancies.

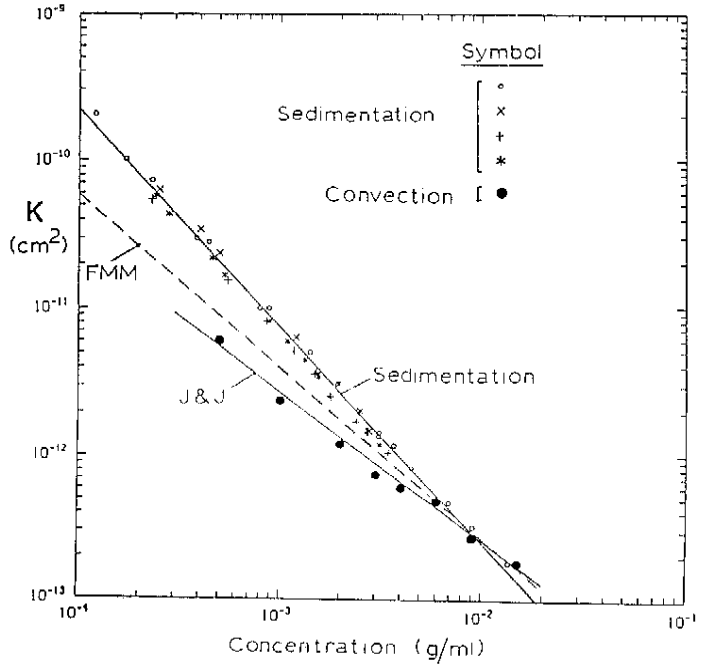

Figure 1 The permeability of hyaluronic acid as a function of concentration. FMM is the prediction of the fiber matrix model; J & J is the best fit of perfusion (convection) data from Jackson and James [1]. Adapted from Ethier [4].

2. Modelling the permeability of hyaluronic acid: the pearl necklace model. A major problem with the fiber matrix model is its assumption of homogeneity. The polymer fibers are not straight but take a path like that of a self-avoiding random walk. Thus the model must consider the hydrodynamic interactions between different parts of the same fiber. This leads to a variety of inter-fiber spacings with most of the flow will be carried through the larger spaces. While it might be possible to modify the fiber matrix model to allow for this nonuniformity, Kirkwood and Riseman [5] introduced the pearl necklace model that can account for this effect naturally.

In this model, each monomer is assumed to behave as a small sphere of radius a_o. The monomers are assumed to be joined by links with negligible flow resistance. (Note that although hyaluronic acid is actually composed of dimers, we refer to this unit as a monomer in what follows.) The viscous

drag on a polymer is then just the sum of the forces on each of the monomers, thus allowing the permeability to be determined as:

$$K = \frac{\mu}{c\,f} \tag{2}$$

where μ is the solvent viscosity, c is the number of monomers per unit volume and f is the frictional coefficient per monomer (force/induced velocity). If the monomers (or pearls) are sufficiently far apart, then the drag force on each can be found using Stokes' law, and the permeability becomes:

$$K = \frac{2}{9}\, a_o^2\, \Phi^{-1} \tag{3}$$

This neglects the hydrodynamic interaction between monomer units of the same polymer chain. "Actually, the peripheral elements of the chain must perturb the flow in the neighborhood of the interior elements in such a manner that they are partially shielded from hydrodynamic interaction with the exterior fluid" [5]. The magnitude of this shielding depends upon the distribution of the monomers, and we must therefore consider the configuration of a randomly coiled polyelectrolyte.

The configurational statistics of polyelectrolytes. The configuration of a polymer can be regarded as that of a self-avoiding random walk with a step size equal to the length of several monomers. The actual step length (L) depends on the flexibility of the bond between the monomers and, for a polyelectrolyte, on charge interactions. This length is known as the Kuhn statistical segment length--for hyaluronic acid in a 0.2M saline solution, it is 9.5 nm or 10 dimer units [14].

Flory [15] showed that for a random walk of a polymer with σ statistical units of length L, the radius of gyration (R_g: the root-mean-square distance of the segments from the center of mass of the polymer) varies as:

$$R_g = \sqrt{\sigma/6}\, L \tag{4}$$

Note that if a polymer chain contains N monomers of length L_o, then $\sigma = N(L_o/L)$. Flory also showed that a self-avoiding random walk leads to a somewhat greater radius of gyration and found that in this case:

$$R_g \sim \sigma^{3/5}\, L \tag{5}$$

For a self-avoiding walk of a polyelectrolyte, the constraints are more severe: the electrostatic repulsions between segments lead to greater probabilities for the more extended configurations, since compact configurations will have relatively higher free energy than more expanded ones. Hermans and Overbeek [16] calculated the free energy of a randomly coiled polyelectrolyte and determined the configuration that minimized this quantity. Their modelling indicated that the expansion of the polymer is determined by both the Debye length (λ) and the number of statistical segments (σ).

As their model implicitly includes the dependence of the statistical segment length on the Debye length, the length scale L in equation (5) is

replaced with the monomer length L_o (and σ with N), with the result that:

$$R_g = 1.4 \left[\frac{\lambda}{L_o}\right]^{2/5} \left[\frac{L_B}{L_o}\right]^{1/5} N^{3/5} L_o \qquad (6)$$

where L_B is the Bjerrum length, a natural length scale for polyelectrolyte solutions, and has a value of 0.7 nm for water at 20°C [17]. Johnson [18] has used the Hermans-Overbeek model to determine the radius of gyration of hyaluronic acid and found that:

$$R_g = 0.022\ M^{3/5}\ S^{-1/5} \quad (nm) \qquad (7)$$

where M is the molecular weight of the hyaluronic acid and S is the molar salinity of the solvent (NaCl). This approach, however, overpredicts the dependence of R_g on S: counter-ion condensation will decrease the ionization of the polymer at low solvent salinity levels [19]. Since the configurational entropy is decreased at high degrees of ionization (by expanding the polymer), a large proportion of the counter-ions (Na^+) must bind to the polyelectrolyte thus neutralizing part of the polymer charge and increasing the entropy. Johnson [18] used data from the literature for the dependence of R_g on S to account for this effect and modified equation (7) to give:

$$R_g = 0.025\ M^{0.6}\ S^{-0.08} \quad (nm) \qquad (8)$$

For $M=1x10^6$ (end-to-end length 2.4 μm) and S=0.15**M** (physiologic saline), we find that hyaluronic acid would have a radius of gyration of approximately 0.1 μm.

The permeability of hyaluronic acid. Kirkwood and Riseman [5] used the pearl necklace model to determine the permeability of a polymer solution. In their model, the fluid velocity of each monomer is calculated as the sum of the unperturbed velocity that would exist in the solvent in the absence of the polymer molecule and the summed far field velocity contribution from all "nearby" monomers, calculated from Oseen's solution [5] and evaluated at the position of the particular monomer. The ratio of this induced velocity to the unperturbed velocity reflects the increased permeability due to hydrodynamic shielding. In this calculation, "nearby" monomers are defined as those whose position is statistically correlated with the monomer under consideration and depends on the concentration of the polymer solution.

In the dilute regime, the polymer molecules are well separated in space and the molecular envelopes do not overlap. Thus each monomer is correlated with all other monomers on the same macromolecule, and no others. Kirkwood and Riseman [5] used this approach to show that the friction factor for a single macromolecule ($\hat{f}$) is:

$$\hat{f} = 0.655\ (6\pi\mu R_g) \qquad (9)$$

The form of this result indicates that an isolated polymer molecule behaves hydrodynamically like a solid particle with a radius equal to 0.655 of the radius of gyration of the macromolecule: the solvent prefers to flow around the macromolecule rather than pass through it.

Kirkwood and Riseman assumed a random walk configuration for the polymer fibers in deriving equation (9). Johnson [18] corrected this result to account for the self-avoiding nature of the random walk, and found that the only correction required in this expression was the replacement of the coefficient 0.655 with 0.5, and of course the use of R_g based upon a self-avoiding walk. For hyaluronic acid, R_g is given by equation (8) and thus recognizing that $f=\hat{f}/N$, the permeability in the dilute regime is found to be:

$$K = 5.5\times10^{-17}\ M^{0.4}\ S^{0.08}\ \Phi^{-1} \quad (cm^2) \tag{10}$$

This result compares well with data: Johnson [18] found that a good representation of published results for dilute hyaluronic acid solutions with S=0.2M is $K=4.8\times10^{-17}\ M^{0.4}\ \Phi^{-1}$. Thus the permeability (or more properly in this regime, the sedimentation rate) depends on both the salinity of the solvent and the molecular weight of the polymer.

As the concentration of polymer in the solution is increased, the molecular domains of the individual macromolecules begin to overlap and entangle, and the semi-dilute regime is entered. The solid fraction at which the molecular domains first must overlap is designated as Φ^* and is dependent on the radius of gyration of the isolated macromolecules. DeGennes [6,20] has elegantly analyzed this regime and demonstrated the existence of a single characteristic length scale (ζ):

$$\zeta = R_g \left[\frac{\Phi}{\Phi^*}\right]^{-3/4} \tag{11}$$

This result follows from the assumption that, with entanglement, the characteristic length scale must be independent of the molecular weight of the polymer.

Whereas before overlap a monomer's position in space is correlated with all other monomers of the same chain, following overlap it is correlated only with those monomers within a distance ζ; deGennes [6] calls this region the "blob". The number of monomers contained within the "blob" (N_b) is found as $N_b=N(\Phi/\Phi^*)^{-5/4}$ where N is the number of monomers in one polymer chain.

To find the permeability in the semi-dilute regime, we follow the analysis used for a dilute polymer solution, but replace R_g in equation (9) with ζ to characterize the "blob" (and use the self-avoiding random walk coefficient of 0.5). Recognizing that $\Phi^*=N(4/3\pi a_o^3)/(4/3\pi R_g^3)$, we find:

$$K = \frac{2}{9}\ (0.5)^{-1}\ R_g^2\ (\Phi/\Phi^*)^{-3/2} \tag{12}$$

and hence, for hyaluronic acid,

$$K = 2.5\times10^{-16}\ S^{0.2}\ \Phi^{-1.5} \quad (cm^2) \tag{13}$$

Thus, in the semi-dilute regime, the permeability is independent of the molecular weight of the polymer (as it must be for a self-consistent scaling law) but still dependent on the solvent salinity. A decrease in salinity increases the radius of gyration of the macromolecule (equation 8)

producing a more homogeneous monomer distribution and consequently a lower permeability.

For polyelectrolytes, there exists a limitation on the minimum value of the correlation length (ς). Specifically, this length scale cannot be smaller than the statistical segment length (L). Using equation (11), this criterion becomes:

$$\Phi < \left[\frac{R_g}{L}\right]^{4/3} \Phi^* \qquad (14)$$

For solid fractions higher than this, the statistical segment length becomes the relevant length scale, and the solution is well-described as a set of randomly-oriented "needles" (the statistical segments). In such a homogeneous regime, the fiber matrix model can be used to estimate the permeability. This regime does not exist for freely rotating polymer chains ($L=L_o$) as the length scale calculated in equation (11) never becomes sufficiently small.

Whereas equation (14) could in principle be used to determine the solid fraction (Φ_p) at which the polymer solution becomes homogeneous, the Kuhn length L is not well-characterized for different solvent salinities. A more direct procedure is to determine the solid fraction at which the permeability found using equation (12) (the semi-dilute regime) is equal to that determined by equation (1) (the fiber matrix model). The result for hyaluronic acid is:

$$\Phi_p = 0.013\ S^{0.6} \qquad (15)$$

Figure 2 summarizes the results of this section for two molecular weights of hyaluronic acid ($M=10^6$ and 10^7) and two levels of solvent salinity (S=0.01 and 0.15M). The figure shows that the permeability is a function of both the polymer molecular weight and the solvent salinity in the dilute regime, independent of the polymer molecular weight in the semi-dilute regime and independent of both of these parameters in the homogeneous regime. Note that relatively low solid fractions are needed for the solution to be characterized as homogeneous.

These results can be used to explain the discrepancy identified by Ethier [4] concerning data for the sedimentation rate of hyaluronic acid (in 0.2M saline), which can be summarized as:

$$K = 1.6\times10^{-16}\ \Phi^{-1.47} \qquad (cm^2) \qquad (16)$$

These data were taken at solid fractions varying from approximately 10^{-4} to 10^{-2} and thus we would expect the permeability to be described by the model for the semi-dilute regime. Comparing with equation (13), we see that the agreement is excellent. Thus one of the discrepancies identified by Ethier is resolved: the concentrations of hyaluronic acid used in the sedimentation experiments were lower than those required for the fiber matrix model to apply.

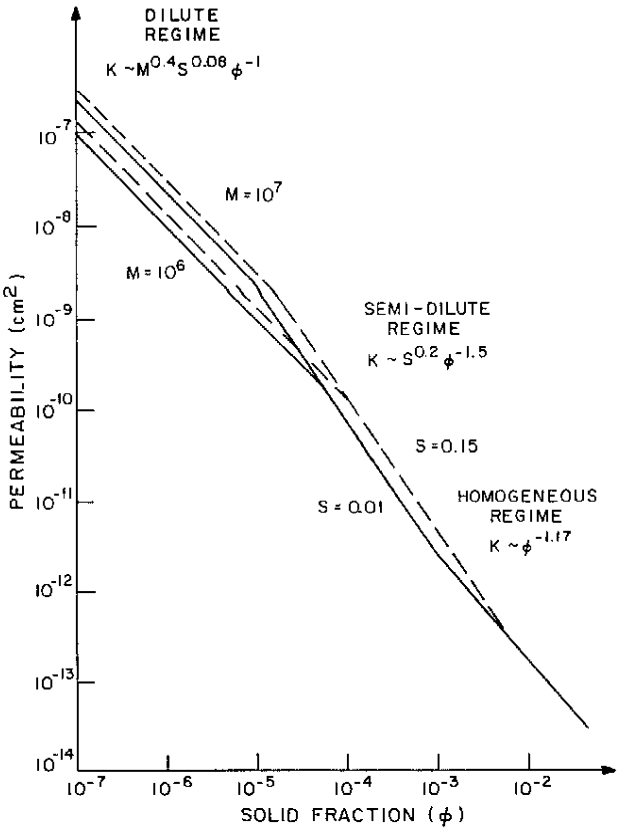

Figure 2 Summary of the dependence of the permeability of hyaluronic acid on solid fraction in the three concentration regimes. Shown are predictions for hyaluronic acid molecular weights of 10^6 and 10^7 and solvent salinities of 0.01 and 0.15**M**.

3. Concentration polarization. Ethier [4] also examined data from a study [1] in which the permeability of hyaluronic acid was determined by perfusing 0.01**M** saline through a layer of hyaluronic acid backed by a filter with a 0.1 μm pore diameter. Although the concentrations of hyaluronic acid tested were similar to those of the sedimentation studies, different results were obtained (Figure 1). These perfusion (or convection) results also differed from the predictions of the fiber matrix model. Ethier concluded that these discrepancies were due to concentration polarization. Here we examine this possibility further.

When solvent flows through a membrane (or filter) whose pores are small enough to prevent the solute from passing, the solute concentration is greatest at the membrane face and falls with distance upstream. This phenomenon is known as "concentration polarization".

Two descriptions of this process are conventionally given. In one, the convection of polymer molecules toward the membrane is balanced by a

diffusion of polymer molecules away from it. In a second, the viscous forces dragging the polymer molecules toward the membrane are balanced by osmotic expansive forces that oppose this compression of the polymer layer. In fact, these two approaches can be shown to be equivalent [21], and are related through the generalized form of the Stokes-Einstein diffusion coefficient:

$$D = \frac{K \Phi}{\mu} \frac{d\Pi}{d\Phi} \qquad (17)$$

where D is the concentration-dependent mutual diffusion coefficient of the polymer and Π is the osmotic pressure of the polymer solution.

Following the approach based on osmotic pressure, an expression is required that relates the osmotic pressure of a hyaluronic acid solution to its solid fraction (or concentration). Johnson [18] has reviewed the literature and found that the following expression roughly represents the available data:

$$\Pi = 2 \times 10^{8} M^{-0.1} S^{-0.5} \Phi^{2} \quad (\text{dynes/cm}^2) \qquad (18)$$

Note that as the salinity of the solution is decreased, the osmotic pressure increases. This is a result of the increased Debye sheath size around the polymer fibers that leads to greater repulsion between the fibers.

We now consider a steady-state concentration polarization layer of a fixed amount of solute on a filter or membrane through which solvent freely passes. Two force balances are considered: one for the solvent passing through the polymer layer, and one for the polymer molecules themselves.

Within the solvent, the pressure forces driving flow through the polymer layer and the osmotic forces drawing fluid into the layer are balanced by the viscous drag forces. We characterize this force balance using a modified Darcy's law in which the driving potential for flow (Q) is the difference between the thermodynamic pressure (P) and the osmotic pressure (Π) within the solvent:

$$\frac{d}{dx} (P - \Pi) = \frac{\mu Q}{K A} \qquad (19)$$

Here A is the cross-sectional area facing flow and the positive x direction is opposite to the direction of flow.

A similar force balance must exist on the polymer fibers themselves, as they are, on average, stationary. The solvent exerts a drag force on the polymer fibers driving them toward the filter while this force is opposed by the osmotic force tending to swell the polymer layer. The force balance then requires:

$$\frac{d}{dx} (\Pi) = - \frac{\mu Q}{K A} \qquad (20)$$

Here the drag force on the fibers is represented by the Darcy term that acts in the opposite direction on the polymer fibers than on the solvent. Combining equation (19) and (20), we obtain the result first found by Wijmans et al. [21] using the Gibbs-Duhem relationship that:

$$\frac{dP}{dx} = 0 \qquad (21)$$

Thus, there is no pressure drop within the polymer layer and the irreversibility generated results in a loss of chemical potential of the solvent.

After the solvent passes through the polymer layer, it passes through the filter and its osmotic pressure becomes zero. Thus if $(P-\Pi)$ is to remain constant across the filter (assuming negligible flow resistance in the filter), we must have $\Delta P=\Pi \mid_{x=0}$: the entire pressure drop occurs across the filter. In fact, we can use this as a criterion for the extent to which concentration polarization will occur in a particular experiment: the process will continue to until the osmotic pressure at the filter face is equal to the applied pressure drop.

Johnson [18] solved equation (20) using equation (18) to characterize the osmotic pressure, and either equation (1) or (13) to characterize the permeability. He found that the length of the concentration polarized layer (h) could be related to the initial unpolarized length (h_o) and the initial osmotic pressure (Π_o, determined by the unpolarized polymer layer solid fraction Φ_o) at a given pressure drop by:

$$\frac{h}{h_o} \sim \left[\Pi_o / \Delta P \right]^{1/2} \qquad (22)$$

He further found that the pressure drop across the polymer layer/filter could be determined as:

$$\Delta P = \text{const} \; S^{\alpha} \left[\frac{\mu Q \Phi_o h_o}{A} \right]^{\beta} \qquad (23)$$

where:

PERMEABILITY MODEL	const	α	β
Homogeneous Regime (Equation 1)	5.7×10^{15}	0.05	1.09
Semi-dilute Regime (Equation 13)	1.7×10^{18}	-0.1	1.33

and ΔP is expressed in dynes/cm^2.

Figure 3 shows the prediction of the two equation (solid line is for the homogeneous regime; dashed line is for the semi-dilute regime) for the experimental conditions investigated by Jackson and James [1] at a perfusion pressure of 6×10^4 dynes/cm^2; the data points shown are their experimental results. It can be seen that the fiber matrix model, modified to include the effects of concentration polarization, gives reasonable agreement with the data, with the exception of the two points at the lowest concentrations. These two points may be anomalous due to insufficient appreciation of the time scales required for concentration polarization [18].

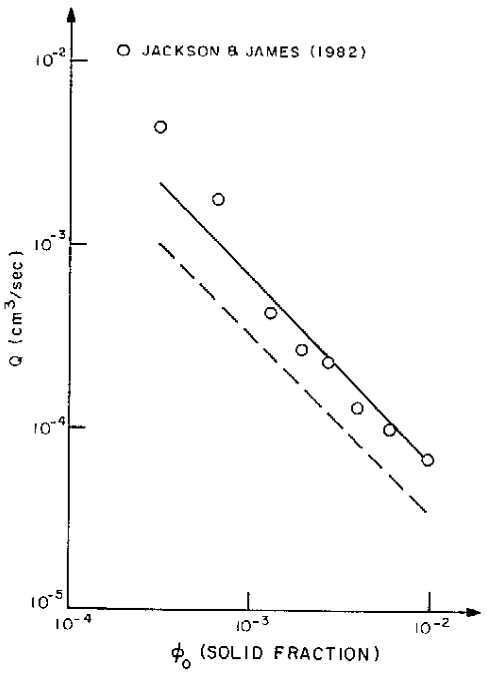

Figure 3 Predictions for the flowrate at a given pressure drop ($6x10^4$ dynes/cm^2) for the conditions investigated by Jackson and James [1]. The solid line is the prediction from the fiber matrix model while the dashed line is from the pearl necklace model (each result includes the effect of concentration polarization). The data shown is from Jackson and James [1].

These results can be used to explain the difference between the sedimentation data and perfusion data examined by Ethier. While the initial concentrations in the perfusion experiments were in the semi-dilute regime, concentration polarization increased the concentration of polymer in the vicinity of the filter such that the concentrations there were in the homogeneous regime. The character observed in the experiments is that associated with the low permeability layer close to the filter.

Effect of solvent salinity. To demonstrate further the importance of concentration polarization on the pressure drop across a polymer layer, the effects of solvent salinity were investigated. Equation (23) and the subsequent table predict a different dependence of the pressure drop on solvent salinity for the homogeneous regime than for the semi-dilute regime. In the homogeneous regime, the coefficient α is positive indicating that a decreased solvent salinity will lead to a decreased pressure drop across the polymer layer. This is a consequence of the increased Debye sheath around the polymer fibers that increases the osmotic pressure of the solution (equation 18), expanding the polymer layer and thereby decreasing the flow resistance.

By contrast, in the semi-dilute regime the coefficient α is negative. While a reduction in solvent salinity still produces osmotic expansion of the polarized layer, a second mechanism dominates the change in pressure drop. The solvent salinity level affects the macromolecular configuration, and this has a significant effect on the permeability in the semi-dilute regime as indicated by equation (13). This effect exerts a greater influence on the flow resistance than does the osmotic expansion of the polymer layer and thus the coefficient α is negative in this regime.

To test these concepts, experiments were conducted using the setup is shown in Figure 4. Hyaluronic acid is placed upstream of a 0.05 μm Nuclepore filter in filter holder #2. A syringe pump drives prefiltered saline through the hyaluronic acid layer at a constant flowrate while the pressure is monitored. Three sequential tests were run using (1) 0.15**M** saline, (2) 0.0143**M** saline and (3) 0.15**M** saline again. In each case the test was continue until the pressure reached a steady level from which the flow resistance was determined.

Typical results from this procedure are shown in Figure 5. In all experiments, a decrease in solvent salinity resulted in a significant decrease in the pressure drop across the polymer layer. This result was qualitatively consistent with the predictions of a concentration polarized

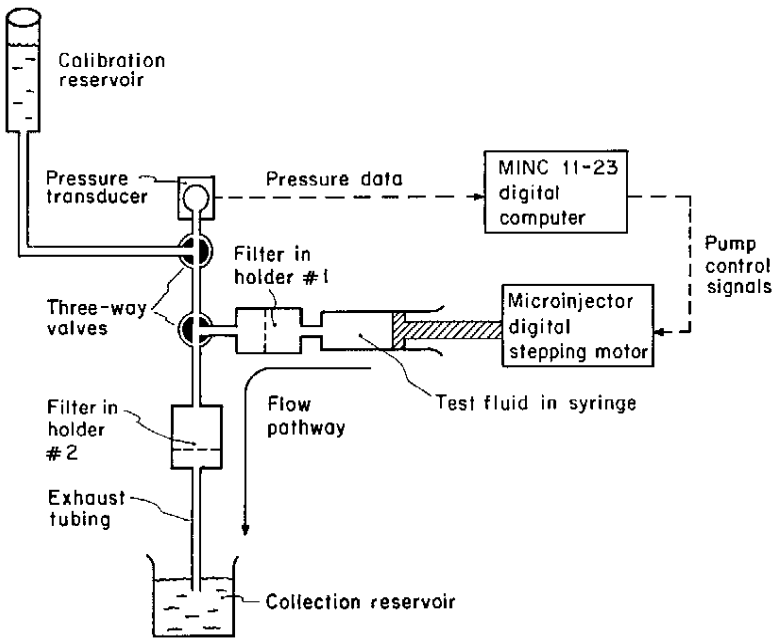

Figure 4 Experimental setup used to investigate the permeability of hyaluronic acid.

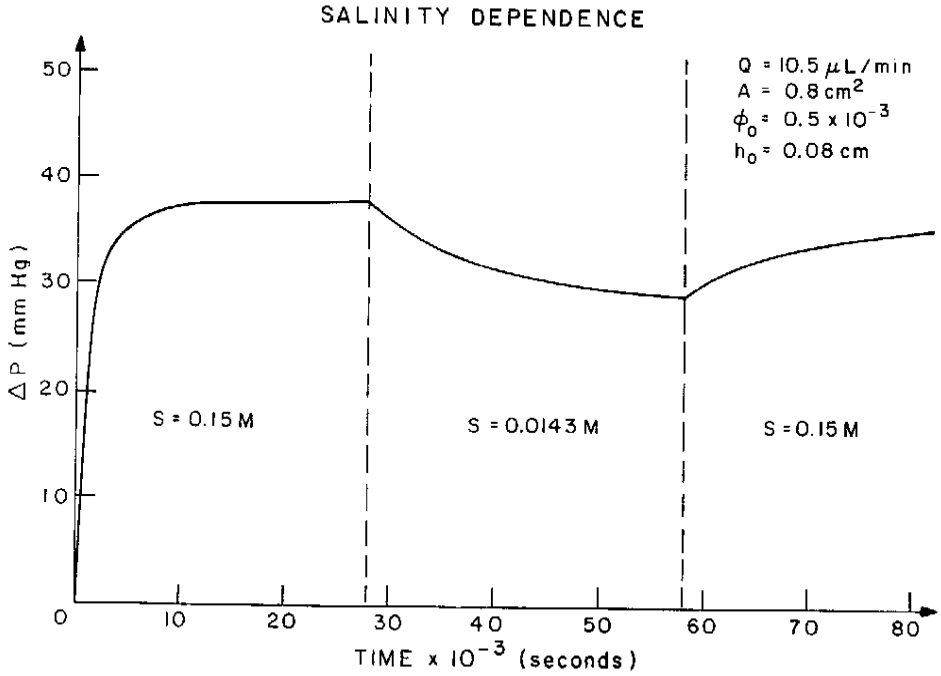

Figure 5 Results of an experiment to determine the dependence of the pressure drop across a hyaluronic acid layer as a function of solvent salinity. The parameters used are listed.

layer in the homogeneous regime. It also further supported the importance of concentration polarization in determining the permeability of a polymer layer in perfusion experiments.

However, the dependence of flow resistance on salinity is greater than expected. Allowing for the flow resistance of the filter itself (9.6×10^7 dynes sec/cm^5) the coefficient α is found to be 0.15-0.35 compared with the predicted value of 0.05, a result common to all of the experiments conducted. No explanation for this result has yet been found.

4. Conclusions. We have examined several discrepancies raised by Ethier [4] concerning the permeability of hyaluronic acid. We have found that by recognizing different concentration regimes for the permeability of hyaluronic acid and accounting for concentration polarization, these discrepancies could be resolved.

Furthermore, it is of interest to note that for most physiological cases, the concentration of glycosaminoglycans will be close to, or greater than that required for the homogeneous regime to be applicable. Thus the fiber matrix model should give a good approximation of the flow resistance of physiological polymer solutions as may occur in the extracellular matrix. However, the effects of cross-linking and of mixtures of different

macromolecules (such as proteins) still require investigation. Also of interest would be to determine whether the concentration polarization occurring in these experiments might also occur physiologically.

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