

DESCRIPTION

Title of Invention: CAPILLARY ARRAY

Technical Field

[0001]

The present disclosure relates to a capillary array.

Background Art

[0002]

A capillary array electrophoresis apparatus is widely used which includes a plurality of quartz glass capillaries filled with an electrolyte solution or an electrophoresis separation medium such as an electrolyte solution containing a polymer gel or a polymer and which performs electrophoretic analysis in parallel. Compared to the conventional capillary electrophoresis apparatuses using one capillary, the capillary array electrophoresis apparatus can not only improve the analysis throughput, but also can reduce the analysis cost per sample. The most widely used capillary array electrophoresis apparatuses are the 3500 Series Genetic Analyzer and the 3730 Series Genetic Analyzer commercially available from Thermo Fisher Scientific Inc. In the 3500 Series Genetic Analyzer, electrophoretic analysis can be performed in parallel in 8 or 24 capillaries, and in the 3730 Series Genetic Analyzer, electrophoretic analysis

can be performed in parallel in 48 or 96 capillaries. In any case, laser irradiation portions of the plurality of capillaries (portions irradiated with the laser in the capillary array) are arranged on the same plane in a state where the polyimide coating is removed. This same plane is referred to as an array plane. The array of the plurality of capillaries is referred to as a capillary array. When the capillary array is composed of N capillaries, the capillary numbers 1 to N are assigned to each capillary in order of arrangement from the end. During the electrophoresis, the plurality of capillaries are simultaneously irradiated with a laser beam by introducing the laser beam from the side of the array plane, thus inducing fluorescence to be emitted from each capillary, and the emitted fluorescence is spectrally dispersed and detected at the same time. The method of simultaneously irradiating a plurality of capillaries with a laser beam which is incident from the side of the array plane is referred to as a multifocus method. The method is described in detail in PTL 1. In the multifocus method, each capillary acts as a convex lens. The laser beam is repeatedly condensed along the array plane and is advanced through the capillary array, whereby the plurality of capillaries can be simultaneously irradiated. As a result, the same number of samples as the number of the capillaries can be subjected to DNA sequencing or DNA

fragment analysis in parallel. As described in PTL 1, regarding the laser irradiation portions of a plurality of capillaries, in a case where the outer radius of the capillary is defined as R (the outer diameter is $2R$), the inner radius is defined as r (the inner diameter is $2r$), the refractive index of the capillary material is defined as n_2 , the refractive index of a medium outside the capillaries is defined as n_1 , the refractive index of a medium inside the capillaries (separation medium) is defined as n_3 , the distance between an incident position of a laser beam and an array plane is defined as x ($\leq r$), and when setting to $x = r/2$, the refraction angle when the laser beam is transmitted through one capillary is expressed by the following Formula (1).

[0003]

[Mathematical Formula 1]

$$\Delta\theta = 2 \cdot \left\{ -\sin^{-1}\left(\frac{r}{2 \cdot R}\right) + \sin^{-1}\left(\frac{r \cdot n_1}{2 \cdot R \cdot n_2}\right) - \sin^{-1}\left(\frac{n_1}{2 \cdot n_2}\right) + \sin^{-1}\left(\frac{n_1}{2 \cdot n_3}\right) \right\} \quad \dots (1)$$

[0004]

The refraction angle is expressed by the above. Each capillary acts as a concave lens when $\Delta\theta > 0$ is satisfied and a convex lens when $\Delta\theta < 0$ is satisfied. By setting the conditions to satisfy $\Delta\theta < 0$, multifocus functions, and it becomes possible to simultaneously irradiate the plurality of capillaries with the laser beam. On the other hand, when

the conditions satisfy $\Delta\theta > 0$, the multifocus does not function, and the laser beam diffuses from the array plane. Therefore, the simultaneous irradiation of the plurality of capillaries with the laser beam becomes impossible. The material of the capillary is generally quartz glass, and the refractive index thereof is fixed at $n_2 = 1.46$. It is understood from Formula (1) that the smaller n_1 and the larger n_3 are, the stronger the convex lens effect of each capillary is (the concave lens effect is weakened). On the other hand, the larger n_1 and the smaller n_3 are, the stronger the concave lens effect of each capillary is.

[0005]

Even in a case where the multifocus functions, the strength of the laser beam is attenuated as it advances through the capillary array because of the loss of the laser beam due to reflection at the interface between the medium outside the capillary and the capillary and at the interface between the medium inside the capillary and the capillary, and the obtained fluorescence intensity is also attenuated accordingly. In a case where the fluorescence intensities greatly vary between the capillaries, a plurality of samples cannot be analyzed under equivalent conditions, which is disadvantageous. (Meanwhile, although the fluorescence intensity is regarded as being representative of a signal intensity in the embodiment described later, signal

intensities other than the fluorescence intensity, for example, scattering intensity and light absorbance, may also be used) Therefore, in the 3500 Series Genetic Analyzer and the 3730 Series Genetic Analyzer, a laser beam oscillating from one laser source is split into two. The two laser beams are incident from both sides of the array plane, thus allowing the multifocus to function for each. In this manner, the sum of the intensity of the laser beam incident from one side of the array plane and the intensity of the laser beam incident from the other side of the array plane is allowed to be uniform. A configuration in which the laser beam is incident from only one side of the array plane is referred to as single-side irradiation. A configuration in which the laser beams are incident from both sides of the array plane is referred to as double-side irradiation. Whether the multifocus functions or not is common to both the single-side irradiation and the double-side irradiation. When the capillary array includes N capillaries, in the case of the single-side irradiation, the capillary number n of the capillary at the end on which the laser beam is incident is set to $n = 1$. The capillary number n of the capillary at the end from which the laser beam exits is set to $n = N$. In the case of the double-side irradiation, the capillary number n of the capillary at one end is set to $n = 1$. The capillary number of the capillary at the opposite end is set to $n = N$.

[0006]

Among the irradiation intensities and the fluorescence intensities of the plurality of capillaries in the same capillary array, it is preferable to set the lowest irradiation intensity and the fluorescence intensity to as large value as possible. It has been empirically found that, assuming to be 1 the fluorescence intensity expected when the laser beam oscillating from the laser source irradiates at full intensity the inside of one capillary, sensitivity that is suitable for practical use is obtained if the minimum value (MIN) of the fluorescence intensity satisfies $\text{MIN} \geq 0.2$. In addition, it is preferable that variation in the irradiation intensities and the fluorescence intensities is small among the plurality of capillaries in the same capillary array. It has been empirically found that, in a case where the coefficient of variation (CV) for the fluorescence intensity satisfies $\text{CV} \leq 20\%$, or $\text{CV} \leq 15\%$ depending on the situation, different samples can be analyzed under equivalent conditions. These are referred to as practical performance of the capillary array electrophoresis apparatus. In the present disclosure, since it is assumed that the fluorophore concentration in the laser irradiation irradiation portion of each capillary is constant, the fluorescence intensity and the laser irradiation intensity have the same meaning.

[0007]

In the DNA sequencing or the DNA fragment analysis performed by the 3500 Series Genetic Analyzer and the 3730 Series Genetic Analyzer, a polymer solution containing a denaturing agent urea at a high concentration is used as a separation medium in order to separate DNA fragments contained in a sample by electrophoresis in a single-stranded state. In practice, POP-4, POP-6, and POP-7, which are the separation media commercially available for use in the 3500 Series Genetic Analyzer and the 3730 Series Genetic Analyzer, all contain 8 M urea. The refractive index of the polymer solution containing 8 M urea rises to $n_3 = 1.41$, while the refractive index of water is 1.33. The convex lens effect of each capillary is thus strengthened, which is an advantageous condition for the multifocus.

[0008]

According to the configuration based on PTL 1, arranged in the air are laser irradiation portions of a plurality of capillaries having an outer diameter $2R = 323 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ in the 3500 Series Genetic Analyzer. That is, $n_1 = 1.00$ is used. In this case, according to Formula (1) above, since $\Delta\theta = -1.3^\circ$ is satisfied, it is understood that each capillary has the convex lens effect. Therefore, since the multifocus functions, simultaneous irradiation of 8 or 24 capillaries with a laser beam is

possible. However, in this configuration, up to about 24 capillaries can be simultaneously irradiated, since the loss of the laser beam due to reflection is great at the interface between an air layer outside the capillary and the capillary (quartz glass).

[0009]

Therefore, according to the configuration disclosed in PTL 2, the number of capillaries that can be simultaneously irradiated is increased in the 3730 Series Genetic Analyzer. In the 3730 Series Genetic Analyzer, arranged in a fluorine solution having a refractive index $n_1 = 1.29$ are laser irradiation portions of a plurality of capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$. In this case, according to Formula (1) above, since $\Delta\theta = -0.69^\circ$ is satisfied, it is understood that each capillary has the convex lens effect and the multifocus functions. Furthermore, the number of capillaries that can be simultaneously irradiated is increased, since the loss of the laser beam due to reflection is reduced at the interface between a fluorine solution layer outside the capillary and the capillary (quartz glass). Therefore, simultaneous irradiation of 48 or 96 capillaries with a laser beam becomes possible.

[0010]

In the configuration disclosed in NPL 1, the number of

capillaries that can be simultaneously irradiated is further increased. In this configuration, arranged in a matching solution having a refractive index $n_1 = 1.46$ are laser irradiation portions of a plurality of capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$. Furthermore, among the plurality of arranged capillaries, the odd-numbered capillaries from one end are used for analysis (hereinafter, referred to as analysis capillaries), and the even-numbered capillaries are used as rod lenses (hereinafter, referred to as lens capillaries). That is, the analysis capillaries and the lens capillaries are alternately arranged. The refractive index of a medium inside the analysis capillaries (separation medium) is set to $n_3 = 1.41$, and the refractive index of a medium inside the lens capillaries is set to $n_4 = 1.53$. The materials of both types of capillaries are quartz glass, and the refractive index thereof is $n_2 = 1.46$. Furthermore, the number of capillaries that can be simultaneously irradiated is further increased, since the loss of the laser beam due to reflection is zero at the interface between a matching solution layer outside the capillary and the capillary (quartz glass). In addition, the definition of the maximum number of capillaries that can be simultaneously irradiated with a laser beam is described on P. 2874 to P. 2875 in NPL 1. In a case where the incident intensity in the single-

side irradiation is assumed to be 100%, the number obtained by doubling the number of capillaries that attenuates the laser beam intensity to 50% is the maximum number of capillaries that can be simultaneously irradiated. The maximum number of capillaries that can be simultaneously irradiated is defined in this manner, since the irradiation intensity at each capillary is expected to be uniform when a capillary array having such number of capillaries is subjected to the double-side irradiation. According to this definition, the maximum number of capillaries in the configuration of PTL 2 is 150, and the maximum number of capillaries in the configuration of NPL 1 is 550.

[0011]

As in NPL 1, the analysis capillaries and the lens capillaries are alternately arranged in the capillary array in PTL 3. The capillary numbers $n = 1, 2, \dots, N$ are assigned only to the analysis capillaries in order from the end of the capillary array. In other words, the total number of capillaries including the analysis capillaries and the lens capillaries is $2 \times N$.

Citation List

Patent Literature

[0012]

PTL 1: JP 3654290 B2

PTL 2: JP 5039156 B2

PTL 3: JP 3559648 B2

Non Patent Literature

[0013]

NPL 1: Electrophoresis 2006, 27, 2869-2879

Summary of Invention

Technical Problem

[0014]

Here, it is evaluated what the number of capillaries is that can be simultaneously irradiated, which is determined by taking the loss of light due to reflection into consideration and whether or not there is practical performance in the above known techniques. Such evaluation is performed for the first time in the present disclosure. In order to perform approximate evaluation of the transmittance of a laser beam by taking the loss thereof due to reflection into consideration, assumed to be θ° is the incident angle of the laser beam incident on the interface between two types of media having different refractive indices. The reflectance, when light is incident on an interface between a medium having a refractive index n_1 and a medium having a refractive index n_2 at an incident angle of θ° , is defined as $\text{ref} = \{(n_1 - n_2)/(n_1 + n_2)\}^2$, and the transmittance is defined as $\text{tra} = 1 - \text{ref}$. Thus, the transmittance T , when the laser beam is transmitted through

one capillary, is approximately obtained by the following Formula (2).

[0015]

[Mathematical Formula 2]

$$T = \left\{ 1 - \left(\frac{n_1 - n_2}{n_1 + n_2} \right)^2 \right\}^2 \cdot \left\{ 1 - \left(\frac{n_2 - n_3}{n_2 + n_3} \right)^2 \right\}^2 \quad \dots (2)$$

[0016]

Under the conditions of the 3500 Series Genetic Analyzer based on PTL 1 described above, T is calculated to be T = 93%. In practice, the laser beam contains a component of which the incident angle is not 0°, and the transmittance of the laser beam is slightly smaller than the value obtained from Formula (2). Therefore, Formula (2) represents ideal transmittance. In the case of the single-side irradiation, when the irradiation intensity of laser incident on the capillary of the capillary number n = 1 is assumed to be 1, the laser irradiation intensity at the capillary of the capillary number n is expressed by the following Formula (3).

[0017]

[Mathematical Formula 3]

$$L(n) = T^{n-1} \quad \dots (3)$$

[0018]

That is, when the number of capillaries is set to N = 24 in the 3500 Series Genetic Analyzer, the laser irradiation intensity is attenuated to 93% every time the laser passes

through one capillary in the capillary array, and the laser irradiation intensity decreases to 0.19 at the capillary of $n = 24$. On the other hand, in the case of the double-side irradiation, when the irradiation intensities of laser incident on the capillaries of the capillary numbers $n = 1$ and $n = N$ are each assumed to be 0.5, the laser irradiation intensity at the capillary of the capillary number n is expressed by the following Formula (4).

[0019]

[Mathematical Formula 4]

$$L(n) = 0.5 \cdot (T^{n-1} + T^{N-n}) \dots (4)$$

[0020]

Unlike the case of the single-side irradiation, since the attenuation of the intensities of the laser beams incident from both sides of the array plane is offset, the uniformity of the laser irradiation intensity at each capillary is improved, and the minimum laser irradiation intensity is increased. Note that the laser irradiation intensity is the highest at the capillaries located at both ends of the capillary array ($n = 1$ and $n = N$) and that the laser irradiation intensity is the lowest at the capillary located at the center of the capillary array (in a case where N is an odd number, $n = (N + 1)/2$ is used, and in a case where N is an even number, $n = N/2$ and $n = N/2 + 1$ are used). That is, when a graph is created with the horizontal axis n

and the vertical axis $L(n)$, a convex downward distribution is obtained. Under the conditions of the 3500 Series Genetic Analyzer, when the number of capillaries is set to $N = 24$, the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 24$) are obtained as 0.60, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 12$ and $n = 13$) are obtained as 0.44, thus satisfying $\text{MIN} \geq 0.2$ for practical performance. Furthermore, the coefficient of variation for the laser irradiation intensities at the 24 capillaries is obtained as 11%, thus satisfying $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance.

[0021]

However, under the conditions of the 3500 Series Genetic Analyzer, when the number of capillaries is set to $N = 48$, the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 48$) are obtained as 0.52, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 24$ and $n = 25$) are obtained as 0.19, and thus $\text{MIN} \geq 0.2$ for the practical performance is not satisfied. Furthermore, the coefficient of variation for the laser irradiation intensity is obtained as 35%, and thus both $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance are

not satisfied. In other words, even when the double-side irradiation is adopted, the uniformity of the laser irradiation intensity at each capillary decreases, and the minimum laser irradiation intensity decreases. Therefore, it is difficult to simultaneously irradiate the 48 capillaries under such conditions.

[0022]

Under the conditions of the 3730 Series Genetic Analyzer based on PTL 2, $T = 99\%$ is obtained according to Formula (2), and the transmittance is significantly improved compared to that under the conditions of the 3500 Series Genetic Analyzer. Moreover, when the number of capillaries is set to $N = 48$ in Formula (4), the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 48$) are obtained as 0.78, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 24$ and $n = 25$) are obtained as 0.74, thus satisfying $\text{MIN} \geq 0.2$. Furthermore, the coefficient of variation for the laser irradiation intensity is obtained as 1%, thus satisfying $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance. In addition, when the number of capillaries is set to $N = 96$ in Formula (4), the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 96$) are obtained as 0.65, and the laser irradiation intensities at

the capillaries located at the center of the capillary array ($n = 48$ and $n = 49$) are obtained as 0.55, thus satisfying $\text{MIN} \geq 0.2$. Furthermore, the coefficient of variation for the laser irradiation intensity is obtained as 5%, thus satisfying $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance. As described above, the uniformity of the laser irradiation intensities at 48 and 96 capillaries is improved, and the minimum laser irradiation intensity increases, whereby simultaneous irradiation of the 48 and 96 capillaries becomes possible.

[0023]

In order to compare the configuration of PTL 3 with those of PTL 2 and NPL 1, the conditions are standardized within a possible range. In the configuration of PTL 3, laser irradiation portions of a plurality of capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged in water having a refractive index $n_1 = 1.33$. The refractive index of a medium inside the analysis capillaries (separation medium) is set to $n_3 = 1.41$. The refractive index of a medium inside the lens capillaries is set to $n_4 = 1.46$. The materials of both types of capillaries are made of quartz glass having $n_2 = 1.46$. In this case, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +0.03^\circ$, while the refraction angle at one lens capillary is obtained as

$\Delta\theta_B = -2.1^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = -2.07^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions. As described above, a method for evaluating whether or not the multifocus functions using the value of $\Delta\theta_A + \Delta\theta_B$ is discovered in the present disclosure. Under the present conditions, according to Formula (2), the transmittance of one analysis capillary is obtained as $T_A = 99.5\%$, and the transmittance of one lens capillary is obtained as $T_B = 99.6\%$. Therefore, the transmittance of one set of one analysis capillary and one lens capillary is obtained as $T = T_A \times T_B = 99.1\%$. In this case, when the number of the analysis capillaries is set to $N = 96$ in Formula (4), the laser irradiation intensities at the analysis capillaries located at both ends of the capillary array ($n = 1$ and $n = 96$) are obtained as 0.71, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 48$ and $n = 49$) are obtained as 0.64, thus satisfying $\text{MIN} \geq 0.2$. Furthermore, the coefficient of variation for the laser irradiation intensity is obtained as 3%, thus satisfying $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance.

[0024]

In all of the known techniques described above, the separation media contain high concentrations of urea having

$n_3 = 1.41$. On the other hand, separation media in capillary electrophoresis apparatuses using one capillary do not always contain a high concentration of urea, and various types of separation media are used. For example, a separation medium for separating DNA fragments by electrophoresis in a double-stranded state does not contain urea, and a refractive index thereof is $n_3 = 1.33$, which is the same as that of water. That is, the refractive indices of separation media used in capillary electrophoresis can be generally various values from $1.33 \leq n_3 \leq 1.41$. In recent years, in order to increase throughput or reduce cost of electrophoretic analysis using such various types of separation media, it is required that the various types of separation media are used in a capillary array electrophoresis apparatus.

[0025]

However, in the configurations of all of the known techniques described above, the convex lens effect of each capillary is lost, and the concave lens effect is strengthened when setting to $n_3 = 1.33$, and thus the multifocus does not function. In other words, it becomes impossible to perform parallel electrophoretic analysis using a plurality of capillaries. Specifically, it is as follows.

[0026]

When $n_3 = 1.33$ in the 3500 Series Genetic Analyzer based on PTL 1, $\Delta\theta = +1.3^\circ$ according to Formula (1), whereby it is understood that each capillary has the concave lens effect. Therefore, the multifocus does not function, and simultaneous irradiation of 8 or 24 capillaries with a laser beam becomes impossible.

[0027]

When setting to $n_3 = 1.33$ in the 3730 Series Genetic Analyzer based on PTL 2, $\Delta\theta = +2.9^\circ$ is obtained according to Formula (1), whereby it is understood that each capillary has the concave lens effect. Therefore, the multifocus does not function, and it becomes impossible to perform simultaneous irradiation of 48 or 96 capillaries with a laser beam.

[0028]

When setting to $n_3 = 1.33$ in the configuration based on NPL 1, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +6.6^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.0^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = +3.6^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the concave lens effect, and the multifocus does not function. When setting to $n_3 = 1.41$ in the configuration based on NPL 1, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +2.4^\circ$,

while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.0^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = -0.6^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions. P. 2875 of NPL 1 describes that the configuration of NPL1 functions advantageously even in a case where $n_3 = 1.33$. However, according to the definition of the maximum number of capillaries in NPL 1 described above, the maximum number of capillaries in the case of $n_3 = 1.33$ is only about 8, as can be seen from FIG. 11 of NPL 1. Therefore, the configuration of NPL 1 does not function in the case of $n_3 = 1.33$.

[0029]

When setting to $n_3 = 1.33$ in the configuration based on PTL 3, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +3.7^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -2.1^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = +1.6^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the concave lens effect, and the multifocus does not function. Therefore, a plurality of capillaries cannot be simultaneously irradiated with a laser beam.

[0030]

In view of such a situation, the present disclosure proposes a technique that enables electrophoretic analysis

even when using various separation media having any refractive indices within a range of $1.33 \leq n_3 \leq 1.41$ (can also correspond to separation media having refractive indices outside the range of $1.33 \leq n_3 \leq 1.41$ as a matter of course) in a capillary array electrophoresis apparatus.

Solution to Problem

[0031]

In order to solve the above problems, the present disclosure proposes, for example, a capillary array including laser irradiation portions which are collectively irradiated with a laser beam for N analysis capillaries used in electrophoretic analysis and laser irradiation portions which are collectively irradiated with the laser beam for $N \pm 1$ lens capillaries not used in the electrophoretic analysis, wherein N is an integer of 2 or more, wherein the laser irradiation portions of analysis capillaries and the laser irradiation portions of the lens capillaries are alternately arranged approximately on the same array plane, and wherein, when the outer radius is defined as R , the inner radius is defined as r , the refractive index of a medium on the outside is defined as n_1 , and the refractive index of a material is defined as n_2 for each of the N analysis capillaries in the laser irradiation portions and the $N \pm 1$ lens capillaries in the laser irradiation portions, the refractive index of a

medium on the inside of the N analysis capillaries in the laser irradiation portions is defined as n_3 , and the refractive index of a medium on the inside of the $N \pm 1$ lens capillaries in the laser irradiation portions is defined as n_4 , and when it is assumed that $n_3 < 1.36$ is satisfied, R, r, n_1 , n_2 , and n_4 satisfy a predetermined relationship.

[0032]

Additional features related to the present disclosure will become apparent from the description in the present specification and the accompanying drawings. In addition, aspects of the present disclosure are achieved and realized by elements, combinations of various elements, and aspects in the following detailed description and appended claims.

It should be understood that the description in the present specification is merely exemplary, and is not intended to limit the claims or application examples of the present disclosure in any way.

Advantageous Effects of Invention

[0033]

According to the technique of the present disclosure, it is possible to perform, in a capillary array electrophoresis apparatus, electrophoretic analysis using various separation media having any refractive indices within the range of $1.33 \leq n_3 \leq 1.41$. In particular, it is

possible to perform capillary electrophoretic analysis using a separation medium having a low refractive index which is the same as or close to the refractive index of water having 1.33. As a result, it is possible to greatly expand the range of applying the capillary array electrophoresis apparatus capable of improving analysis throughput or reducing analysis cost per sample.

Problems, configurations, and effects other than those described above will be clarified by the following description of embodiments.

Brief Description of Drawings

[0034]

[FIG. 1] FIG. 1 is a diagram illustrating a configuration example of a capillary array electrophoresis apparatus.

[FIG. 2] FIG. 2 is a diagram illustrating a configuration example of an optical system of the capillary array electrophoresis apparatus.

[FIG. 3] FIG. 3 is a diagram illustrating a configuration example showing coordination between a sensor and a computer.

[FIG. 4] FIG. 4 is a diagram illustrating a configuration of a capillary array based on PTL 1 and laser beam ray tracing results.

[FIG. 5] FIG. 5 is a diagram showing relative fluorescence intensity distributions of the capillary array based on PTL 1.

[FIG. 6] FIG. 6 is a diagram illustrating a configuration of a capillary array of the present disclosure and laser beam ray tracing results.

[FIG. 7] FIG. 7 is a diagram showing relative fluorescence intensity distributions of the capillary array of the present disclosure.

[FIG. 8] FIG. 8 is a diagram illustrating a configuration of a capillary array based on PTL 2 and laser beam ray tracing results.

[FIG. 9] FIG. 9 is a diagram showing relative fluorescence intensity distributions of the capillary array based on PTL 2.

[FIG. 10] FIG. 10 is a diagram showing relative fluorescence intensity distributions of a capillary array based on NPL 1.

[FIG. 11] FIG. 11 is a diagram showing relative fluorescence intensity distributions of the capillary array based on NPL 1.

[FIG. 12] FIG. 12 is a diagram illustrating a configuration of a capillary array based on PTL 3 and laser beam ray tracing results.

[FIG. 13] FIG. 13 is a diagram showing relative

fluorescence intensity distributions of the capillary array based on PTL 3.

[FIG. 14] FIG. 14 is a diagram illustrating a configuration of a capillary array of the present disclosure and laser beam ray tracing results.

[FIG. 15] FIG. 15 is a diagram showing relative fluorescence intensity distributions of the capillary array of the present disclosure.

[FIG. 16] FIG. 16 is a diagram illustrating a configuration of the capillary array of the present disclosure and laser beam ray tracing results.

[FIG. 17] FIG. 17 is a diagram showing relative fluorescence intensity distributions of the capillary array of the present disclosure.

[FIG. 18] FIG. 18 is a diagram illustrating a configuration of the capillary array of the present disclosure and laser beam ray tracing results.

[FIG. 19] FIG. 19 is a diagram showing relative fluorescence intensity distributions of the capillary array of the present disclosure.

[FIG. 20] FIG. 20 is a diagram showing relative fluorescence intensity distributions of the capillary arrays of the present disclosure.

[FIG. 21] FIG. 21 is a diagram for describing the influence of a refractive index on the outside of a capillary

on relative fluorescence intensities and coefficient of variation therefor.

[FIG. 22] FIG. 22 is a diagram for describing the influence of an outer diameter of a capillary on relative fluorescence intensities and coefficient of variation therefor.

[FIG. 23] FIG. 23 is a diagram illustrating a configuration example of a capillary array in which analysis capillaries and lens capillaries are alternately arranged.

Description of Embodiments

[0035]

The technique of the present disclosure relates to a capillary array electrophoresis apparatus that simultaneously analyzes a plurality of samples by simultaneously irradiating a plurality of capillaries with a laser beam and by detecting fluorescence emitted from each capillary at the same time during electrophoresis performed using the plurality of capillaries.

[0036]

(A) Outline of Technique of Present Disclosure

The present disclosure mainly proposes a technique that enables the use of a separation medium having a low refractive index that is equivalent to that of water, which is 1.33, or is lower than 1.36. In a case where the

separation medium having a low refractive index is used, multifocus does not function even when a technique disclosed in any of the known examples (PTLs 1 to 3 and NPL 1) is applied, and it is difficult to simultaneously irradiate a plurality of capillaries with a laser beam.

[0037]

The present disclosure also proposes a technique by which capillary electrophoretic analysis can be performed by using not only the separation medium having a low refractive index described above, but also a separation medium having a high refractive index, typically, a refractive index of 1.36 or higher and 1.42 or lower. The maximum number of capillaries that can be simultaneously irradiated is preferably large, and can be set to 24 or more, or set to 48 or more depending on the situation. As described above, among the irradiation intensities and the fluorescence intensities of the plurality of capillaries in the same capillary array, it is preferable to set the lowest irradiation intensity and the fluorescence intensity to as large value as possible. It has been empirically found that, assuming to be 1 the fluorescence intensity expected when the laser beam oscillating from the laser source irradiates at full intensity the inside of one capillary, sensitivity suitable for practical use is obtained if the minimum value (MIN) of the fluorescence intensity satisfies $\text{MIN} \geq 0.2$. In

addition, the smaller variation in the irradiation intensities and the fluorescence intensities among the plurality of capillaries in the same capillary array is, the more preferable it is. It has been empirically found that, when the coefficient of variations (CVs) for the irradiation intensity and the fluorescence intensity satisfy $CV \leq 20\%$, or $CV \leq 15\%$ depending on the situation, it is possible to analyze different samples under equivalent conditions. The present disclosure aims to satisfy such requirements for the practical performance of the capillary array electrophoresis apparatus.

[0038]

As a result of performing intensive studies under the above object, when the capillary outer diameter is set to $2R = 126 \mu\text{m}$, the capillary inner diameter is set to $2r = 50 \mu\text{m}$, the outside of a capillary is provided with air having a refractive index $n_1 = 1.00$, the material of the capillary is made of quartz glass having a refractive index $n_2 = 1.46$, and the inside of the capillary holds a separation medium having a refractive index $n_3 = 1.33$ in each capillary in a capillary array, $\Delta\theta = -3.2^\circ$ is obtained according to Formula (1). Therefore, it was found that each capillary exhibits a convex lens effect, and the multifocus functions. The 3500 Series Genetic Analyzer based on PTL 1 is different from when setting to $n_3 = 1.33$, in that the outer diameter

2R of the capillary is reduced from 323 μm to 126 μm . As a result, the concave lens effect of each capillary is converted to the convex lens effect.

[0039]

When the number of capillaries is set to $N = 24$, and the above conditions are substituted into Formula (2) and Formula (4), the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 24$) are obtained as 0.59, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 12$ and $n = 13$) are obtained as 0.42, thus satisfying $\text{MIN} \geq 0.2$ for the practical performance. Furthermore, the coefficient of variation for the laser irradiation intensities at the 24 capillaries is obtained as 12%, thus satisfying $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance. As a result of further studies, it was found that, when the outer diameter 2R of the capillary was set to 220 μm or less, since $\Delta\theta < 0$ is satisfied the convex lens functions. Generalizing without limiting to the case where the inner diameter of the capillary was set to $2r = 50 \mu\text{m}$, it was found that, since $\Delta\theta < 0$ is satisfied when setting to $R/r \leq 4.4$, the convex lens functions. A separation medium having a low refractive index $n_3 = 1.33$ is not studied in PTL 1. That is, the conditions described above are found for the first time in the technique of the

present disclosure.

[0040]

Furthermore, in a case where the capillary outer diameter is set to $2R = 126 \mu\text{m}$, and the capillary inner diameter is set to $2r = 50 \mu\text{m}$, when the refractive indices of a separation medium inside the capillary are set to $n_3 = 1.34$, 1.35 , and 1.36 , $\Delta\theta = -3.5^\circ$, -3.8° , and -4.2° , respectively, according to Formula (1), it was found that each capillary exhibits the convex lens effects and the multifocus functions. As a result of further studies, it was found that in a case where the outer diameter $2R$ of the capillary was set to $240 \mu\text{m}$ or less, $264 \mu\text{m}$ or less, or $293 \mu\text{m}$ or less, since $\Delta\theta < 0$ is satisfied, the convex lens functions. By generalization, when setting to $R/r \leq 4.8$, $R/r \leq 5.3$, or $R/r \leq 5.9$, since $\Delta\theta < 0$ is satisfied, the convex lens functions. In other words, it was found that the value of R/r preferably satisfies $R/r < 5.9$ when using a separation medium having a low refractive index of lower than 1.36 . Such a separation medium having a low refractive index is not studied in PTL 1. That is, the conditions described above are found for the first time in the technique of the present disclosure.

[0041]

On the other hand, when the number of capillaries is set to $N = 48$ under the conditions in which the capillary

outer diameter is set to $2R = 126 \mu\text{m}$, the capillary inner diameter is set to $2r = 50 \mu\text{m}$, the outside of the capillaries is provided with air having a refractive index $n_1 = 1.00$, the material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$, and the insides of the capillaries hold a separation medium having a refractive index $n_3 = 1.33$, the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 48$) are obtained as 0.51, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 24$ and $n = 25$) are obtained as 0.17 according to Formula (2) and Formula (4), and thus $\text{MIN} \geq 0.2$ for the practical performance is not satisfied. Furthermore, the coefficient of variation for the laser irradiation intensities at the 48 capillaries is obtained as 38%, and thus both $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance are not satisfied. Therefore, the present conditions are not suitable for simultaneous irradiation of 48 or more capillaries.

[0042]

A novel configuration was thus devised which enables the simultaneous irradiation of 48 or more capillaries with a laser beam while using a separation medium having a low refractive index. Similarly to the configurations shown in NPL 1 and PTL 3, a capillary array is formed by alternately

arranging analysis capillaries and lens capillaries. Here, the numbers of the analysis capillaries and the lens capillaries are not necessarily the same. In a case where both ends of the capillary array are analysis capillaries, N analysis capillaries and $N-1$ lens capillaries may be alternately arranged, where N is an integer of 2 or more. In a case where both ends of the capillary array are used as lens capillaries, N analysis capillaries and $N+1$ lens capillaries may be alternately arranged. The capillary numbers $n = 1, 2, \dots, N$ are assigned only to the analysis capillaries. Laser irradiation portions of a plurality of capillaries having an outer diameter $2R = 126 \text{ }\mu\text{m}$ and an inner diameter $2r = 50 \text{ }\mu\text{m}$ are arranged in a fluorine solution having a refractive index $n_1 = 1.25$. The material of the capillaries made of quartz glass having a refractive index $n_2 = 1.46$. The insides of the analysis capillaries hold a separation medium having a refractive index $n_3 = 1.33$. The insides of the lens capillaries hold a matching solution having a refractive index $n_4 = 1.46$. In this case, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +2.0^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.3^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = -1.3^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions. Under the

present conditions, according to Formula (2), the transmittance of one analysis capillary is obtained as $T_A = 98.4\%$, and the transmittance of one lens capillary is obtained as $T_B = 98.8\%$. Therefore, the transmittance of one set of one analysis capillary and one lens capillary is obtained as $T = T_A \times T_B = 97.2\%$. In this case, when the number of the analysis capillaries is set to $N = 48$ in Formula (4), the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 48$) are obtained as 0.63, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 24$ and $n = 25$) are obtained as 0.51 according to Formula (2) and Formula (4), thus satisfying $\text{MIN} \geq 0.2$ for the practical performance. Furthermore, the coefficient of variation for the laser irradiation intensities at the 48 capillaries is obtained as 7%, thus satisfying both $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance.

[0043]

Next, when the number of the capillaries is set to $N = 72$, the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 72$) are obtained as 0.57, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 36$ and $n = 37$) are obtained as 0.36

according to Formula (2) and Formula (4), thus satisfying $\text{MIN} \geq 0.2$ for the practical performance. Furthermore, the coefficient of variation for the laser irradiation intensities at the 72 capillaries is obtained as 14%, thus satisfying both $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance. In addition, when the number of the capillaries is set to $N = 96$, the laser irradiation intensities at the capillaries located at both ends of the capillary array ($n = 1$ and $n = 96$) are obtained as 0.53, and the laser irradiation intensities at the capillaries located at the center of the capillary array ($n = 48$ and $n = 49$) are obtained as 0.26 according to Formula (2) and Formula (4), thus satisfying $\text{MIN} \geq 0.2$ for the practical performance. Furthermore, the coefficient of variation for the laser irradiation intensities at the 96 capillaries is obtained as 24%, and thus $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ for the practical performance are not satisfied. It is needless to say that, under the above conditions, the performance of all of the above indices is improved by returning $n_3 = 1.33$ to $n_3 = 1.41$. Except for changing $n_3 = 1.41$ to $n_3 = 1.33$, the present configuration is significantly different from the configuration of PTL 2, the configuration of NPL 1, and the configuration of PTL 3. In PTL 2, the lens capillaries are not used, and the refractive index of the medium on the outside of the capillary is set to $n_1 = 1.29$, which are all

different from the configuration of the present disclosure. Furthermore, in NPL 1, the refractive index of the medium on the outside of the capillary is set to $n_1 = 1.46$, and the inside of the lens capillary holds a solution having a high refractive index $n_4 = 1.53$, which are all different from the configuration of the present disclosure. In addition, in PTL 3, the refractive index of the medium on the outside of the capillary is set to $n_1 = 1.33$, which is different from the configuration of the present disclosure. As described above, such differences represent different functions arising from essentially different structures, and are not due to mere design changes.

[0044]

Hereinafter, each embodiment of the present disclosure will be described in detail. Although each embodiment will be separately described below, the techniques shown in each embodiment are not exclusive and can be combined with each other as appropriate.

[0045]

(B) First Embodiment

<Configuration Example of Capillary Array Electrophoresis Apparatus>

FIG. 1 is a diagram illustrating a configuration example of a capillary array electrophoresis apparatus. In the present capillary array electrophoresis apparatus,

double-stranded DNA fragment analysis is performed in addition to the DNA sequencing and single-stranded DNA fragment analysis performed in the conventional capillary array electrophoresis apparatuses. In the present embodiment, using 24 capillaries (note that only 4 capillaries are shown in FIG. 1), DNA sequencing is first performed on samples different in each capillary, and then the double-stranded DNA fragment analysis is performed on samples different in each capillary. The samples for the DNA sequencing contain single-stranded DNA fragments of various lengths labeled with 4 types of fluorophores corresponding to the 4 types of bases. The electrophoresis separation medium with which fills each capillary when performing the DNA sequencing is a polymer solution containing, as a denaturing agent, 8M urea, its refractive index of the polymer solution being $n_3 = 1.41$. By contrast, the samples for the double-stranded DNA fragment analysis contain double-stranded DNA fragments of various lengths labeled with 2 types of fluorophores. A double-stranded DNA fragment labeled with one fluorophore is defined as a PCR product, and a double-stranded DNA fragment labeled with the other fluorophore is defined as a size marker. The electrophoresis separation medium with which fills each capillary when performing the double-stranded DNA fragment analysis is a polymer solution which does not contain urea

as a denaturing agent, its refractive index of the polymer solution being $n_3 = 1.33$. One analysis session was performed by the following steps (i) to (vi).

[0046]

(i) First, sample injection ends 2 of 24 capillaries 1 were immersed in a cathode-side buffer solution 6, and sample elution ends 3 were connected to an anode-side buffer solution 7 via a polymer block 9.

[0047]

(ii) Next, a valve 10 of the polymer block 9 was closed, the piston of a syringe 11 connected to the polymer block 9 was pushed down to pressurize the polymer solution in the syringe, and the inside of each capillary 1 was filled with the polymer solution from the sample elution end 3 toward the sample injection end 2.

[0048]

(iii) Subsequently, the valve 10 was opened, a different sample was injected into each capillary 1 from the sample injection end 2 by an electric field, and then a high voltage was applied between a cathode 4 and an anode 5 by a power source 8, thus starting capillary electrophoresis. DNA fragments labeled with the multiple types of fluorophores were electrophoresed from the sample injection end 2 toward the sample elution end 3.

[0049]

(iv) Concurrently, a position in each capillary 1 at which the DNA fragments were electrophoresed to a certain distance from the sample injection end 2 was defined as a laser irradiation portion 14, and the laser irradiation portions 14 were collectively irradiated with a laser beam 13 oscillated from a laser source 12 by a multifocus method. Here, the coating of each capillary 1 in the vicinity of the laser irradiation portion 14 was removed in advance. Each of the capillaries 1 was arranged on an array plane in the vicinity of the laser irradiation portion 14, and the laser beam 13 was condensed and allowed to be incident along the array plane from the side of the array plane. Although FIG. 1 depicts the irradiation with the laser beam 13 as being single-side irradiation for the sake of simplicity, double-side irradiation was performed in reality by splitting the laser beam 13 into two.

[0050]

(v) Then, the DNA fragments labeled with the multiple types of fluorophores were electrophoresed in each capillary 1 and irradiated with the laser beam 13 when passing through the laser irradiation portion 14, whereby the labeled fluorophores were excited, and fluorescence was emitted. That is, the multiple types of fluorophores emitted fluorescence from 24 emission points (laser irradiation portions). Each fluorescence intensity changed from moment

to moment with the electrophoresis.

[0051]

(vi) Finally, the sample injected into each capillary was analyzed by detecting multiple colors of the fluorescence emitted from each emission point and analyzing the obtained time-series data.

[0052]

Although the above steps (i) to (vi) are common to the case of performing the DNA sequencing and the case of performing the double-stranded DNA fragment analysis, the polymer solution and the buffer solution are appropriately changed. That is, the capillary array electrophoresis apparatus of the present embodiment can, for example, execute a plurality of analysis modes with different conditions while switching among the plurality of analysis modes including a first analysis mode for the double-stranded DNA fragment analysis and a second analysis mode for the DNA sequencing. In each analysis mode, it is effective to appropriately change the condition for the electrophoretic analysis according to the purpose thereof. There are, as changeable conditions for electrophoretic analysis, a controlled temperature of the capillary, an electric field strength during the electrophoresis, an electric field strength and a sample injection time during the sample injection, a laser irradiation intensity, an exposure time for the sensor, and

the like. For example, it is effective to change the controlled temperature of the capillary in each analysis mode, for example, by adjusting the temperature of the capillary to 30°C in the first analysis mode and adjusting the temperature of the capillary to 60°C in the second analysis mode. Note that the terms "first" and "second" are merely added for the sake of convenience to distinguish among the analysis modes and do not indicate the order in which the analysis modes are executed. In the above example, the refractive index of the electrophoresis separation medium in the DNA fragment analysis is set to $n_3 = 1.33$, and the refractive index of the electrophoresis separation medium in the DNA sequencing is set to $n_3 = 1.41$. Therefore, the refractive index of the electrophoresis separation medium in the first analysis mode is set to $n_3 < 1.36$, and the refractive index of the electrophoresis separation medium in the second analysis mode is set to $n_3 \geq 1.36$. According to circumstances, it is possible to set to $1.33 \leq n_3 < 1.36$ the refractive index of the electrophoresis separation medium in the first analysis mode and to set to $1.36 \leq n_3 \leq 1.42$ the refractive index of the electrophoresis separation medium in the second analysis mode. The analysis session consisting of the steps (i) to (vi) can also be repeated multiple times. For example, a number of different samples can be analyzed by analyzing samples 1 to 24 in the first analysis session,

analyzing samples 25 to 48 in the second analysis session, and so on. In this case, the DNA sequencing may be repeated using the same polymer solution and buffer solution, or the DNA sequencing may be switched in the middle to the double-stranded DNA fragment analysis. Any application can be selected in any analysis session.

[0053]

<Configuration Example of Optical System Performing Fluorescence Detection>

FIG. 2 is a cross-sectional diagram illustrating a configuration example of an optical system that performs fluorescence detection in the capillary array electrophoresis apparatus. The present optical system is located on the back side of the laser irradiation portions 14 in FIG. 1. Similarly to FIG. 1, FIG. 2 depicts single-side irradiation of an array of 4 capillaries, but double-side irradiation of an array of 24 capillaries was performed in reality. The capillaries 1 arranged on the array plane were simultaneously irradiated with the laser beam 13 by multifocus irradiation. Each of the laser irradiation portions 14 of the capillaries 1 serves as a fluorescence emission point 20. Fluorescence 21 emitted from each emission point 20 was collectively collimated by a condenser lens 15. The laser beam was blocked by a laser cut filter 16 and transmitted through a transmission grating 17 to

disperse the wavelength in the central axis direction of each capillary, whereby imaging points 22 were each formed on a sensor 19 by an imaging lens 18. The sensor 19 may be an area sensor such as a CCD or a CMOS or a sensor capable of simultaneously measuring a plurality of imaging points 22 such as a photodiode array. In reality, each imaging point 22 is subjected to wavelength dispersion in the depth direction of FIG. 2, but a single wavelength portion of each imaging point 22 is schematically depicted in FIG. 2.

[0054]

In such an optical system, the light condensing efficiency decreases as the distance from an optical axis 23 of the optical system increases. As shown in FIG. 2, such decrease in the light condensing efficiency occurs, since the converging angle of the fluorescence 21 emitted from the emission point 20 distant from the optical axis 23 is reduced by the vignetting effect of the optical system. Therefore, even in a case where fluorescence of an equal intensity is emitted from each emission point 20, the fluorescence intensity at the imaging point 22 decreases as the distance between the corresponding emission point 20 and the optical axis 23 increases. How much vignetting effect exists, that is, an optical system correction coefficient based on the vignetting effect is determined by the optical system and can be examined by calculation or experiment. Using the

optical system correction coefficient based on the vignetting effect, the fluorescence intensity at each imaging point 22 can be calculated from the fluorescence intensity at each emission point 20.

[0055]

<Configuration Example of System for Data Analysis and Apparatus Control>

FIG. 3 is a diagram illustrating a configuration example showing coordination between the sensor and a computer. The optical system is a part of the capillary array electrophoresis apparatus. The sensor is a part of the optical system. The computer is connected to the capillary array electrophoresis apparatus. The computer not only performs data analysis, but also controls the capillary array electrophoresis apparatus. Condition setting for the data analysis and condition setting for the capillary array electrophoresis apparatus control are performed through an input unit such as a touch panel, a keyboard, or a mouse. Time-series raw data of signals output from the sensor is sequentially stored in a memory. Analysis parameter information stored in the database inside an HDD is also stored in the memory. Using the analysis parameter information stored in the memory, a CPU analyzes the time-series raw data stored in the memory, derives time-series analysis data, sequentially stores the time-series analysis

data in the memory, and displays the time-series analysis data at the same time on a monitor corresponding to a display unit. The analysis result can also be collated with information on network through network interface NIF.

[0056]

<Configuration Example of Conventional (PTL 1) Capillary Array>

FIG. 4(a) is a cross-sectional diagram illustrating a configuration of a capillary array of the 3500 Series Genetic Analyzer based on PTL 1. The laser irradiation portions of 24 capillaries having an outer diameter $2R = 323 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $370 \mu\text{m}$. The outside of the capillaries is provided with air having a refractive index $n_1 = 1.00$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$.

[0057]

FIG. 4(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when single-side irradiation with a laser beam having a diameter of $50 \mu\text{m}$ was performed from the left side in a case where the insides of the capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus clearly functions, the insides of all 24 capillaries can be efficiently irradiated. This corresponds

to the fact that $\Delta\theta = -1.3^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the convex lens effect.
[0058]

On the other hand, FIG. 4(c) is a diagram showing the results of performing the same laser beam ray tracing under the above conditions in a case where the insides of the capillaries hold a separation medium having a low refractive index $n_3 = 1.33$. Since the multifocus clearly does not function, the laser beam diffuses from the capillary array and cannot efficiently irradiate the entire capillary array. This corresponds to the fact that $\Delta\theta = +1.3^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the concave lens effect.

[0059]

<Relative Fluorescence Intensity Distribution According to Conventional (PTL 1) Capillary Array Configuration>

FIG. 5(a) is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 4(b) and (c) are reproduced in the case of double-side irradiation. Defining the number of the leftmost capillary in FIG. 4 as 1, the capillary numbers are sequentially assigned to the capillaries toward the right side. The relative fluorescence intensity is fluorescence intensity calculated from the irradiation

intensity at each capillary by taking the loss of the laser beam due to reflection into consideration under the assumption that a constant concentration of a fluorophore exists in the laser irradiation portion of each capillary. Assumed to be 1 is the fluorescence intensity expected when the laser beam oscillating from the laser source irradiates at full intensity the inside of one capillary. In the calculation for the double-side irradiation, it was assumed that the laser beam is irradiated to the capillary array from both sides thereof at half the full intensity. The graphs correspond to the laser irradiation intensity at each capillary expressed by Formula (2) and Formula (4). However, while Formula (2) and Formula (4) are approximate equations which assume that the incident angle of the laser beam on an interface between different media is set to 0° , the graphs are the results calculated based on the actual incident angles obtained by the laser beam ray tracing and are thus more accurate. Subsequent similar graphs shown in FIGS. 7(a), 9, 11, 13, 15, 17, 19, and 20 are also more accurate results calculated based on the actual incident angles. In the case of $n_3 = 1.41$ in FIG. 5(a), the minimum value of the relative fluorescence intensity in the 24 capillaries is obtained as $\text{MIN} = 0.42$, and the coefficient of variation (= standard deviation of relative fluorescence intensities/mean value of relative fluorescence intensities) is obtained as

CV = 11%, whereby it is found that $\text{MIN} \geq 0.2$, $\text{CV} \leq 20\%$, and $\text{CV} \leq 15\%$ for the practical performance are satisfied. The distribution of the relative fluorescence intensities with respect to the capillary numbers is convex downward, since the intensity of the laser beam is attenuated as the laser beam advances through the capillary array due to the loss of the laser beam by reflection, despite the fact that the multifocus is functioning. On the other hand, in the case of $n_3 = 1.33$, $\text{MIN} = 0.068$ and $\text{CV} = 74\%$ are obtained, indicating that none of the requirements for the practical performance are satisfied.

[0060]

FIG. 5(b) is a diagram showing the relative fluorescence intensity of each capillary obtained by correcting the optical system by taking the vignetting effect of the optical system of the 3500 Series Genetic Analyzer into consideration along with the results in FIG. 5(a), in other words, by multiplying the results in FIG. 5(a) by an optical system correction coefficient based on the vignetting effect. In the case of $n_3 = 1.41$, the convex downward distribution of the relative fluorescence intensities with respect to the capillary numbers and the distribution of the optical system correction with respect to the capillary numbers cancel each other, and thus the distribution of the relative fluorescence intensities

obtained by correcting the optical system becomes flat. As a result, the minimum value $MIN = 0.42$ of the fluorescence intensity did not change, but the coefficient of variation was significantly decreased to $CV = 0.76\%$. As a matter of course, all requirements for the practical performance were satisfied. On the other hand, in the case of $n_3 = 1.33$, since $MIN = 0.066$ and $CV = 61\%$ are obtained, which were not significantly changed, the requirements for the practical performance were still not satisfied.

[0061]

<Configuration Example of Capillary Array According to First Embodiment>

FIG. 6(a) is a cross-sectional diagram illustrating a configuration example of a capillary array based on a first embodiment. The laser irradiation portions of 24 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. The outside of the capillaries is provided with air having a refractive index $n_1 = 1.00$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$.

[0062]

FIG. 6(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when single-side irradiation with a laser beam having

a diameter of 50 μm was performed from the left side in a case where the insides of the capillaries were a separation medium having a high refractive index $n_3 = 1.41$. The multifocus clearly functions, and the insides of all 24 capillaries can be efficiently irradiated. This corresponds to the fact that $\Delta\theta = -5.8^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the convex lens effect. [0063]

On the other hand, FIG. 6(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the capillaries held a separation medium having a low refractive index $n_3 = 1.33$. The multifocus clearly functions, and the insides of all 24 capillaries can be efficiently irradiated in this case as well. This corresponds to the fact that $\Delta\theta = -3.2^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the convex lens effect. As described above, allowing each capillary to exhibit the convex lens effect and the multifocus to function in both a separation medium having a high refractive index ($n_3 \geq 1.36$) and a separation medium having a low refractive index ($n_3 < 1.36$), which cannot be realized by any of the known examples, is realized for the first time by the technique of the present disclosure. That is, in the capillary array electrophoresis apparatus of the present embodiment, the multifocus

functions in both of the first analysis mode having $n_3 < 1.36$ and the second analysis mode having $n_3 \geq 1.36$.

[0064]

<Relative Fluorescence Intensity Distribution According to Capillary Array Configuration of First Embodiment (FIG. 6)>

FIG. 7(a) is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 6(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 = 1.41$ in FIG. 7(a), the minimum value of the relative fluorescence intensity in the 24 capillaries is obtained as $\text{MIN} = 0.42$, and the coefficient of variation is obtained as $\text{CV} = 11\%$, whereby it is found that $\text{MIN} \geq 0.2$, $\text{CV} \leq 20\%$, and $\text{CV} \leq 15\%$ for the practical performance are satisfied. Similarly, in the case of $n_3 = 1.33$, since $\text{MIN} = 0.40$ and $\text{CV} = 12\%$ are obtained, the practical performance is thus satisfied as well.

[0065]

FIG. 7(b) is a diagram showing the relative fluorescence intensity of each capillary obtained by correcting the optical system by taking the vignetting effect of the optical system of the 3500 Series Genetic Analyzer into consideration along with the results in FIG. 7(a), in other words, by multiplying the results in FIG. 7(a) by an

optical system correction coefficient based on the vignetting effect. As a result of correcting the optical system, $MIN = 0.42$ and $CV = 9.0\%$ are obtained in the case of $n_3 = 1.41$, and $MIN = 0.40$ and $CV = 10\%$ are obtained in the case of $n_3 = 1.33$, thus satisfying the practical performance as well.

[0066]

According to FIG. 7, unlike the case of FIG. 5, the relative fluorescence intensity is not changed much regardless of whether or not the optical system correction is performed. This is attributable to the fact that the total width of the capillary array in FIG. 6, which is defined as $155\ \mu\text{m interval} \times (24\ \text{capillaries} - 1\ \text{capillary}) = 3.6\ \text{mm}$, is narrower than the total width of the capillary array in FIG. 4, which is defined as $370\ \mu\text{m interval} \times (24\ \text{capillaries} - 1\ \text{capillary}) = 8.5\ \text{mm}$. In other words, the distance between each capillary and the optical axis is shorter, and thus the vignetting effect of the optical system is small.

[0067]

As a result, in the case of $n_3 = 1.41$ in the capillary array of the present embodiment shown in FIG. 6, $CV = 11\%$ is only reduced to $CV = 9\%$ by the optical system correction due to the vignetting effect of the optical system, whereas $CV = 11\%$ is greatly reduced to $CV = 0.76\%$ by the optical system

correction due to the vignetting effect of the optical system in the case of $n_3 = 1.41$ in the capillary array of the 3500 Series Genetic Analyzer shown in FIG. 4. Similarly, $CV = 12\%$ is only reduced to $CV = 10\%$ by the optical system correction due to the vignetting effect of the optical system in the case of $n_3 = 1.33$ in the capillary array of the present embodiment.

[0068]

<Conclusion of First Embodiment>

As described above, it has become clear that each capillary exhibits the convex lens effect, and the multifocus functions in the configuration of the first embodiment in the case of using a separation medium having any refractive index within the range of $n_3 \geq 1.33$, including $n_3 = 1.41$. Furthermore, as a modification example of the present configuration, even in the case of using an arbitrary capillary of $R/r \leq 4.4$, for example, an arbitrary capillary having an outer diameter $2R \leq 220 \mu\text{m}$ when the inner diameter is fixed at $2r = 50 \mu\text{m}$, it is possible to cause the multifocus to function, since each capillary exhibits the convex lens effect under the condition of $n_3 \geq 1.33$.

[0069]

(C) Second Embodiment

In the first embodiment, the case where the outside of the capillary is provided with air (refractive index $n_1 =$

1.00) was described. In a second embodiment, a case where the outside of the capillary is not provide with air (refractive index $n_1 \neq 1.00$) will be described. Even in such a case, according to the technique of the present disclosure, each capillary exhibits the convex lens effect, and the multifocus functions in the case of using a separation medium having any refractive index within the range of $n_3 \geq 1.33$, including $n_3 = 1.41$.

[0070]

<Configuration Example of Conventional (PTL 2) Capillary Array>

FIG. 8(a) is a cross-sectional diagram illustrating a configuration of a capillary array of the 3730 Series Genetic Analyzer based on PTL 2. The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. The outside of the capillaries is provide with a fluorine solution having a refractive index $n_1 = 1.29$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$.

[0071]

FIG. 8(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of $50 \mu\text{m}$ from the left side in a case

where the insides of the capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 96 capillaries can be efficiently irradiated. This corresponds to the fact that $\Delta\theta = -0.69^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the convex lens effect.

[0072]

On the other hand, FIG. 8(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the capillaries held a separation medium having a low refractive index $n_3 = 1.33$. Since the multifocus does not function, the laser beam diffuses from the capillary array and cannot efficiently irradiate the entire capillary array. This corresponds to the fact that $\Delta\theta = +2.9^\circ$ is obtained according to Formula (1), and thus each capillary exhibits the concave lens effect.

[0073]

<Relative Fluorescence Intensity Distribution According to Conventional (PTL 2) Capillary Array Configuration>

FIG. 9(a) is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 8(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 =$

1.41, the minimum value of the relative fluorescence intensity in the 96 capillaries is obtained as $\text{MIN} = 0.63$, and the coefficient of variation is obtained as $\text{CV} = 3.2\%$, whereby it is found that $\text{MIN} \geq 0.2$, $\text{CV} \leq 20\%$, and $\text{CV} \leq 15\%$ for the practical performance are satisfied. On the other hand, in the case of $n_3 = 1.33$, since $\text{MIN} = 0.00067$ and $\text{CV} = 192\%$ are obtained, it is found that the requirements for the practical performance are not satisfied.

[0074]

<Configuration Example of Conventional (NPL 1) Capillary Array>

FIG. 10(a) is a cross-sectional diagram illustrating a configuration of a capillary array based on NPL 1. The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The outside of the capillaries is provided with a matching solution having a refractive index $n_1 = 1.46$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The refractive index of a medium on the inside of the lens capillaries is set to $n_4 = 1.53$.

[0075]

FIG. 10(b) is a diagram showing the results of

performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of 50 μm from the left side in a case where the insides of the analysis capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 96 capillaries can be efficiently irradiated. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +2.4^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.0^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = -0.6^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions.

[0076]

On the other hand, FIG. 10(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the analysis capillaries held a separation medium having a low refractive index $n_3 = 1.33$. Since the multifocus does not function, the laser beam diffuses from the capillary array and cannot efficiently irradiate the entire capillary array. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +6.6^\circ$, while the refraction angle at one

lens capillary is obtained as $\Delta\theta_B = -3.0^\circ$. In this case, since $\Delta\theta_A + \Delta\theta_B = +3.6^\circ$ is obtained, one set of one analysis capillary and one lens capillary exhibits the concave lens effect, and the multifocus does not function.

[0077]

<Relative Fluorescence Intensity Distribution According to Conventional (NPL 1) Capillary Array Configuration>

FIG. 11(a) is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 10(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 = 1.41$, the minimum value of the relative fluorescence intensity in the 48 analysis capillaries is obtained as $MIN = 0.58$, and the coefficient of variation is obtained as $CV = 7\%$, whereby it is found that $MIN \geq 0.2$, $CV \leq 20\%$, and $CV \leq 15\%$ for the practical performance are satisfied. On the other hand, in the case of $n_3 = 1.33$, $MIN = 0.00247$ and $CV = 193\%$ are obtained, whereby it is found that that the requirements for the practical performance are not satisfied.

[0078]

<Configuration Example of Conventional (PTL 3) Capillary Array>

FIG. 12(a) is a cross-sectional diagram illustrating a configuration example of a capillary array based on PTL 3.

The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The outside of the capillaries is provide with water having a refractive index $n_1 = 1.33$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The refractive index of a medium on the inside of the lens capillaries is set to $n_4 = 1.53$.

[0079]

FIG. 12(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of $50 \mu\text{m}$ from the left side in a case where the insides of the analysis capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 96 capillaries can be efficiently irradiated. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +0.03^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -2.1^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = -2.07^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary exhibits the convex lens

effect, and the multifocus functions.

[0080]

On the other hand, FIG. 12(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the analysis capillaries held a separation medium having a low refractive index $n_3 = 1.33$. Since the multifocus does not function, the laser beam diffuses from the capillary array and cannot efficiently irradiate the entire capillary array. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +3.7^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -2.1^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = +1.6^\circ$ is obtained. Thus, one set of one analysis capillary and one lens capillary exhibits the concave lens effect, and the multifocus does not function. Therefore, a plurality of capillaries cannot be simultaneously irradiated with a laser beam in the case of using a separation medium having a low refractive index.

[0081]

<Relative Fluorescence Intensity Distribution
According to Conventional (FIG. 12) Capillary Array
Configuration>

FIG. 13 is a diagram showing relative fluorescence intensity of each capillary when the results of the single-

side irradiation shown in FIGS. 12(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 = 1.41$, the minimum value of the relative fluorescence intensity in the 48 analysis capillaries is obtained as $MIN = 0.79$, and the coefficient of variation is obtained as $CV = 1\%$, whereby it is found that $MIN \geq 0.2$, $CV \leq 20\%$, and $CV \leq 15\%$ for the practical performance are satisfied. On the other hand, in the case of $n_3 = 1.33$, $MIN = 0.00975$ and $CV = 119\%$ are obtained, whereby it is found that that the requirements for the practical performance are not satisfied. [0082]

<Configuration Example of Capillary Array According to Second Embodiment>

FIG. 14(a) is a cross-sectional diagram illustrating a configuration example of a capillary array of the second embodiment. The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The outside of the capillaries is provided with a fluorine solution having a refractive index $n_1 = 1.29$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The refractive index of a medium on the inside of the lens capillaries is set to $n_4 = 1.46$.

Since $n_2 = n_4 = 1.46$ is satisfied, rod lenses having an outer diameter $2R = 126 \mu\text{m}$ and a refractive index of 1.46 may be used instead of the lens capillaries. However, it is usually difficult to match the outer diameter of a capillary and the outer diameter of a rod lens. Therefore, it is easier to match the outer diameters of both capillaries by using capillaries having the same specification and the same lot for both the analysis capillary and the lens capillary.

[0083]

FIG. 14(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of $50 \mu\text{m}$ from the left side in a case where the insides of the analysis capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 96 capillaries can be efficiently irradiated. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = -0.7^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -2.7^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = -3.4^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions.

[0084]

On the other hand, FIG. 14(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the analysis capillaries held a separation medium having a low refractive index $n_3 = 1.33$. Although the multifocus functions, since the laser beam slightly diffuses from the capillary array, the entire capillary array cannot be irradiated very efficiently. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +2.9^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -2.7^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = +0.2^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary slightly exhibits the concave lens effect, and the multifocus function is deteriorated. However, it is possible to simultaneously irradiate each capillary with high efficiency, compared to the results obtained by the conventional methods shown in FIGS. 10(c) and 12(c).

[0085]

<Relative Fluorescence Intensity Distribution According to Capillary Array Configuration of Second Embodiment (FIG. 14)>

FIG. 15 is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 14(b) and (c) are reproduced

in the case of double-side irradiation. In the case of $n_3 = 1.41$, the minimum value of the relative fluorescence intensity in the 48 analysis capillaries is obtained as $MIN = 0.68$, and the coefficient of variation is obtained as $CV = 2\%$, whereby it is found that $MIN \geq 0.2$, $CV \leq 20\%$, and $CV \leq 15\%$ for the practical performance are satisfied. On the other hand, in the case of $n_3 = 1.33$, $MIN = 0.42$ and $CV = 11\%$ is obtained, whereby it is found that that $MIN \geq 0.2$ and $CV \leq 20\%$ are satisfied, whereas $CV \leq 15\%$ is not satisfied. Therefore, a method of simultaneously irradiating 48 or more analysis capillaries with a laser beam with higher efficiency is proposed next.

[0086]

<Another Configuration Example of Capillary Array According to Second Embodiment>

FIG. 16(a) is a cross-sectional diagram illustrating a configuration example of the capillary array of the second embodiment. The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The outside of the capillaries is provided with a fluorine solution having a refractive index $n_1 = 1.25$. The material of the capillaries is made of quartz glass having a

refractive index $n_2 = 1.46$. The specifications of the fluorine solution having a refractive index $n_1 = 1.25$ are different from those of the fluorine solution having a refractive index $n_1 = 1.29$, which is used in FIGS. 8 and 14, and are not adopted in the scope of the known techniques. Although reducing the refractive index on the outside of the capillaries can enhance the convex lens effect of each capillary, it also increases the loss of the laser beam due to reflection at the same time. Therefore, it is unclear whether the reduction of the refractive index on the outside of the capillaries is effective for the simultaneous irradiation of 48 or more analysis capillaries. Meanwhile, the fluorine solution having a refractive index $n_1 = 1.25$ can be, for example, Fluorinert (registered trademark) commercially available from 3M. The refractive index of a medium on the inside of the lens capillaries is set to $n_4 = 1.46$.

[0087]

FIG. 16(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of 50 μm from the left side in a case where the insides of the analysis capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 96

capillaries can be efficiently irradiated. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = -1.4^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.3^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = -4.7^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions.

[0088]

On the other hand, FIG. 16(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the analysis capillaries held a separation medium having a low refractive index $n_3 = 1.33$. The multifocus functions, and the insides of all 96 capillaries can be efficiently irradiated. This is attributable to the fact that, according to Formula (1), the refraction angle at one analysis capillary is obtained as $\Delta\theta_A = +2.0^\circ$, while the refraction angle at one lens capillary is obtained as $\Delta\theta_B = -3.3^\circ$, and thus $\Delta\theta_A + \Delta\theta_B = -1.3^\circ$ is obtained. Therefore, one set of one analysis capillary and one lens capillary exhibits the convex lens effect, and the multifocus functions.

[0089]

<Relative Fluorescence Intensity Distribution
According to Capillary Array Configuration of Second

Embodiment (FIG. 16)>

FIG. 17 is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 16(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 = 1.41$, the minimum value of the relative fluorescence intensity in the 48 analysis capillaries is obtained as $MIN = 0.54$, and the coefficient of variation is obtained as $CV = 6\%$, whereby it is found that $MIN \geq 0.2$, $CV \leq 20\%$, and $CV \leq 15\%$ for the practical performance are satisfied. On the other hand, in the case of $n_3 = 1.33$, $MIN = 0.47$ and $CV = 8\%$ is obtained, whereby it is found that that $MIN \geq 0.2$, $CV \leq 20\%$, and $CV \leq 15\%$ are satisfied. In other words, the present configuration is a suitable method for simultaneously irradiating 48 or more analysis capillaries with a laser beam.

[0090]

<Another Configuration Example of Capillary Array According to Second Embodiment>

FIG. 18(a) is a cross-sectional diagram of a configuration of the capillary array of the present embodiment. The laser irradiation portions of 192 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 96 analysis capillaries and 96 lens

capillaries are alternately arranged in the capillary array. The outside of the capillaries is provided with a fluorine solution having a refractive index $n_1 = 1.25$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The refractive index of a medium on the inside of the lens capillaries is set to $n_4 = 1.46$.

[0091]

FIG. 18(b) is a diagram showing the results of performing, under the above conditions, laser beam ray tracing when performing single-side irradiation with a laser beam having a diameter of 50 μm from the left side in a case where the insides of the analysis capillaries held a separation medium having a high refractive index $n_3 = 1.41$. Since the multifocus functions, the insides of all 192 capillaries can be efficiently irradiated. The refraction angle at each capillary is equivalent to that in the case of FIG. 16(b).

[0092]

On the other hand, FIG. 18(c) is a diagram showing the results of performing, under the above conditions, the same laser beam ray tracing in a case where the insides of the analysis capillaries held a separation medium having a low refractive index $n_3 = 1.33$. The multifocus functions, and the insides of all 192 capillaries can be efficiently irradiated. The refraction angle at each capillary is

equivalent to that in the case of FIG. 16(c).

[0093]

<Relative Fluorescence Intensity Distribution
According to Capillary Array Configuration of Second
Embodiment (FIG. 18)>

FIG. 19 is a diagram showing relative fluorescence intensity of each capillary when the results of the single-side irradiation shown in FIGS. 18(b) and (c) are reproduced in the case of double-side irradiation. In the case of $n_3 = 1.41$, the results are obtained in which the minimum value of the relative fluorescence intensity in the 96 analysis capillaries is obtained as $\text{MIN} = 0.30$, and the coefficient of variation is obtained as $\text{CV} = 20\%$, whereby it is found that $\text{MIN} \geq 0.2$ and $\text{CV} \leq 20\%$ for the practical performance are satisfied, whereas $\text{CV} \leq 15\%$ is not satisfied. On the other hand, in the case of $n_3 = 1.33$, $\text{MIN} = 0.23$ and $\text{CV} = 27\%$ are obtained, whereby it is found that that $\text{MIN} \geq 0.2$ and is satisfied, whereas $\text{CV} \leq 20\%$ and $\text{CV} \leq 15\%$ are not satisfied. However, the present configuration clearly provides a suitable method for simultaneously irradiating 96 or more analysis capillaries with a laser beam, compared to the case where $n_3 = 1.33$ in FIG. 9 (PTL 2).

[0094]

<Change in Number of Capillaries>

Similarly to FIGS. 16 to 19, FIG. 20 is a diagram

showing relative fluorescence intensity of each analysis capillary when performing double-side irradiation with a laser beam in the case of arranging 24, 48, 72, and 96 analysis capillaries and 24, 48, 72, and 96 lens capillaries having an outer diameter $2R = 126 \text{ }\mu\text{m}$ and an inner diameter $2r = 50 \text{ }\mu\text{m}$ on the same plane at an interval of $155 \text{ }\mu\text{m}$. The outside of the capillaries is provided with a fluorine solution having a refractive index $n_1 = 1.25$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The insides of the analysis capillaries hold a separation medium having a low refractive index $n_3 = 1.33$. The refractive index of the medium on the inside of the lens capillaries is set to $n_4 = 1.46$. That is, in FIG. 20, the graph of the black rhomboid-shaped plots for the 48 analysis capillaries is the same as the graph for $n_3 = 1.33$ in FIG. 17. The graph of the black square plots for the 96 analysis capillaries is the same as the graph for $n_3 = 1.33$ in FIG. 19. As described above, it is understood that the configuration of the present embodiment is suitable for simultaneous irradiation of various numbers of analysis capillaries from 24 to 96 with a laser beam. Needless to say, the configuration of the present embodiment is also effective for 24 or less or 96 or more analysis capillaries.

[0095]

(D) Third Embodiment

In a third embodiment, evaluated is the influence of the refractive index of the medium on the outside of the capillaries in the configuration of the capillary array of the second embodiment shown in FIG. 16. The laser irradiation portions of 96 capillaries having an outer diameter $2R = 126 \mu\text{m}$ and an inner diameter $2r = 50 \mu\text{m}$ are arranged on the same plane at an interval of $155 \mu\text{m}$. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The insides of the analysis capillaries hold a separation medium having a low refractive index $n_3 = 1.33$. The refractive index of the medium on the inside of the lens capillaries is set to $n_4 = 1.46$.

[0096]

FIG. 21(a) shows relative fluorescence intensities of 48 analysis capillaries when changing the refractive index n_1 on the outside of the capillaries from 1.20 to 1.33 under the above conditions, the maximum values thereof being indicated by black triangle plots, the mean values thereof being indicated by black circle plots, and the minimum value thereof being indicated by black square plots. It is understood from the results that $\text{MIN} \geq 0.2$ for the practical performance is satisfied in the case of $n_1 \leq 1.31$. Furthermore, $\text{MIN} \geq 0.3$ and $\text{MIN} \geq 0.4$ are satisfied, and

higher performance is obtained by setting n_1 within the ranges of $n_1 \leq 1.30$ and $1.23 \leq n_1 \leq 1.29$.

[0097]

FIG. 21(b) shows coefficient of variations for the relative fluorescence intensities of the 48 analysis capillaries when changing the refractive index n_1 on the outside of the capillaries from 1.20 to 1.33 under the same conditions as in FIG. 21(a). It is understood from the results that $CV \leq 20\%$ for the practical performance is satisfied in the case of $n_1 \leq 1.30$. Furthermore, it is understood that $CV \leq 15\%$ for the practical performance is satisfied in the case of $1.21 \leq n_1 \leq 1.29$. In addition, it is understood that $CV \leq 10\%$ is satisfied, indicating higher performance, in the case of $1.24 \leq n_1 \leq 1.28$.

[0098]

$n_1 = 1.25$ in FIG. 16 is a condition under which $CV \leq 10\%$ is obtained, and $MIN = 0.47$ and $CV = 8\%$ are actually obtained as shown in FIG. 17. $n_1 = 1.29$ in FIG. 14 is a condition under which $CV \leq 15\%$ is obtained, whereas $CV \leq 10\%$ is not obtained, and $MIN = 0.42$ and $CV = 11\%$ are actually obtained as shown in FIG. 15. In other words, it is clear from FIG. 21 that $n_1 = 1.25$ is a more preferable condition than $n_1 = 1.29$. Overall, it is understood from the above that higher performance is obtained in the case of $1.24 \leq n_1 \leq 1.28$, and the highest performance is obtained in the case of $n_1 = 1.26$.

[0099]

(E) Fourth Embodiment

In a fourth embodiment, evaluated are the influences of the outer diameter of the capillaries and the ratio of the outer diameter to the inner diameter in the configuration of the capillary array of the second embodiment shown in FIG. 16. The laser irradiation portions of 96 capillaries having an inner diameter $2r = 50 \text{ } \mu\text{m}$ are arranged on the same plane. 48 analysis capillaries and 48 lens capillaries are alternately arranged in the capillary array. The outside of the capillaries is provided with a fluorine solution having a refractive index $n_1 = 1.25$. The material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$. The insides of the analysis capillaries hold a separation medium having a low refractive index $n_3 = 1.33$, and the insides of the lens capillaries hold a matching solution having a refractive index $n_4 = 1.46$.

[0100]

FIG. 22(a) shows relative fluorescence intensities of 48 analysis capillaries when changing the outer diameter $2R$ of the capillaries from $75 \text{ } \mu\text{m}$ to $250 \text{ } \mu\text{m}$ under the above conditions, the maximum values thereof being indicated by black triangle plots, the mean values thereof being indicated by black circle plots, and the minimum value thereof being indicated by black square plots. The interval in the

capillary arrangement is set to a value obtained by adding 29 μm to the outer diameter $2R$. It is understood from the results that $\text{MIN} \geq 0.2$ for the practical performance is satisfied in the case of the outer diameter $2R \leq 190 \mu\text{m}$. Furthermore, $\text{MIN} \geq 0.3$ and $\text{MIN} \geq 0.4$ are satisfied, and higher performance is obtained by setting $2R$ within the ranges of $2R \leq 175 \mu\text{m}$ and $90\mu\text{m} \leq 2R \leq 150 \mu\text{m}$. In other words, it is understood that $\text{MIN} \geq 0.2$ for the practical performance is satisfied when setting the ratio of the outer diameter to the inner diameter to $R/r \leq 3.8$. In addition, $\text{MIN} \geq 0.3$ and $\text{MIN} \geq 0.4$ are satisfied, and higher performance is obtained by setting R/r within the ranges of $R/r \leq 3.5$ and $1.8 \leq R/r \leq 3.0$.

[0101]

FIG. 22(b) shows coefficient of variations for the relative fluorescence intensities of the 48 analysis capillaries when changing the outer diameter $2R$ of the capillaries from 75 μm to 250 μm under the same conditions as in FIG. 22(a). It is understood from the results that $\text{CV} \leq 20\%$ for the practical performance is satisfied when setting the outer diameter to $2R \leq 175 \mu\text{m}$. Furthermore, it is understood that $\text{CV} \leq 15\%$ for the practical performance is satisfied when setting to $85 \mu\text{m} \leq 2R \leq 160 \mu\text{m}$. In addition, it is understood that $\text{CV} \leq 10\%$ is satisfied, indicating higher performance, when setting to $100 \mu\text{m} \leq 2R \leq 140 \mu\text{m}$.

In other words, it is understood that $CV \leq 20\%$ for the practical performance is satisfied when setting the ratio of the outer diameter to the inner diameter to $R/r \leq 3.5$. Moreover, it is understood that $CV \leq 15\%$ for the practical performance is satisfied when setting to $1.7 \leq R/r \leq 3.2$. In addition, it is understood that $CV \leq 10\%$ is satisfied, indicating higher performance, when setting to $2.0 \leq R/r \leq 2.8$.

[0102]

Overall, it is understood from the above that the highest performance is obtained when setting to $100 \mu\text{m} \leq 2R \leq 140 \mu\text{m}$, that is, $2.0 \leq R/r \leq 2.8$.

[0103]

(F) Fifth Embodiment

<Generalization of Technique of Present Disclosure>

A fifth embodiment generalizes features of the configuration of the capillary array of the present disclosure in which analysis capillaries and lens capillaries are alternately arranged. Here, the numbers of the analysis capillaries and the lens capillaries are not necessarily the same. When using analysis capillaries for both ends of the capillary array, N analysis capillaries and N-1 lens capillaries may be alternately arranged, where N is an integer of 2 or more. When using lens capillaries for both ends of the capillary array, N analysis capillaries and

N+1 lens capillaries may be alternately arranged. Hereinafter, the term "capillary" indicates both "analysis capillary" and "lens capillary". In the laser irradiation portion of the capillary, the outer radius of the capillary is defined as R (the outer diameter is 2R), the inner radius is defined as r (the inner diameter is 2r), the refractive index of the medium on the outside of the capillary is defined as n_1 , the refractive index of the material of the capillary is defined as n_2 , the refractive index of the medium on the inside of the analysis capillary (separation medium) is defined as n_3 , and the refractive index of the medium on the inside of the lens capillary is defined as n_4 . In the case of defining as θ_A the refraction angle when a laser beam is transmitted through one analysis capillary is, and defining as θ_B the refraction angle when the laser beam is transmitted through one lens capillary, the following Formula (5) rather than Formula (1) expresses the refraction angle when the laser beam is transmitted through one set of one analysis capillary and one lens capillary.

[0104]

[Mathematical Formula 5]

$$\Delta\theta_A + \Delta\theta_B = 2 \cdot \left\{ -2 \cdot \sin^{-1}\left(\frac{r}{2 \cdot R}\right) + 2 \cdot \sin^{-1}\left(\frac{r \cdot n_1}{2 \cdot R \cdot n_2}\right) - 2 \cdot \sin^{-1}\left(\frac{n_1}{2 \cdot n_2}\right) + \sin^{-1}\left(\frac{n_1}{2 \cdot n_3}\right) + \sin^{-1}\left(\frac{n_1}{2 \cdot n_4}\right) \right\} \dots (5)$$

[0105]

As has been clarified in the second to fourth

embodiments so far, in the configuration of the technique of the present disclosure, the condition for the multifocus to function is given as $\Delta\theta_A + \Delta\theta_B \leq 0$. This condition is found for the first time in the technique of the present disclosure. In particular, in a case where the insides of analysis capillaries are filled with a separation medium having a low refractive index, it is necessary that $\Delta\theta_A + \Delta\theta_B \leq 0$ is satisfied under the condition of, specifically, $n_3 < 1.36$, ideally, $n_3 \leq 1.35$, more ideally, $n_3 \leq 1.34$, and ultimately, $n_3 = 1.33$. These are not realized in any of the known examples. Furthermore, in order to reduce the loss of a laser beam due to reflection on a lens capillary, a condition of $n_2 = n_4$ is preferable. In this case, Formula (5) is modified into the following Formula (6).

[0106]

[Mathematical Formula 6]

$$\Delta\theta_A + \Delta\theta_B = 2 \cdot \left\{ -2 \cdot \sin^{-1} \left(\frac{r}{2 \cdot R} \right) + 2 \cdot \sin^{-1} \left(\frac{r \cdot n_1}{2 \cdot R \cdot n_2} \right) - \sin^{-1} \left(\frac{n_1}{2 \cdot n_2} \right) + \sin^{-1} \left(\frac{n_1}{2 \cdot n_3} \right) \right\} \dots (6)$$

[0107]

The refraction angle is also expressed by Formula (6) when a rod lens having a refractive index of n_2 is used instead of the lens capillary.

[0108]

<Regarding Ratio between Analysis Capillaries and Lens Capillaries>

Hereinbefore, the analysis capillaries and the lens capillaries were alternately arranged at a ratio of 1:1, but the ratio is not necessarily 1:1. For example, when one lens capillary is used for two analysis capillaries, it is sufficient that the convex lens effect is exhibited as a whole and the multifocus functions. In this case, the capillaries may be arranged so that one set of two analysis capillaries and one lens capillary is set as a unit and so that a plurality of units are repeated. It is not necessary that the units are repeated over the entire capillary array. The units may be repeated in a part of the capillary array. In general, when, defining m as a positive integer, one lens capillary is used for m analysis capillaries, that is, when one set of m analysis capillaries and one lens capillary is set as a unit, it is necessary that $m\Delta\theta_A + \Delta\theta_B \leq 0$ is satisfied as the following Formula (7), in order for the convex lens effect to be exhibited and the multifocus to function.

[0109]

[Mathematical Formula 7]

$$m \cdot \Delta\theta_A + \Delta\theta_B = 2 \cdot \left\{ -(m+1) \cdot \sin^{-1} \left(\frac{r_1}{2 \cdot R} \right) + (m+1) \cdot \sin^{-1} \left(\frac{r_1 \cdot n_1}{2 \cdot R \cdot n_2} \right) - (m+1) \cdot \sin^{-1} \left(\frac{r_2}{2 \cdot n_2} \right) + m \cdot \sin^{-1} \left(\frac{r_2}{2 \cdot n_1} \right) + \sin^{-1} \left(\frac{n_1}{2 \cdot n_2} \right) \right\} \dots (7)$$

[0110]

In the case of $m = 1$, Formula (7) is the same as Formula (5).

[0111]

On the other hand, as has been clarified in the embodiments so far, simultaneous irradiation of all analysis capillaries with a laser beam becomes difficult when the loss of the laser beam due to reflection on the capillary is great, even in a case where the multifocus functions. In a case where the transmittance when a laser beam is transmitted through one analysis capillary is defined as T_A , and the transmittance when the laser beam is transmitted through one lens capillary is defined as T_B , the transmittance when the laser beam is transmitted through one set of one analysis capillary and one lens capillary is expressed by the following Formula (8) rather than Formula (1).

[0112]

[Mathematical Formula 8]

$$T_A \times T_B = \left\{ 1 - \left(\frac{n_1 - n_2}{n_1 + n_2} \right)^2 \right\}^4 \cdot \left\{ 1 - \left(\frac{n_2 - n_3}{n_2 + n_3} \right)^2 \right\}^2 \cdot \left\{ 1 - \left(\frac{n_2 - n_4}{n_2 + n_4} \right)^2 \right\}^2 \quad \dots (8)$$

[0113]

Furthermore, in order to reduce the loss of a laser beam due to reflection on a lens capillary, a condition of $n_2 = n_4$ is preferable. In this case, Formula (8) is modified into the following Formula (9).

[0114]

[Mathematical Formula 9]

$$T_A \times T_B = \left\{ 1 - \left(\frac{n_1 - n_2}{n_1 + n_2} \right)^2 \right\}^4 \cdot \left\{ 1 - \left(\frac{n_2 - n_3}{n_2 + n_3} \right)^2 \right\}^4 \quad \dots (9)$$

[0115]

The transmittance is also expressed by Formula (9) in a case where a rod lens having a refractive index of n_2 is used instead of the lens capillary.

[0116]

When performing double-side irradiation with a laser beam in a capillary array in which N analysis capillaries and N lens capillaries are alternately arranged, the laser irradiation intensity at the analysis capillary located at the center of the capillary array is minimized. The capillary number of the analysis capillary located at the center of the capillary array is set to $n = (N + 1)/2$ when N is an odd number, and is set to $n = N/2$ or $n = N/2 + 1$ when N is an even number. Therefore, the minimum value of the laser irradiation intensity is expressed by the following Formula (10) rather than Formula (4) when N is an odd number.

[0117]

[Mathematical Formula 10]

$$\text{MIN} = (T_A \times T_B)^{\frac{N-1}{2}} \dots (10)$$

[0118]

When N is defined as an even number, the minimum value of the laser irradiation intensity is expressed by the following Formula (11).

[0119]

[Mathematical Formula 11]

$$\text{MIN} = (T_A \times T_B)^{\frac{N}{2}-1} \dots (11)$$

[0120]

In order to satisfy the practical performance, it is necessary that $\text{MIN} \geq 0.2$ is satisfied using Formula (10) or Formula (11). In particular, in order to realize the simultaneous irradiation of 24 or more and 48 or more analysis capillaries with a laser beam, it is necessary that $\text{MIN} \geq 0.2$ is satisfied under the conditions of $N = 24$ and $N = 48$. When setting to $N = 48$ in Formula (11), it is only required that $T_A \times T_B \geq 93\%$ is satisfied in order to satisfy $\text{MIN} \geq 0.2$. These conditions are found for the first time in the present disclosure. In particular, when the insides of analysis capillaries are filled with a separation medium having a low refractive index, it is necessary that $\text{MIN} \geq 0.2$ is satisfied under the condition of, specifically, $n_3 < 1.36$, ideally, $n_3 \leq 1.35$, more ideally, $n_3 \leq 1.34$, and ultimately, $n_3 = 1.33$.

[0121]

It is possible to approximately obtain from Formula (4) the coefficient of variation CV for the laser irradiation intensities at N analysis capillaries. The maximum value MAX of the laser irradiation intensity is obtained at the capillaries located at both ends of the capillary array ($n = 1$ and $n = N$). The minimum value MIN of the laser

irradiation intensity is obtained at the capillary located at the center of the capillary array ($n = (N + 1)/2$ when N is defined as an odd number, and $n = N/2$ or $n = N/2 + 1$ when N is defined as an even number). MAX is expressed by the following Formula (12) rather than Formula (4) regardless of whether N is an odd number or an even number.

[0122]

[Mathematical Formula 12]

$$MAX = 0.5 \cdot \{(T_A \times T_B)^{N-1} + 1\} \quad \dots (12)$$

[0123]

In this case, CV can be approximated by dividing the value obtained by dividing $MAX - MIN$ by the average value between MAX and MIN by 3. That is, CV is expressed by the following Formula (13).

[0124]

[Mathematical Formula 13]

$$CV = \frac{2 \cdot (MAX - MIN)}{3 \cdot (MAX + MIN)} \quad \dots (13)$$

[0125]

In order to satisfy the practical performance, it is necessary that $CV \leq 20\%$ and $CV \leq 15\%$ are satisfied using Formula (10) or (11), Formula (12), and Formula (13).

[0126]

As described above, in order to obtain higher practical

performance, it is necessary that the three conditions, (i) $\Delta\theta_A + \Delta\theta_B \leq 0$ or $m\Delta\theta_A + \Delta\theta_B \leq 0$, (ii) $\text{MIN} \geq 0.2$, and (iii) $\text{CV} \leq 20\%$ or $\text{CV} \leq 15\%$, are satisfied at the same time for efficient simultaneous irradiation of a plurality of analysis capillaries with a laser beam. In particular, when the insides of the analysis capillaries are filled with a separation medium having a low refractive index, it is necessary that all of these conditions are satisfied at the same time under the condition of, specifically, $n_3 < 1.36$, ideally, $n_3 \leq 1.35$, more ideally, $n_3 \leq 1.34$, and ultimately, $n_3 = 1.33$.

[0127]

(G) Sixth Embodiment

A sixth embodiment presents a specific configuration of the capillary array in which analysis capillaries and lens capillaries are alternately arranged. Hereinafter, the term "capillary" indicates both "analysis capillary" and "lens capillary".

[0128]

FIG. 23 is a diagram illustrating the surrounding of the laser irradiation portions 14 of a plurality of capillaries. The capillary array is configured by alternately arranging the laser irradiation portions 14 of a plurality of analysis capillaries 1 and a plurality of lens capillaries 24 on the array plane. The analysis

capillaries 1 are indicated by the dotted lines. The lens capillaries 24 are indicated by the solid lines. The laser beam 13 is incident from the side of the array plane and is simultaneously irradiated to the laser irradiation portion 14 of each capillary.

[0129]

FIG. 23 depicts only the vicinity of the laser irradiation portion 14 within the entire analysis capillary 1, whereas the entire lens capillary 24 is depicted in the drawing. In other words, the entire length of the lens capillary is shorter than the entire length of the analysis capillary. The lens capillaries are shorter, since only the laser irradiation portions 14 of the lens capillaries need to be present. As a result, it is possible to reduce the amount of the capillaries consumed as well as to simplify the entire capillary array. The insides of the lens capillaries are filled with a medium having a high refractive index. For example, when the material of the capillaries is made of quartz glass having a refractive index $n_2 = 1.46$, the insides of the lens capillaries are preferably filled with a matching solution having a refractive index $n_4 = 1.46$. It is also effective to seal both ends of the lens capillaries so that the solution filling the lens capillaries does not escape from the lens capillaries due to evaporation or the like. Furthermore, as shown in FIG. 23, both ends of

a plurality of lens capillaries are preferably bundled and sealed together using sealing portions 25. As a result, the entire capillary array can be further simplified. For binding the sealing portion 25 with the lens capillaries, it is convenient to use an adhesive.

[0130]

Although the case of using quartz glass capillaries having a refractive index $n_2 = 1.46$ for both the analysis capillaries and the lens capillaries has been described above, a quartz glass rod may be used instead of the lens capillary, and the glass rod and the analysis capillary may have equal outer diameters. The entire length of the quartz glass rod can be shorter than the entire length of the analysis capillary in this case as well.

Reference Signs List

[0131]

- 1 capillary (analysis capillary)
- 2 sample injection end
- 3 sample elution end
- 4 cathode
- 5 anode
- 6 cathode-side buffer solution
- 7 anode-side buffer solution
- 8 power source
- 9 polymer block

- 10 valve
- 11 syringe
- 12 laser source
- 13 laser beam
- 14 laser irradiation portion
- 15 condenser lens
- 16 laser cut filter
- 17 transmission grating
- 18 imaging lens
- 19 sensor
- 20 emission point
- 21 fluorescence
- 22 imaging point
- 23 optical axis
- 24 lens capillary
- 25 sealing portion

CLAIMS

[Claim 1]

A capillary array comprising:

laser irradiation portions which are collectively irradiated with a laser beam for N analysis capillaries used in electrophoretic analysis; and

laser irradiation portions which are collectively irradiated with the laser beam for $N \pm 1$ lens capillaries not used in the electrophoretic analysis,

wherein N is an integer of 2 or more,

wherein the laser irradiation portions of the analysis capillaries and the laser irradiation portions of the lens capillaries are alternately arranged approximately on a same array plane, and

wherein, when an outer radius is defined as R, an inner radius is defined as r, a refractive index of a medium on an outside is defined as n_1 , and a refractive index of a material is defined as n_2 for each of the N analysis capillaries in the laser irradiation portions and the $N \pm 1$ lens capillaries in the laser irradiation portions, a refractive index of a medium on an inside of the N analysis capillaries in the laser irradiation portions is defined as n_3 , and a refractive index of a medium on an inside of the $N \pm 1$ lens capillaries in the laser irradiation portions is defined as n_4 , and when it is assumed that $n_3 < 1.36$ is satisfied, R, r, n_1 , n_2 , and

n_4 satisfy the following.

[Mathematical Formula 1]

$$-2 \cdot \sin^{-1}\left(\frac{r}{2 \cdot R}\right) + 2 \cdot \sin^{-1}\left(\frac{r \cdot n_1}{2 \cdot R \cdot n_2}\right) - 2 \cdot \sin^{-1}\left(\frac{n_1}{2 \cdot n_2}\right) + \sin^{-1}\left(\frac{n_1}{2 \cdot n_3}\right) + \sin^{-1}\left(\frac{n_1}{2 \cdot n_4}\right) \leq 0$$

[Claim 2]

The capillary array according to claim 1, wherein $n_3 \leq 1.34$ is satisfied.

[Claim 3]

The capillary array according to claim 1, wherein, when a transmittance of each of the N analysis capillaries is defined as T_A , a transmittance of each of the $N \pm 1$ lens capillaries is defined as T_B , and $T_A \times T_B$ is expressed by the following formula,

[Mathematical Formula 2]

$$T_A \times T_B = \left\{1 - \left(\frac{n_1 - n_2}{n_1 + n_2}\right)^2\right\}^4 \cdot \left\{1 - \left(\frac{n_2 - n_3}{n_2 + n_3}\right)^2\right\}^4$$

Wherein, when N is defined as an odd number, the following relationship is satisfied, and

[Mathematical Formula 3]

$$(T_A \times T_B)^{\frac{N-1}{2}} \geq 0.2$$

and wherein N is defined as an even number, the following relationship is satisfied.

[Mathematical Formula 4]

$$(T_A \times T_B)^{\frac{N}{2}-1} \geq 0.2$$

[Claim 4]

The capillary array according to claim 1, wherein, when a transmittance of each of the N analysis capillaries is defined as T_A , a transmittance of each of the $N \pm 1$ lens capillaries is defined as T_B , $T_A \times T_B$ is expressed by the following formula,

[Mathematical Formula 5]

$$T_A \times T_B = \left\{ 1 - \left(\frac{n_1 - n_2}{n_1 + n_2} \right)^2 \right\}^4 \cdot \left\{ 1 - \left(\frac{n_2 - n_3}{n_2 + n_3} \right)^2 \right\}^4$$

MAX is expressed by the following formula, and

[Mathematical Formula 6]

$$\text{MAX} = 0.5 \cdot \{(T_A \times T_B)^{N-1} + 1\}$$

MIN is expressed by the following formula when N is defined as an odd number, or

[Mathematical Formula 7]

$$\text{MIN} = (T_A \times T_B)^{\frac{N-1}{2}}$$

by the following formula when N is defined as an even number,

[Mathematical Formula 8]

$$\text{MIN} = (T_A \times T_B)^{\frac{N}{2}-1}$$

the following relationship is satisfied.

[Mathematical Formula 9]

$$\frac{2 \cdot (\text{MAX} - \text{MIN})}{3 \cdot (\text{MAX} + \text{MIN})} \leq 20\%$$

[Claim 5]

The capillary array according to claim 4, wherein the following relationship is satisfied.

[Mathematical Formula 10]

$$\frac{2 \cdot (\text{MAX} - \text{MIN})}{3 \cdot (\text{MAX} + \text{MIN})} \leq 15\%$$

[Claim 6]

The capillary array according to claim 1, wherein $1.23 \leq n_1 \leq 1.29$ is satisfied.

[Claim 7]

The capillary array according to claim 6, wherein $1.24 \leq n_1 \leq 1.28$ is satisfied.

[Claim 8]

The capillary array according to claim 1, wherein $1.8 \leq R/r \leq 3.0$ is satisfied.

[Claim 9]

The capillary array according to claim 8, wherein $2.0 \leq R/r \leq 2.8$ is satisfied.

[Claim 10]

The capillary array according to claim 1, wherein $n_2 = n_4 = 1.46 \pm 0.01$ is satisfied.

[Claim 11]

The capillary array according to claim 1, wherein 1.33

$\leq n_3 < 1.36$ is satisfied.

[Claim 12]

The capillary array according to claim 1, wherein the capillary array has a plurality of analysis modes including a first analysis mode in which $1.33 \leq n_3 < 1.36$ is satisfied and a second analysis mode in which $1.36 \leq n_3 \leq 1.42$ is satisfied.

[Claim 13]

The capillary array according to claim 1, wherein $N \geq 48$ is satisfied.

[Claim 14]

A capillary array comprising:

laser irradiation portions which are collectively irradiated with a laser beam for N analysis capillaries used in electrophoretic analysis; and

laser irradiation portions which are collectively irradiated with the laser beam for $N \pm 1$ lens capillaries not used in the electrophoretic analysis,

wherein N is an integer of 2 or more,

wherein the laser irradiation portions of the analysis capillaries and the laser irradiation portions of the lens capillaries are alternately arranged approximately on a same array plane, and

wherein, when an outer radius is defined as R , an inner radius is defined as r , a refractive index of a medium on an

outside is defined as n_1 , and a refractive index of a material is defined as n_2 for each of the N analysis capillaries in the laser irradiation portions and the $N \pm 1$ lens capillaries in the laser irradiation portions, a refractive index of a medium on an inside of the N analysis capillaries in the laser irradiation portions is defined as n_3 , and a refractive index of a medium on an inside of the $N \pm 1$ lens capillaries in the laser irradiation portions is defined as n_4 , the relationships $1.23 \leq n_1 \leq 1.29$, $n_2 = n_4 = 1.46 \pm 0.01$, $1.33 \leq n_3 < 1.36$, and $R/r \leq 3.5$ are satisfied.

[Claim 15]

The capillary array according to claim 14, wherein $1.24 \leq n_1 \leq 1.28$ is satisfied.

[Claim 16]

The capillary array according to claim 14, wherein $2.0 \leq R/r \leq 2.8$ is satisfied.

[Claim 17]

The capillary array according to claim 14, wherein $N \geq 48$ is satisfied.

[Claim 18]

A capillary array comprising:

laser irradiation portions which are collectively irradiated with a laser beam for N analysis capillaries used in electrophoretic analysis; and

laser irradiation portions which are collectively

irradiated with the laser beam for $N \pm 1$ lens capillaries not used in the electrophoretic analysis,

wherein N is an integer of 2 or more,

wherein the laser irradiation portions of the analysis capillaries and the laser irradiation portions of the lens capillaries are alternately arranged approximately on a same array plane, and

wherein, when an outer radius is defined as R , an inner radius is defined as r , a refractive index of a medium on an outside is defined as n_1 , and a refractive index of a material is defined as n_2 for each of the N analysis capillaries in the laser irradiation portions and the $N \pm 1$ lens capillaries in the laser irradiation portions, a refractive index of a medium on an inside of the N analysis capillaries in the laser irradiation portions is defined as n_3 , and a refractive index of a medium on an inside of the $N \pm 1$ lens capillaries in the laser irradiation portions is defined as n_4 , the capillary array has a plurality of analysis modes including a first analysis mode in which $1.33 \leq n_3 < 1.36$ is satisfied and a second analysis mode in which $1.36 \leq n_3 \leq 1.42$ is satisfied, under the conditions where $1.23 \leq n_1 \leq 1.29$, $n_2 = n_4 = 1.46 \pm 0.01$, and $R/r \leq 3.5$ are satisfied.

[Claim 19]

The capillary array according to claim 18, wherein $1.24 \leq n_1 \leq 1.28$ is satisfied.

[Claim 20]

The capillary array according to claim 18, wherein $2.0 \leq R/r \leq 2.8$ is satisfied.

[Claim 21]

The capillary array according to claim 18, wherein $N \geq 48$ is satisfied.

[Claim 22]

A capillary array comprising:

laser irradiation portions which are collectively irradiated with a laser beam for N analysis capillaries used in electrophoretic analysis; and

laser irradiation portions which are collectively irradiated with the laser beam for $N \pm 1$ lens capillaries not used in the electrophoretic analysis a,

wherein N is an integer of 2 or more,

wherein the laser irradiation portions of the analysis capillaries and the laser irradiation portions of the lens capillaries are alternately arranged approximately on a same array plane, and

wherein a length of the N analysis capillaries is longer than a length of the $N \pm 1$ lens capillaries.