# Brownian Motion and Electrophoretic Transport in Agarose Gels Studied by Epifluorescence Microscopy and Single Particle Tracking Analysis

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The motion of fluorescent latex beads and circular DNA in agarose gels is investigated by epifluorescence computer-enhanced microscopy. The individual trajectories are obtained and the diffusion dynamics are determined by averaging over an ensemble of trajectories. It was found that the diffusion of latex beads in agarose gels is characterized by the scaling relation $(\Delta x - \overline{\Delta x})^2 \sim t^{2/d_W}$ with $d_W = 3.1 \pm 0.3$, in the gel concentration range 0.6%−1.2%. This indicates that the structure of the holes in agarose gels is fractal on the scale from 0.2 to 15 $\mu$m that has been studied and different from those of percolating clusters. If an electric field is applied, $d_W$ measured in the direction of the field decreases and can even reach values lower than 2; this means that the diffusion increases at long time. The mobility vs gel concentration graph is found to be well fitted with a polynomial expression in agreement with recent computer calculations. Finally our preliminary results on DNA show that the motion of M13 circular DNA molecules is governed by the same dependencies as those of the latex particles.

## 1. Introduction

The Ogston−Morris−Rodbard−Chrambach model (OMRCH)[1−3] of gel electrophoresis is currently used for describing the transport of particles, proteins, and small DNA molecules in agarose or polyacrylamide gels. Nevertheless some studies prove that the basic assumptions of OMRCH are unrealistic. The main problem is that the electric field creates an anisotropy of the system causing a difference in the longitudinal and transverse diffusion coefficients of migrating particles as well as in the probability of site occupation.[4] A second source of uncertainties is the gel structure. Several studies[5−8] prove that some aggregates in agarose gels always are present, which violates the assumption that the density of the fibers is uniform at least on the scale of the aggregates. In this case, a fractal description of the pores should be more realistic. As demonstrated by Saxton[9,10] obstacles with a fractal geometry[11] are much more effective for trapping the particles inside the pores than obstacles with a homogeneous random distribution. However no sufficient proof that the agarose structure is fractal could be found in the literature. Electron microscopy of agarose gels[7] gives some pictures very similar to those of fractal aggregates.[12,13] We have treated these pictures by the box method[12,13] and have found that the mass scales roughly as predicted by the diffusion-limited cluster−cluster aggregation (DLCA) model[14] (Figure 1). However the statistics are bad and we could not use enough data to draw a final conclusion about the gel structure.

Despite of the existence of theoretical and computer simulation results,[1−4] an experimental study of diffusion (biased and not biased) of particles in gels seemed to be likely in order to give additional clearness on this topic. The longitudinal diffusion coefficient is related to the band broadening, which seems to be a key stone for further improvements of zone gel electrophoresis.

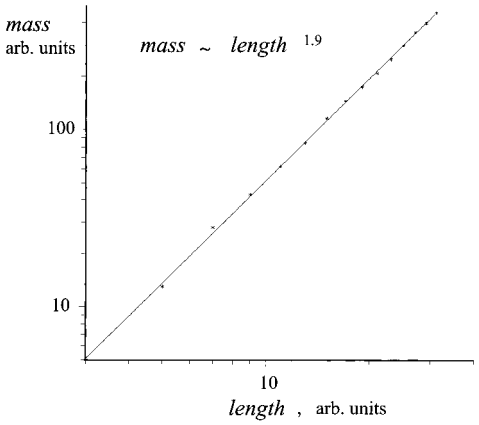


**Figure 1.** log−log plot of mass vs size dependence, obtained from Figure 2c of ref 7.

A video-microscopy investigation of diffusion and biased diffusion of fluorescent latex beads and circular DNA in agarose gels is reported in this paper. The microscopy observation of Brownian motion was first used by Perrin[15] for studying the diffusion process in fluids. At present this method is strongly developed due to the digital image processing techniques and to enhanced computer power. It was successfully applied for investigation of concentrated suspensions,[16] in membranes[17,18] and in liquid−gas interfaces.[19,20] Fluorescence microscopy has been applied for investigation of dynamics of large DNA molecules in gels[21,23] and polymer solutions,[24] in the presence of an electric field. However, no quantitative determination of the diffusion coefficients is reported. Video phase-contrast light microscopy is used by Griess and Serwer[25] to observe the motion

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of individual latex spheres in agarose gels, but again without quantitative determination of the diffusion coefficients and mobility.

## 2. Theoretical Background

The random walk diffusion on an Euclidean lattice or on a lattice containing isolated random distributed obstacles of concentration $p$ is described by the classical Fick's law

$$\overline{r^2(t)} = 6Dt \tag{1}$$

where $\overline{r^2(t)}$ is the mean square displacement of the diffuser during time $t$ and $D$ is the diffusion coefficient.

The electrophoretic transport adds one more term to eq 1; thus

$$\overline{r^2(t)} = 6Dt + B^2t^2 \tag{2}$$

where $B$ is the mean drift velocity.

Equation 1 can be generalized for the case of a random walk process on fractals[26−28]

$$\overline{r^2(t)} = \sim t^{2/d_W} \tag{3}$$

where $d_W$ is defined as the fractal dimension of the walk. In general we have $d_W > 2$ since the diffuser could be temporarily trapped in some isolated branches of the fractal, leading to "*dead ends*". In this case a diffusion coefficient depending on distance[29,30] can be defined by

$$D(r) = \overline{dr^2(t)}/dt \tag{4}$$

The diffusion dynamics obtained in this work will be compared with the results obtained from percolation theory since this theory is frequently used for describing the properties of gels. In our case the diffuser moves in the empty spaces between the gel fibers; this is why percolation is less probable in high gel concentrations (note that the percolation threshold in the case of diffusion of particles of finite size depends on both concentration of obstacles and size of particles). We suppose that in low gel concentrations the particles are free to cross the sample and interact on their way with some isolated obstacles. According to the literature, the dynamics must be described, in this case, by eqs 1 and 2.[26−30] Near the percolation concentration ($p_c$), the holes of the gel look as an infinite fractal for the particles, and eq 1 must be replaced by eq 3. Let us mention here that the percolation of holes and obstacles is not necessarily simultaneous. However it can be the case in a three-dimensional lattice. If the concentration of the obstacles is $p \gg p_c$ then, for long times, the distance-depending diffusion coefficient goes to 0 thus reflecting the fact that the diffusing particles are enclosed inside a certain volume and cannot move at a large scale.

The presence of an electric field complicates even more the situation. As shown by Slater and Guo,[4] an electric field creates an anisotropy in the system, causing a difference in the longitudinal and transverse diffusion coefficients of migration particles. This conclusion was given for a regular lattice of obstacles but should also be valid in a random network of connected obstacles. However in this case it is possible that the exponent $d_W$ also depends on the field. The case of biased diffusion on randomly grown percolating clusters was studied by Pandey[31] by computer simulations. It was found that in the case of a concentration of obstacles below the percolation threshold, the exponent depends in a nontrivial way on the bias. Furthermore, on increasing the bias, the exponent approaches its asymptotic value 1 faster, and this up to a characteristic value of the bias beyond which the approach to the asymptotic value becomes again slower. Unfortunately, in this work, the contributions of the Brownian motion and the drift of $\overline{r^2}$ are not separated. To separate the contributions of the bias, we have defined a Cartesian coordinate system in which the $x$ direction coincides with the direction of the electric field. We consider the displacements on $x$ and $y$ axes as random distributed quantities which are characterized by its first and second moment. The first moment $\overline{\Delta x}$, (or $\overline{\Delta y}$) characterizes the drift of the particles, while the second moment $\overline{(\Delta x - \overline{\Delta x})^2}$ (or $\overline{\Delta y - \overline{\Delta y})^2}$) behaves as in a pure diffusion process.[20]

Thus eqs 1−4 can be rewritten as

$$\overline{\Delta x} = B_x t \tag{5}$$

$$\overline{(\Delta x - \overline{\Delta x})^2} \sim t^{2/d_W} \tag{6}$$

$$D_x = \frac{\overline{\mathrm{d}(\Delta x - \overline{\Delta x})^2}}{\mathrm{d}t} \tag{7}$$

The equations for $y$ are similar to (5), (6), and (7).

## 3. Materials and Methods

**(a) Materials and Sample Preparation.** The agarose (Biorad Ultra Pure DNA Grade) solutions were prepared by dissolution in 0.5×TBE at 100 °C. The obtained agarose stock solution was cooled down to 60 °C and then loaded with the 0.1 $\mu$m fluorescent latex microspheres according to the following procedure: the microspheres (Molecular Probes, yellow-green size kit) 2% stock solution was first diluted in pure water 1:200 and bath sonicated for 1 min; this solution of the latex microspheres was then diluted 100−250 times in the agarose stock solution in order to obtain a final concentration which was 1:20000 to 1:50000 the value of the initial concentration of the latex microspheres.

**(b) Apparatus.** The electrophoretic cell was developed by Rampino.[23] A 10 $\mu$L aliquot of the agarose solution containing microspheres was deposited on a microscope coverslip 22 × 40 mm (Clay Adams) with a pipet and then covered with another coverslip 22 × 22 mm (both slips were preheated at 60 °C). The sandwich was cooled and placed as a bridge between two agarose gel blocks in the cell. The field strength was measured by introducing two electrodes in the glass cell. The temperature of the sandwich is also measured during the electrophoresis by a contact thermometer. It was found that the temperature increases of about 0.5 °C during the first 15 s and after that remains constant. Therefore all measurements with applied electric field are performed after 15 s of pre-electrophoresis. We suppose that this temperature rise could increase the measured diffusion coefficients by several percent, but this increase could not be seen in the limit of the standard error of the experiment that was about 10−30%. Therefore it does not affect our conclusions.

**(c) Microscopy and Image Analysis.** Our observations have been performed using an Olympus BH-2 epifluorescence microscope equipped with a 100× Olympus oil-immersion objective, a Hamamatsu C2400-97 system consisting of an single electronic intensifier, and B/W CCD camera (Model XC-77). The $x$ axis of the camera was aligned with the field direction. The video signal was digitized with a Scorpion 16G frame grabber board (Univision) giving maximal resolution of 512 × 512 pixels and 256 gray shade levels and processed by a PC microcomputer (Compaq) with 20 MB RAM and a 33 MHz CPU. The final resolution of the equipment was 0.2 $\mu$m/pixel.

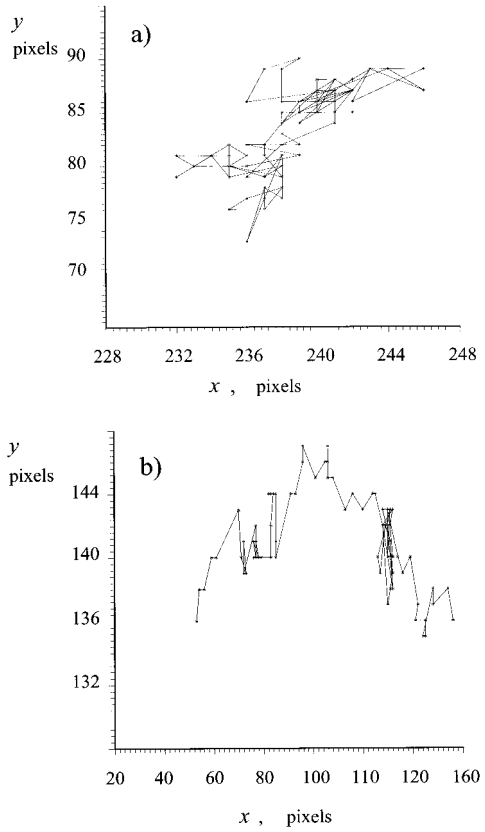


**Figure 2.** Typical trajectory of latex particles of size 0.1 $\mu$m in 0.8% agarose gel, without electric field (a) and with 10 V/cm electric field (b). The field is parallel to the $x$ axis.

The transfer and analysis of the images were performed by using the MoMo (windows application) software, especially written for this project. The transfer could be done both to the RAM and HD in frames of selective size (512 × 512, 256 × 256, or 128 × 128) The maximal grabbing speed was up to 12 images/s in real-time mode. The software gives the possibility to determine trajectories of particles by using a single particle tracking algorithm, as well as to edit, plot, analyze, and report the obtained data. Autotracking with a maximum of 20 objects per image is available. The first moment of the optical intensity is used for tracking the particle's coordinates, as described in ref 20. Each $x,y$ set (trajectory) obtained from the tracking is further analyzed in order to determine the mean displacement $\overline{\Delta x}$ and the mean square displacement $\overline{(\Delta x - \overline{\Delta x})^2}$ of the particles for a given time $\Delta t$.[20] The values of $\overline{\Delta x}$ and $\overline{(\Delta x - \overline{\Delta x})^2}$ obtained for each individual trajectory are plotted vs $\Delta t$. The slope of $\overline{\Delta x}/\Delta t$ plots divided by the electric field strength gives the mobility of the particles (eq 5). A power fit of $\overline{(\Delta x - \overline{\Delta x})^2}$ vs $\Delta t$ was performed in order to find the exponent $d_{W,x}$ according to eq 6. The diffusion coefficient $D_x$ was determined from the initial slope of the $\overline{(\Delta x - \overline{\Delta x})^2}/\Delta t$ plots (eq 7). The transverse diffusion coefficients $D_y$ was determined in the same way from the set of $y$ coordinates of the particles. The coefficients obtained from more than 30 different trajectories, each of them represented by about 100 $x,y$ positions, are averaged for each gel concentration and each field strength in order to minimize the standard deviation of the data. The described analysis of the data has the advantage of giving complete information from each single trajectory, but in some cases the correlation of the data could be significant. That is why it is necessary that the trajectories are as long as possible and sufficient for good statistics.

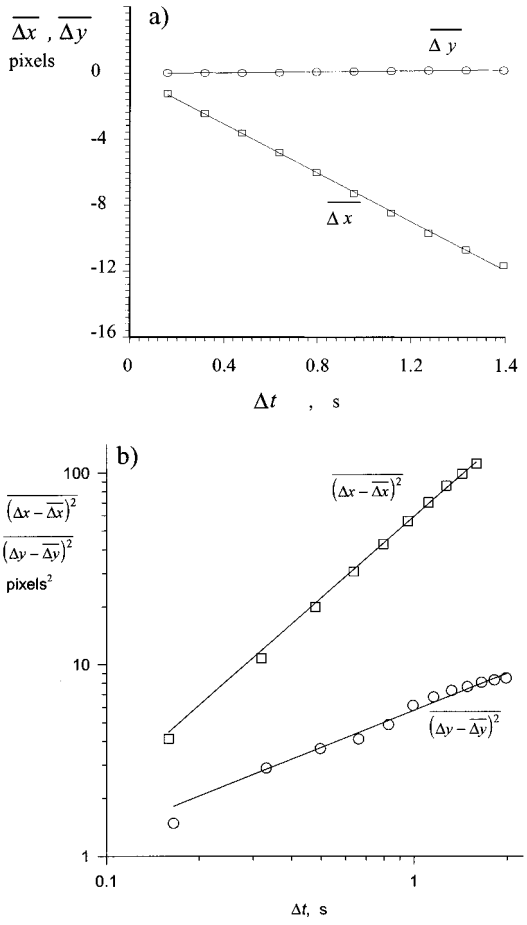


**Figure 3.** (a) Typical plots of $\overline{\Delta x}$ and $\overline{\Delta y}$ vs $\Delta t$ with 10 V/cm electric field (the field is in the $x$ direction). The lines are the best linear fit of the data. (b) Typical plots of $\overline{(\Delta x - \overline{\Delta x})^2}$ vs $\Delta t$ with 10 V/cm electric field and $\overline{(\Delta y - \overline{\Delta y})^2}$ without electric field. The lines are the best power fit of the data.

## 4. Results and Discussion

We observe that the beads of size 0.1 $\mu$m undergo large scale Brownian motion in 0.6%−1.2% agarose gels. A similar behavior is observed with M13 DNA in 0.8% agarose gel. When an electric field is applied, they move in the direction of the field (with fluctuations) as long as the field is present. Typical trajectories in these cases are shown in Figure 2. In contrast, in a 1.4% gel, most of the particles vibrate inside a small area, as if each of them would be enclosed inside a pore. Several beads were completely immobilized.

A more detailed study of diffusion dynamics and mobility of 0.1 $\mu$m particles in 0.6%, 0.8%, 1.0%, 1.2% and 1.4% gels has been done. In the absence of an electric field, we found that $\overline{\Delta x}$ and $\overline{\Delta y}$ are indistinguishable from 0, as expected. In the presence of an electric field $\overline{\Delta x}$ is found to be a linear function of $\Delta t$ while $\overline{\Delta y}$ is not changed (Figure 3a). Typical plots of $\overline{(\Delta x - \overline{\Delta x})^2}$ vs $\Delta t$ with electric field (10 V/cm) and $\overline{(\Delta y - \overline{\Delta y})^2}$ without field is shown in Figure 3b. It can be seen that without field the dependence of mean square displacements on $y$ (the data in the $x$ direction without field are indistinguishable) grows less than linearly with time, in agreement with reports in the literature for Brownian motion on fractals.[27,28] In contrast to the zero field conditions in the presence of electric field this growth is stronger than linear. Therefore for long times the particles are spread in the $x$ direction much more than in the nonbiased Brownian motion or in the biased Brownian motion on regular lattices. Similar behavior (called superdif-

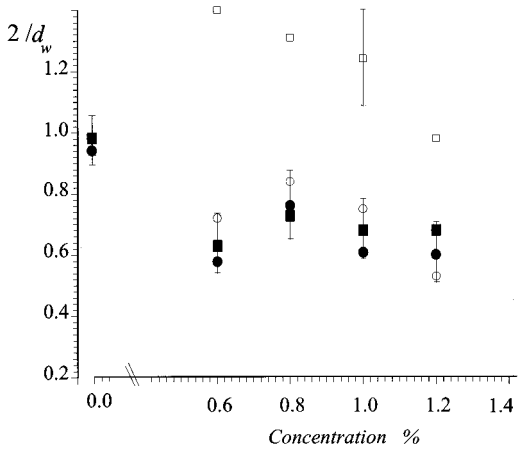


**Figure 4.** Exponent $2/d_W$ vs the gel concentration. The dispersion of the data is given with error bars: □ in *x* and ○ in *y* direction, with a 10 V/cm electric field; ■ in *x* and ● in *y* direction, without an electric field.

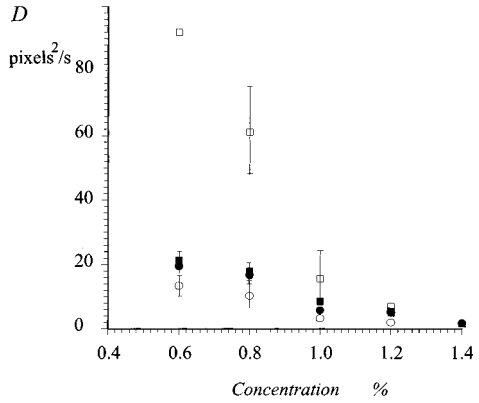


**Figure 5.** Diffusion coefficients *D* vs gel concentration. The dispersion of the data is given with error bars: □ in *x* and ○ in *y* direction with a 10 V/cm electric field; ■ in *x* and ● in *y* direction, without an electric field.

fusion) has been observed in hydrodynamic dispersion in random media.[32] In a 1.4% gel an asymptotic value is reached in the plots of mean square displacements vs *t* for long times. This means that the particles are trapped inside a certain area. Therefore the particles could not percolate in the gel.

In Figure 4 the exponents $2/d_W$ are plotted vs the gel concentration. It can be seen that in absence of field, $2/d_W$ does not depend on the gel concentration within the error limits of the experiment. This behavior means that the particles move in a fractal network, the structure of which is independent of the gel concentration. By averaging the data for all gel concentrations, we find $d_W = 3.1 \pm 0.3$. For Brownian motion on a percolating cluster, the value $d_W = 5.0 \pm 0.2$[33] has been found when averaging over all possible clusters and $d_W = 3.64 \pm 0.05$ when averaging over the clusters larger than the scale of the motion.[27,28] In a recent publication, Barta and Dieska[34] obtained $d_W = 4.21 \pm 0.03$. Regardless of the large scattering, the $d_W$ data found in the literature are larger than those obtained by us. Taking also into account that our value is independent of the gel concentration, we can conclude that the gel holes have a fractal structure in the micrometer scale (the scale studied by us was from 0.2 to 15 $\mu$m). This structure is different from that of a percolation cluster at $p_c$. The $d_W$ obtained by us must have some universal properties, reflecting only the structure of the gel. It is probable that a cluster−cluster aggregation model is suitable for describing the structure of the gel, as already mentioned by Slater and Wu.[35] This suggestion is also confirmed by Figure 1, since we showed that the fractal dimension of the agarose mass distribution is roughly 1.9, *i.e.*, closer to the value predicted by the DLCA model 1.78, while the fractal dimension of a percolated cluster is 2.53.[14]

In the presence of an electric field (10 V/cm), the exponent $2/d_W$ is larger and decreases slowly when the gel concentration is increased (Figure 4). A large number of simulation investigations concerning biased diffusion in disordered media have been reported,[27,28] but unfortunately these results are not directly comparable with our measurements because the authors deal with the root mean square displacement (*R*). Several investigations show a logarithmic time dependence of *R*.[28] Pandey found $R \sim t^{k_e}$ with a time dependent exponent $k_e$.[31] When *t* is very small, diffusion dominates, and when *t* is large, drift dominates (see also eq 2). However, in our measurements, the statistics are poorer and the time scale does not vary as much as that in computer simulations. This is why we cannot find any peculiarity in the time behavior of *R*. In our measurements we found a nearly linear dependence of *R* on time, what simply states that we are in the drift-dominated regime. Working with $\overline{(\Delta x - \overline{\Delta x})^2}$ instead of *R* gives us the possibility to separate the motion due to the diffusion from the one due to the drift. We explain the large decrease of $d_W$ in the field-biased measurements with an additional randomization induced by the field. The particles spend more time in the traps because they are pushed into dead ends by the electric field, but they move faster once they come out of the traps. A suitable picture for the process is that the field creates long-range hops in the space. In a regular lattice this effect gives an increase of the diffusion constants, as found by Slater and Guo,[4] but in fractal media this effect can give $d_W < 2$. The obtained scaling is important from a practical point of view, because it means that the diffusion constant is time dependent and, in the case of $d_W < 2$ , increases for long times giving fuzzy bands. It is likely that an alternating field could help the particles to go out of the traps and in this way reduce the obtained effect of randomization.[25]

The diffusion coefficients calculated from the first slope of $\overline{(\Delta x - \overline{\Delta x})^2}/\Delta t$ are plotted in Figure 5 vs the gel concentration. To be comparable, all diffusion coefficients are calculated in the same time range. We obtain that, in absence of field, $D_x$ and $D_y$ are equal in the limit of reproducibility while, in presence of field, $D_x$ is several times larger than $D_y$. This result supports those obtained in ref 4; however the differences are several times larger than those found in ref 4. This is also due to the nonuniform structure of the gel. Actually, on a fractal medium, the differences between $D_x$ and $D_y$ are time dependent, which can easily be understood from eqs 6 and 7. In the short time scale, $D_x \ll D_y$ while in a long time scale, $D_x \gg D_y$ since for $\Delta t \to 0$, the slope $\overline{(\Delta x - \overline{\Delta x})^2}/t$ goes to infinity if $2/d_W < 1$ and to 0 if $2/d_W > 1$.

In a recent study, Slater and Guo report exact calculations of electrophoretic mobility of particles in different types of gels in two dimensions.[36] It was obtained that the plots of mobility vs gel concentration are better fitted with polynomial than with exponential dependencies (the latter called a Ferguson plot). The exponential fit is predicted by the OMRCH model. The autors point out that the OMRCH model is only a mean-field approximation in which it is assumed that the gel is uniform and structureless. The coefficients in the polynomial expansion obtained by Slater and Guo are related to the structure of the gel. It was pointed out that the mobility could be changed and the separation enhanced for a given particle size by changing the gel structure. The fractal structure of the gel, demonstrated by us, is important from this point of view because it is shows clearly that the OMRCH model is not adequate to describe the electrophoresis in agarose gels. The reduced mobilities (mobil-

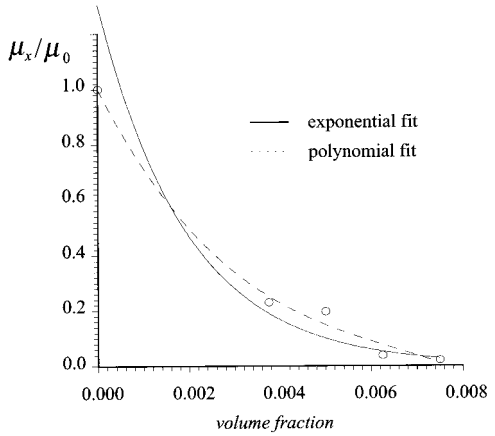


**Figure 6.** Reduced mobility $\mu_x/\mu_0$ vs gel concentration. The gel concentration is given here in volume fraction, supposing that the density of agarose in the gels is 1.6 g/cm$^3$.

ity divided on the mobility in solution) measured by us are plotted in Figure 6. The mobility in solution was measured with a MALVERN Z SIZER 3 apparatus. Qualitatively we can conclude that a polynomial fit of third degree (shown by a dashed line) gives a better result than an exponential one (shown by a solid line). However our results cannot be quantitatively compared to those of Slater and Guo, to some extent because our data are largely spread out, but principally because the calculations presented in ref 36 are for two-dimensional non-fractal gels instead of three-dimensional fractal ones.

A single measurement was also performed with a circular DNA-M13 in a 0.8% agarose gel. Since this DNA is relatively large (gyration radii $\cong$ 200 nm), it is probable that the mechanism of migration in the gel is different from that of particles. Nevertheless we found that the dynamics of migration are quite similar to those of particles. In particular, we found that $2/d_W$ is $0.56 \pm 0.1$ without electric field and $1.09 \pm 0.14$ with electric field. The diffusion coefficient also increases about three times in presence of electric field. The DNA experiment suggests that the transport properties in gels are more influenced by the gel structure than by the nature of diffusing object, in contrast to the generally accepted opinion. However to verify this assumption, more experiments whith different gel concentrations and DNA lengths must be performed.

The behavior of particles in gels obtained by us is consistent with that observed on fractal networks. It is important to point out that the obtained relations are not necessarily valid over distances significantly different from those observed. Our investigation is limited from the resolution of the equipment and the times that the particles stay in focus. At a larger (or shorter) scale the gel could look like a homogeneous network for the migrating particles, thus eqs 1 and 2 are fulfilled. That is, the regime we observed could be characterized as "transient". However the transport properties on large distances can be strongly influenced by that of the "transient" regime. They can be calculated if the size of the fractal clusters is known.[28]

## Conclusions

Our experimental study demonstrates that the motion of latex beads in agarose gels on a micrometric scale is not described by the classical Fick's law, in contrast to the motion in homogenous networks. This could be explained by assuming that the agarose gel has a fractal structure on the scale studied. We found that the Brownian motion in this case is characterized with a scaling exponent $d_W = 3.1 \pm 0.3$ that is independent of the gel concentration. We conclude that the structure of the gel holes is different from that of percolating clusters. If an electric field is applied, $d_W$ measured in the direction of the field decreases and can even reach values lower than 2; this means that the diffusion increases at long time. The mobility vs gel concentration is found to be well fitted with a polynomial expansion, in agreement with recent computer calculations.[36] Finally our preliminary results on DNA show that the motion of M13 circular DNA molecules is governed by the same dependencies as the latex particles.

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