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RHEOLOGY OF SYNOVIAL FLUIDS AND SUBSTITUTE POLYMERS†

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ABSTRACT

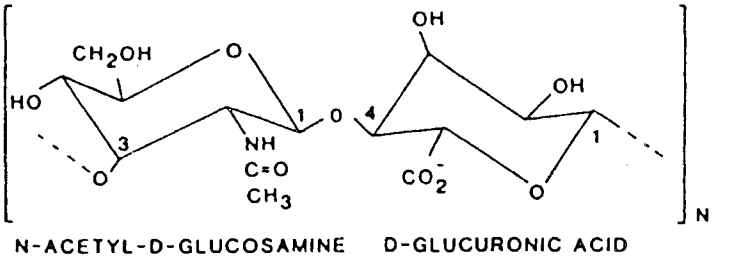
Synovial fluids are highly viscous and viscoelastic solutions responsible for lubrication and damping in joints. Based on work with both healthy and arthrotically deteriorated human knee joint synovia, the rheology of these materials is discussed in terms of an entanglement network. The essential constituent of the dissolved complex is a hyaluronic acid of very high molecular mass (10^7), which is degraded in pathological cases with accompanying rheological deterioration. The network properties are calculated and compared with those of pure hyaluronic acid and with synovia-substituted polymers as guar gum and polyacrylamide. The network parameters reflect clearly the rheological properties and their changes in the case of arthrotic deterioration.

INTRODUCTION

Synovial fluids are highly viscous and viscoelastic fluids responsible for lubrication and damping in joints. Based on work with human knee joint synovia, the rheological properties of both healthy and arthrotically deteriorated synovias were investigated. The main constituent of this fluid is a complex molecular aggregate whose backbone is a hyaluronic acid with a molecular mass of 10^7 for healthy

†Dedicated to Prof. Dr. J. Klein on the occasion of his 60th birthday.

systems. The rheological properties have been measured by studying shear viscosity and solution elasticity in stationary flow. Important parameters are the zero shear viscosity η_0, the critical shear rate $\dot{\gamma}_c$ as a measure for the longest relaxation time Θ', the shear modulus G, and the cross-over point of shear viscosity and shear modulus. It turned out, that healthy synovia have high viscosity, a pronounced shear thinning range, and a high solution elasticity with a plateau region at intermediate shear rates. Pathologically deteriorated synovias have greatly reduced viscosity, a higher critical shear rate, a less pronounced shear thinning range, no plateau in the shear modulus, and a reduced solution elasticity. The deterioration of rheological properties is caused mainly by a degradation of the backbone hyaluronic acid, whereby a decrease to a molecular mass of 10^6 already shows massive effects. Indications for a yield stress were only found with greatly degraded samples. This indicates that the thoroughgoing percolation structure necessary for yield stress requires small particles which can only be produced by a massive degradation. Comparative measurements were made with hyaluronic acid and such synovial substitutes as guar gum and polyacrylamide (Fig. 1). Even with molecular masses up to 10^6 the rheological properties were inferior in comparison with those of a healthy synovial fluid. This is also borne out by reduced relaxation times as obtained from critical shear rates. All these results are interpreted in terms of a freely penetrating entanglement network structure. From rheological data, the entanglement density and the mesh width of the network can be calculated. Obviously these data play the decisive role for the rheological performance of a synovial fluid. Therefore, rheological investigations



hyaluronan

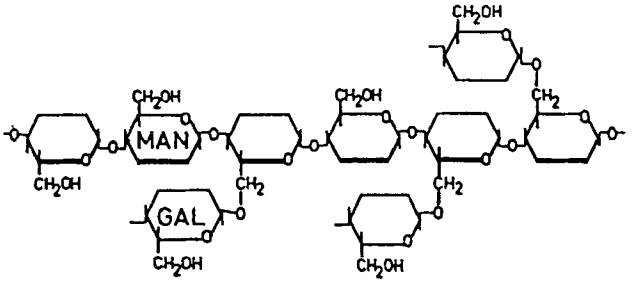


FIG. 1. Basic structural unit of hyaluronan and guar.

with both healthy and pathological synovial fluids can be used on the one hand as a diagnostic aid for the physician, and on the other hand as a means for testing and predicting the performance of synovial substitutes with regard to their rheological properties.

In the relevant literature on both synovial fluids and hyaluronate solutions, we find reports on rheological behavior [1–5] and other properties [6–11]. The older literature is given in a review paper [12] and a recent monograph [13]. While the mentioned works report important information on the general behavior of synovial fluids and hyaluronate solutions, this paper aims at an application of the concept of entanglement network solutions [14] to these physiological fluids and their pathological deterioration in the case of diseases.

SYNOVIAL FLUID—AN ENTANGLEMENT NETWORK SOLUTION

The synovial fluids of diarthrodial joints are solutions in a serumlike solvent of a molecular complex whose backbone is a high molecular mass (10^7) hyaluronan (HA concentration 1.4–3.6 mg·mL^{-1}). Both the high molecular mass and the high concentration of HA are necessary for normal joint function, namely lubrication, damping action, and load bearing. These properties, which stem from the high viscoelasticity of the synovial fluids, are required to prevent mechanical trauma and wear of articular cartilage during load-bearing movement. Further, the high exclusion volume of synovia HA is a barrier for high molecular mass molecules as proteins, but allows the diffusion of low molecular mass materials to the avascular articular cartilage as required for nutrition and elimination of noxious metabolites from the joint gap. HA is composed of disaccharide units of β-D-glucuronic acid linked glycosidually over the 4-position to the 1-position of *N*-acetyl-β-D-glucosamine (cf. Fig. 1). Rheological measurements suggest that in dilute aqueous solution (<1.0 mg·mL^{-1}) HA represents an extended random coil [13], while at higher concentrations (>1.0 mg·mL^{-1}) an entanglement network is formed [15]. It has been suggested that HA in solution is made up of flexible domains and stiffer domains, indicative of strong interchain association. HA oligomers may disrupt these ordered domains by competing for interchain coupling sites.

While HA is basically an extended linear macromolecule, synovial fluid has a more complex structure. The dissolved macromolecules probably have a structure as shown in Fig. 2. It is to be expected that beyond the overlap concentration a dense entanglement network is formed. We have estimated this overlap concentration as $c^x \geq 0.5$ mg/mL from the break in a log η' vs log c plot. This figure agrees with data from the literature [13]. This network guarantees high viscosity, shear thinning, and high elasticity, and therefore load-bearing and damping capacity. The backbone of this gel-like structure is HA, whose concentration in synovial fluid is about 2–3 mg/mL, while the protein concentration is 10–30 mg/mL. The molecular mass of HA in a healthy synovial fluid amounts to 10^7 according to our investigations. In pathologically deteriorated synovial fluids the network is more or less disrupted and the HA is degraded by a factor 10 or even more. This leads to a strong deterioration of all rheological properties, so that the synovial fluid is no longer able to perform its functions.

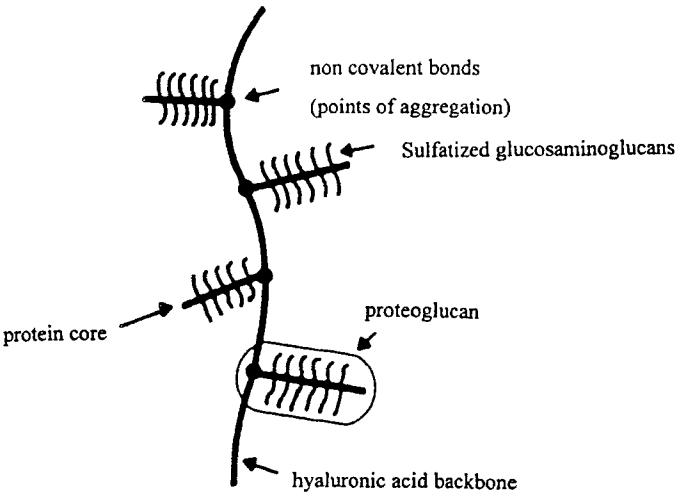


FIG. 2. Hyaluronan complex in synovial fluid, shown schematically.

While studies on the phenomenological rheology of both synovia and HA have been published, a thorough examination of the network conditions in such solutions is missing. Therefore, we have used our extensive experimental data [16] to make such an analysis. We have applied our concept of an interpenetrating entanglement network structure (cf. Fig. 4), as developed some time ago, which proved quite useful to characterize entanglement networks in various synthetic and natural polymers [14]. This approach is used to characterize both healthy and pathological synovial fluids, HA solutions, and several synovia substitutes such as guar and polyacrylamide. We concentrate on network structure as such. The dynamics of these networks is certainly governed by a repetitive motion through fictive "tubes" formed by loops of the entanglements.

Rheological Remarks

The measurements were made in a Contraves Low Shear viscometer LS 100 and in a Rheometrics Mechanical Spectrometer RMX 7200, both with cone-plate geometry. The temperature was 25°C. All measurements have been published previously [15, 16]. From our rheological measurements we obtained, as a function of shear rate $\dot{\gamma}$, the shear stress τ_{12} and the first normal stress difference $\tau_{11} - \tau_{22}$. Therefrom, after the necessary corrections, we calculated the shear viscosity $\eta' = \tau_{12}/\dot{\gamma}$ and the first normal viscosity $\psi_1 = (\tau_{11} - \tau_{22})/\dot{\gamma}^2$. For the sake of convenience, we have expressed the solution elasticity as an apparent shear modulus $G = \tau_{12}^2/(\tau_{11} - \tau_{22})$. From flow curves (plots of $\log \eta'$ vs $\log \dot{\gamma}$) we obtain η_0, the viscosity at zero shear rate, and $\dot{\gamma}_c$, the critical shear rate at which the first deviation from Newtonian flow occurs. It is related to the maximum relaxation time Θ' by $\Theta' =$

$1/\dot{\gamma}_c$. It corresponds approximately to the disentanglement time of the reptation theory. Also, we obtain a crossover point $\dot{\gamma}_{co}$ where the η' and the G curves cross each other. The crossover shear rate (i.e., frequency) is inversely proportional to the molecular mass M. Further, the crossover point is shifted downward for a broad molecular weight distribution.

The rheological behavior of such viscoelastic liquids is phenomenologically often explained with the help of simple models consisting of springs and dashpots, as in the well-known Maxwell model and the Voigt model. We can easily extend this model to include normal stresses by adding another spring placed crosswise, that is, perpendicular to the direction of flow (Fig. 3). In both shear and elongational flow this spring will be compressed and thus generate a negative normal stress $-\tau_{22}$. After cessation of the flow, this stress will give rise to an outwardly directed normal force, which in turn will lead to a blowup of the liquid thread (jet expansion, Barus effect) after removal of the constrainment. Of course, there is also a retractive force due to the normal stress τ_{11}, which generates the recoil effect.

From these rheological data we can calculate the following network parameters (a schematic presentation is given in Fig. 4). First we calculate the entanglement spacing D_N, the distance between two entanglements (mesh width). It corresponds approximately to the "blob size" in the reptation theory. Further, we calculate ν, the number of entanglements per unit volume, and the apparent statistical chain element $A'(c)$, which is a measure of the degree of coiling of a network strand between two entanglements. It depends on the concentration, and its extrapolation to zero concentration yields the true statistical chain element A_0 as obtained in dilute solution. The values of D_n, ν, and $A'(c)$ can be calculated from G in the plateau or from M_e, the molecular mass of a network strand (if available). All these network parameters and their definitions have been amply described in the literature [14].

SYNOVIAL FLUIDS

We have studied synovial fluids from human knee joints for both the healthy and the pathological state. Healthy synovia were postmortem samples; pathological ones were of the arthrotic type (inflammatory, degenerative). The results obtained

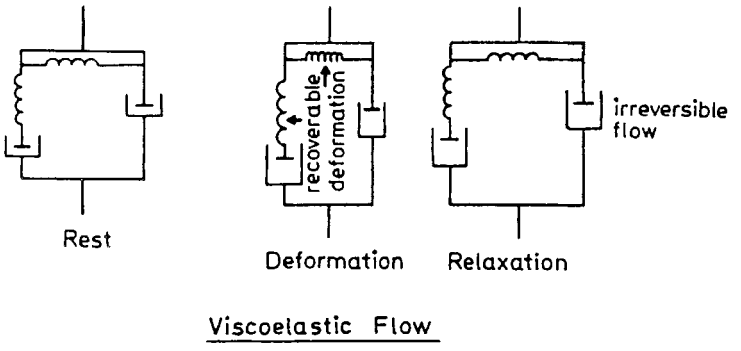
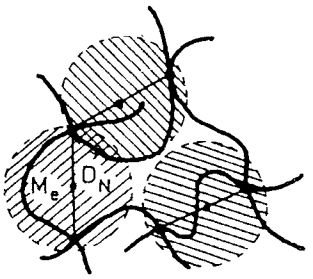


FIG. 3. Rheological model including normal forces.



network condition :

$$D_{coil} > D_N$$

D_N : network spacing

ν : number of entanglements per unit volume

A'(c): degree of coiling of network strand (equivalent network)

FIG. 4. The ideal (equivalent) entanglement network, shown schematically.

from about 200 patients have been published [16]. Therefore, for the purpose of this paper, we selected typical flow curves for each case, and they will be discussed in terms of the entanglement network model.

Healthy Synovia

A typical flow curve is shown in Fig. 5, together with the elasticity curve, namely, a plot of G vs $\dot{\gamma}$. We note a high zero shear viscosity η_0 and a well-pronounced shear thinning. The maximum relaxation time is in the range of 100 seconds, and the crossover shear rate $\dot{\gamma}_{co}$ is around 1. Concerning elasticity, we observe a clear plateau in G in the $\dot{\gamma}$ range between 10^0 and 10^2 s^{-1}. This is also the range in which normal knee movements occur. What we see is a typical flow curve for a highly elastic and viscous entanglement solution with pronounced shear thinning behavior.

Arthrotic Synovia

In arthrotic synoviae we find a characteristic deterioration of the rheological parameters. When η_0 is reduced, the maximum relaxation time is lowered to about 10. $\dot{\gamma}_{co}$ is about 10, which indicates a reduction of the molecular mass. Also, the apparent shear modulus G is reduced and no longer shows a plateau in its dependence on $\dot{\gamma}$. The shear thinning effect is also reduced. All these features indicate a deterioration of the general rheological parameters, in particular of the shear thin-

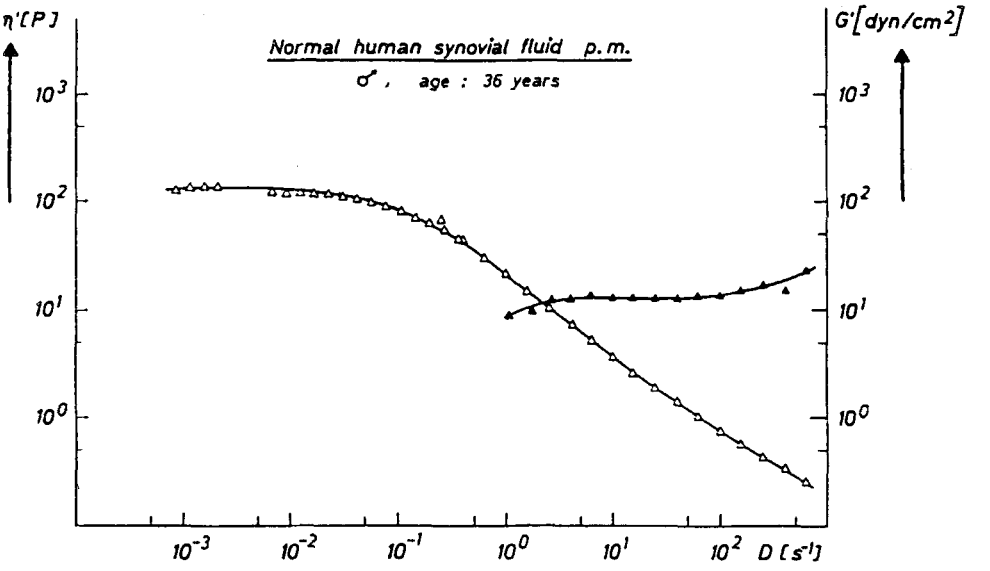


FIG. 5. Flow curve of a normal human synovial fluid.

ning behavior and solution elasticity. Figure 6 shows a comparison between healthy (top) and arthrotic (bottom) synovia; Fig. 7 indicates the ranges in which different synovias are found. Table 1 lists some pertinent rheological parameters for both normal (healthy) and arthrotic synovial fluids.

The structural interpretation of these data is straightforward. In arthrotic synovia, the viscoelasticity is greatly reduced. Therefore, damping as the quotient of dissipated and stored energy is reduced. So is the load-bearing capacity, which depends on the normal force and thus on solution elasticity. Also, the G plateau has disappeared. Obviously, this plateau plays a role in the damping mechanism, since Θ' will decrease within the plateau more slowly than $\dot{\gamma}$ than outside this range. In a few cases we found indications of a yield stress, but only with greatly deteriorated synovia. Yield stress requires the formation of a thoroughgoing percolation network, and this is only possible if short chain fragments are available. Concentration c was not controlled in our studies. In arthritic joints, the total amount of hyaluronan is increased, but c is still lowered due to the increased amount of fluid (effusion).

SUBSTITUTES

Hyaluronic Acid

In Fig. 8 a hyaluronic acid with $M = 4.86 \times 10^6$ is shown. Unfortunately, we have no measurement with a native HA with $M \geq 10^7$. The flow curve of our sample is characteristic for a typical entanglement network and phenomenologically similar to that of a synovia. The maximum relaxation time is, however, much

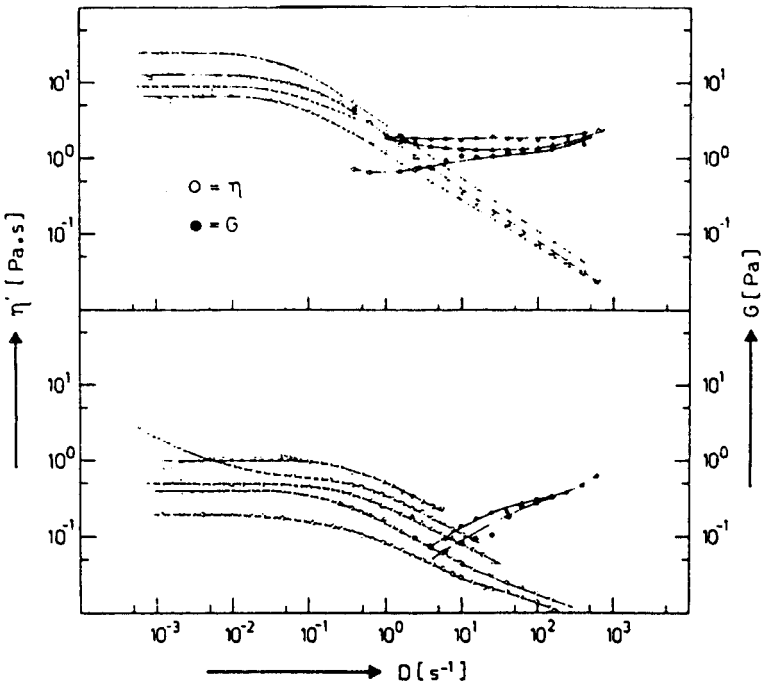


FIG. 6. Comparison of normal (top) and arthrotic (bottom) synovial fluids.

smaller (0.05 second). The HA in this solution represents a rather stiff coil with $A_0 \approx 40$ nm. As all carboxylic groups are dissociated at physiological pH, we actually deal here with hyaluronate molecules.

Guar

In Fig. 9 a flow curve of guar gum in water is shown. We observe the very pronounced flow curve of an entanglement solution. Both zero shear viscosity and maximum relaxation time are high (10 seconds) due to the high concentration of the solution. A_0 is calculated 7 nm, thus the macromolecule is not particularly stiff.

Polyacrylamide

Figure 10 shows a flow curve of polyacrylamide in water. Again we find an entanglement network and a well-pronounced shear thinning flow curve. The maximum relaxation time is again high (10 seconds), but here we have a rather high concentration. The degree of coiling is moderate and similar to guar; we find an A_0 of 7 nm.

Generally speaking, the flow curves of synovia substitutes resemble those of healthy synovia phenomenologically, although with somewhat reduced rheological

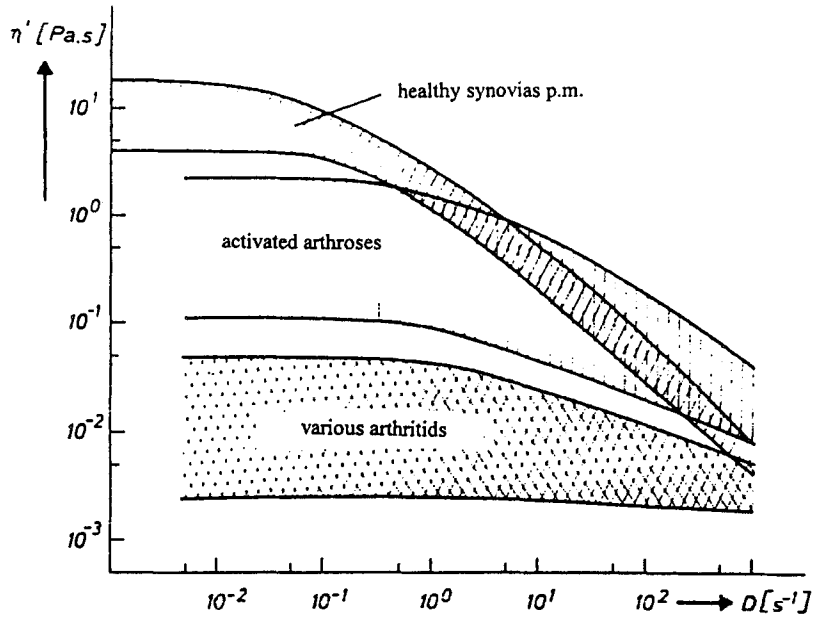


FIG. 7. Viscosity ranges of normal (healthy) and arthrotic synovial fluids.

parameters. Therefore, in order to be used as substitutes, they must be applied in considerably higher concentration. Still, the combination of both viscous and elastic properties does not yet completely match those of synovia. This is due to the fact that healthy synovia represent a solution of a complex, branched macromolecule which exhibits, beside its pronounced viscoelastic properties, a high, nearly gel-like water binding capacity. The substitutes, on the other hand, represent linear macromolecules of a molecular mass lower than that of the native HA backbone by at least one order of magnitude.

TABLE 1. Rheological Parameters for Normal (healthy) and Arthrotic Human Synovial Fluids

Diagnosis	η_0, Pa·s	$\eta_0/\eta_{D=300}$	Θ', seconds	$\Theta' c$, $s \cdot g \cdot cm^{-3}$
Normal	6–12	100	40–100	200–300
Activated, degenerative	0.1–1	5–40	8–20	60–100
Chronic, inflammatory	5×10^{-3}–5×10^{-2}	1–4	0.02–1	0.1–4

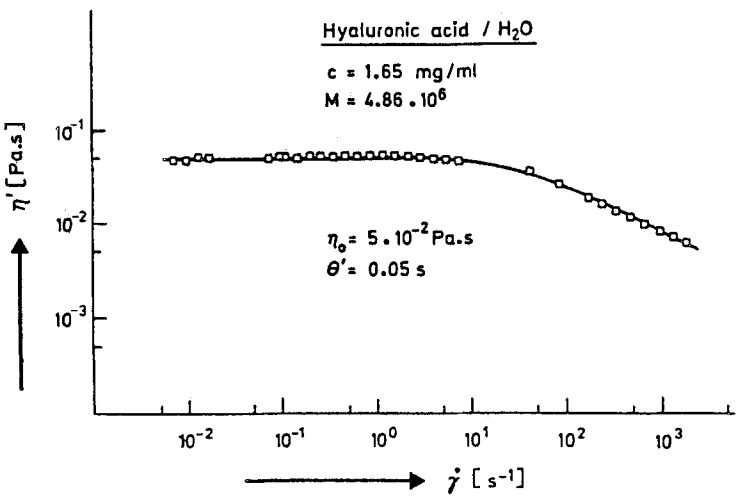


FIG. 8. Flow curve of a hyaluronic acid in water.

INTERPRETATION

The data presented shall now be used to make a comparison in terms of our model of an entanglement network solution. We consider the solution and its structure at rest. The dynamics during flow could be described by a reptation motion, but this is outside our considerations. It must be stressed that we make use of an equivalent model. That is, we calculate parameters for an ideal entanglement network which is equivalent in its measurable parameters to the actual real network. The latter may contain entanglement regions, hampered slippage of the entangle-

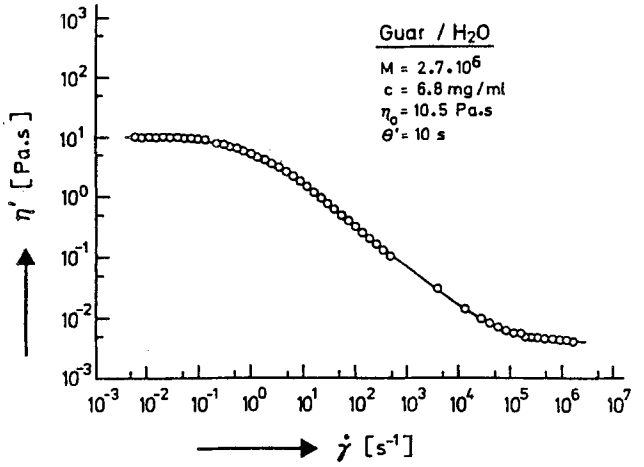


FIG. 9. Flow curve of guar gum in water.

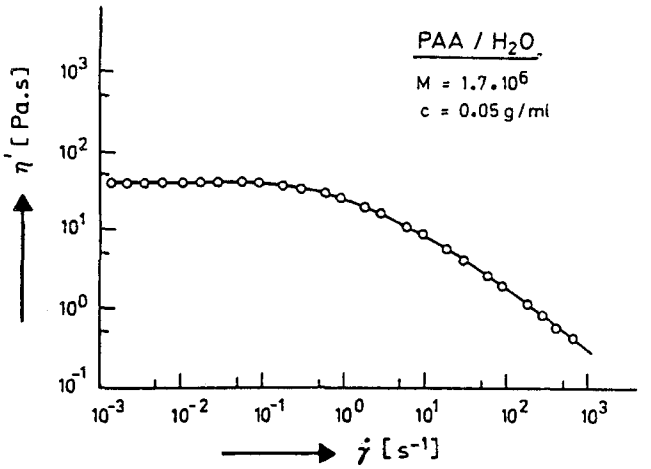


FIG. 10. Flow curve of polyacrylamide (PAA) in water.

ments, and bonding between the network strands. We must also expect, at least in synovia, crosslinks of various strength which will interrupt the reptation.

Our results are compiled in Table 2. We list η_0, $\dot{\gamma}_c$ and its inverse Θ', the mesh size D_N, the number of entanglements per unit volume ν, and the apparent statistical chain element $A'(c)$, which is a measure for the degree of coiling of the network

TABLE 2. Network Parameters for Synovial Fluids and Substituted Polymers

Sample	η_0, Pa·s	$\dot{\gamma}_c$, s^{-1}	Θ', seconds	D_N, nm	ν, m^{-3}	$A'(c)$, nm
Synovia, healthy (human knee joint): c = 2–3 mg/mL	45	10^{-2}	10^2	258	1.11×10^{20}	2.4
Synovia, arthrotic (human knee joint): c = 2–3 mg/mL	0.4	10^{-1}	10	580	1×10^{19}	1.07
Hyaluronic acid/H_2O (human umbilical cord): $M = 4.86 \times 10^6$ c = 1.45 mg/mL	5×10^{-2}	20	0.05	197	2.5×10^{20}	4.2
Guar/H_2O: $M = 2.7 \times 10^6$ c = 6.8 mg/mL	10.5	10^{-1}	10	195	2.6×10^{20}	1.12
PAA/H_2O: $M = 1.7 \times 10^6$ c = 50 mg/mL	40	10^{-1}	10	125	9.8×10^{20}	1.43

strand between entanglements and, of course, will depend on the concentration. For healthy synovia we note a rather high η_0, a high Θ', and both D_N and ν in the expected range. $A'(c)$ is rather low, which indicates a tight network with strongly coiled strands. Of course, as we deal here with a branched and perhaps even cross-linked network, such a small value of $A'(c)$ is to be expected. So these data confirm the view that healthy synovia represent a tight network of a gel-like type which exhibits high elasticity, high shear thinning, and high water uptake. The arthrotic synovia shows an η_0 lower by two orders of magnitude, and therefore also a reduced Θ'. D_N is now larger, which means that the network is partly disrupted. This is also seen in the greatly reduced number of entanglements. $A'(c)$ is also reduced, which indicates either less coiling or reduced mutual penetration of the network strands. Probably the latter effect will take place since the mesh width D_N is increased. Hyaluronic acid has again a reduced η_0 and also strongly reduced Θ'. The mesh width D_N is also reduced, while the number of entanglements is significantly enhanced. $A'(c)$ is also enhanced. This indicates a stiffer macromolecule. Due to its rather free penetration it must lead to the observed high ν value. So, the hyaluronic acid as such behaves as a much stiffer molecule than the backbone-HA in synovia. Still, the value of $A'(c)$ is considerably smaller than A_0 for the diluted solution (40 nm). As we expect here a network with free penetration, we regard this as an indication of the greater number of entanglements in the network. The guar solution has a slightly higher concentration than the previous ones; therefore we observe a relatively high η_0 and also a high Θ'. D_N resembles that of HA, and so does ν. The chain element $A'(c)$ is significantly lower, which indicates a stronger coiling of the macromolecule between entanglements. This is also seen from the A_0 value, which is 9 nm. So we deal here with a rather tight network with a high maximum relaxation time. Polyacrylamide (PAA) was measured in high concentration. Therefore we observe a very high η_0; it is of approximately the same size as with healthy synovia in spite of the latter's 20-fold lower concentration. Accordingly, we also observe a high Θ'. On the other hand, D_N is low and ν is high. $A'(c)$ is rather low, indicating a rather strongly coiled molecule with $A_0 = 7$ nm. The high η_0 and Θ' are here a consequence of the high concentration.

CONCLUSION

Both synovial fluids, hyaluronate, and substitute solutions are of the entanglement network type with dynamic entanglements. However, hyaluronate represents in water solution an "unusual stiff molecule," as it is described in the literature [13]. This is probably caused by stiffening hydrogen bridges along the chain and leads to the high value of the statistical chain element A_0 in the intrinsic viscosity range. Figures around 40 nm are reported in the literature [13]. However, the conformation of this molecule appears rather sensitive to the ionic environment and can be easily altered by addition of salts. So, in synovial fluids the hyaluronate backbone leads to a network with a relatively high mesh width of 258 nm, which explains its high water-carrying capacity. Synovia solutions have high viscosity and high solution elasticity; the latter parameter is more important. The high elasticity is brought about by the relatively long flexible network strands. It is certainly favored by the branched structure of the solute (cf. Fig. 2). The very high molecular mass of the

hyaluronate backbone in healthy synovia ($\approx 10^7$) appears of paramount importance, and every reduction will lead to a deterioration of the performance of the synovial fluid. The striking reduction of the rheological parameters in case of arthrotic states is well suited to explain the failure of the mechanical performance of such pathological synovias. The experiments with synovia substitutes show that at least some of the rheological parameters can be matched with those of healthy synovias, although an enhancement of concentration is required. But the network parameters D_N, ν, and $A'(c)$ teach us that the solution structure is still somewhat different. Therefore, substitute solutions consisting of linear polymers are not completely satisfactory from a rheological point of view. We would probably need polymers of higher molecular mass, and possibly branched ones. Such materials are expected to yield high viscosity and high solution elasticity at reasonably moderate concentrations.

Our data still require extension. We would need flow elasticity curves of a hyaluronate with $M \approx 10^7$, and we would need more data on high molecular mass water-soluble polymers; not only linear, but also branched ones. However, there is certainly hope that it will be possible to tailor substitute solutions which can mimic healthy synovia to a high degree not only in its rheological parameters but also in its network data. Such substitutes could guarantee the proper rheological functioning of joints in pathological cases and so allow the joint to recover by preventing excessive straining and wear in case of arthrotic states.

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