(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 January 2022 (20.01.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/015239 A1

(51) International Patent Classification:
G01N 33/493 (2006.01) *C12Q 1/58* (2006.01)
G01N 33/62 (2006.01) *B01L 3/00* (2006.01)

(21) International Application Number:
PCT/SG2021/050398

(22) International Filing Date:
07 July 2021 (07.07.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10202006783R 16 July 2020 (16.07.2020) SG

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

(54) Title: METHODS AND DEVICES FOR MEASURING URINE OSMOLALITY

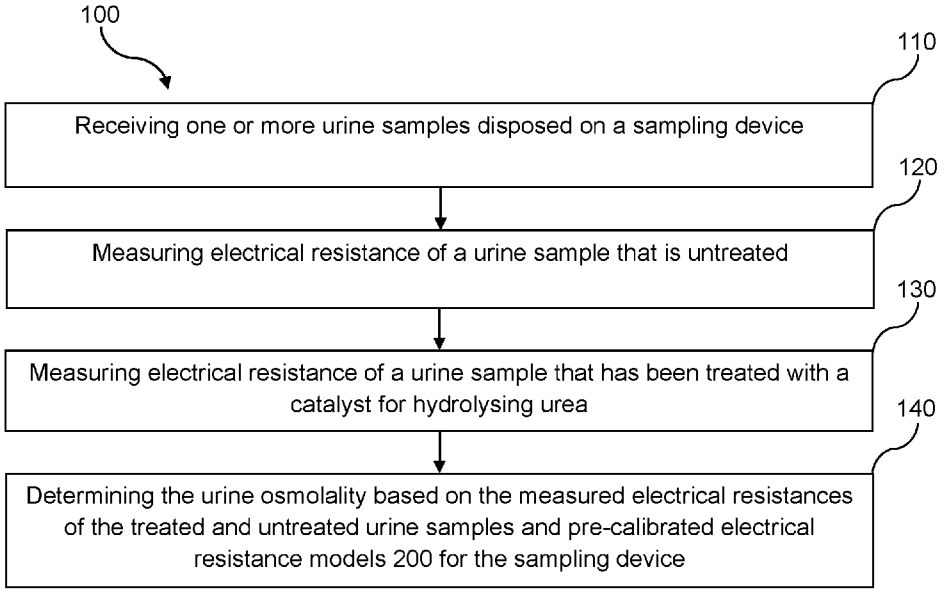

Figure 1A

(57) Abstract: A method (100) for measuring urine osmolality, comprising receiving (110) one or more urine samples disposed on a sampling device, measuring (120) electrical resistance of a urine sample that is untreated, measuring (130) electrical resistance of a urine sample that has been treated with a catalyst for hydrolysing urea, and determining (140) the urine osmolality based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models (200) for the sampling device. The catalyst comprises urease. The invention also teaches a measurement device (850) for measuring urine osmolality, and a sampling device (800) for collecting urine samples for measuring urine osmolality.

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HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

METHODS AND DEVICES FOR MEASURING URINE OSMOLALITY

Cross Reference to Related Applications

The present disclosure claims the benefit of Singapore Patent Application No. 10202006783R filed on 16 July 2020 which is incorporated in its entirety by reference herein.

Technical Field

The present disclosure generally relates to urine osmolality measurement. More particularly, the present disclosure describes various embodiments of methods and devices for measuring urine osmolality.

Background

Urine osmolality is an important indicator for human health and medical conditions. Urine osmolality can aid clinicians in understanding the patient's renal function such as the kidney's ability to concentrate urine and the hydration state of the patient. The urine osmolality value reflects the solute-to-water ratio in urine and is often expressed in milliosmoles per kilogram of water (mOsm/kg) of water. Osmolality, which measures the total number of solutes dissolved in one kilogram of solvent, is often used interchangeably with osmolarity, which measures the total number of solutes per litre of solution. Random urine osmolality values should normally range from 50 to 1200 mOsm/kg of water, while 24-hour urine osmolality values should normally range from 500 to 800 mOsm/kg of water.

An increased level of urine osmolality could be associated with various medical conditions including dehydration, acute kidney injury, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and adrenal insufficiency. On the other hand, a decreased level of urine osmolality could be associated with medical conditions such as diabetes insipidus, excessive fluid intake, kidney failure, and acute renal insufficiency. With a water deprivation period of 12 to 14 hours, the urine osmolality

value should normally be above 850 mOsm/kg of water. If the water deprived urine osmolality value is below 300 mOsm/kg of water, the patient is likely to have diabetes insipidus due to insufficient antidiuretic hormone causing large volume discharge of diluted urine.

Urine osmolality is one of the metrics used in diagnosing nocturia, which is a condition where a person experiences the need to urinate or void one or more times during the night. If the urine osmolality value is significantly lower at night, the person is likely to suffer from nocturia. Nocturia is associated with sleep deprivation due to increased night-time voiding and this has detrimental effects on the person's well-being and can significantly degrade quality of life. Various conditions can cause nocturia and one major cause of nocturia is nocturnal polyuria, where an increased proportion of urine is passed at night than during the day.

Many nocturia cases are poorly managed medically because the appropriate medical therapy for nocturia depends significantly on the underlying aetiology or causation. Due to the uncertain underlying aetiology, nocturia patients are often put on therapeutic trials of different medications which can lead to adverse effects without any proven benefit. Many nocturia patients continue to have unresolved bothersome symptoms despite being on long term follow up, adding to healthcare burden and costs.

Correct diagnosis of the underlying aetiology or causation of nocturia is hence crucial for effective medical therapy. The assessment of nocturia is clinical and a bladder diary is one of the mainstay tools for the nocturia assessment. However, a bladder diary is a crude way to guide management and is inadequate to elucidate the underlying aetiology. As mentioned, urine osmolality is one of the metrics used in diagnosing nocturia. For example, if the underlying cause is nocturnal polyuria, then there will be differences in urine osmolality between normal and those with nocturnal polyuria. Monitoring of urine osmolality at different times of the day serves as an adjunct to the bladder diary. This can help clinicians to have a more thorough understanding of the patient's body conditions and elucidate the underlying aetiology to guide treatment and administer appropriate medical therapy.

However, the patient needs to go to specialized clinics for laboratory urine testing to monitor urine osmolality. These specialized clinics have osmometers which are laboratory benchtop measurement devices that measure urine osmolality based on, for example, the freezing point method. The freezing point osmometer determines the urine's osmotic concentration through freezing point depression, as the freezing point of urine decreases with increasing amounts of solutes in the urine, thus enabling the determination of urine osmolality. These laboratory osmometers are usually bulky and expensive and often require specialized training to operate, resulting in high costs of using the osmometer. Because of the high costs and the time required to visit the specialized clinics, patients would most likely only go there to monitor urine osmolality very occasionally. The irregular urine osmolality values measured by the specialized clinics are often inadequate for clinicians to make an accurate diagnosis of nocturia. As such, patients would still likely continue to have unresolved symptoms and be on long term follow up.

Therefore, in order to address or alleviate at least one of the aforementioned problems and/or disadvantages, there is a need to provide improved methods and devices for measuring urine osmolality.

Summary

According to a first aspect of the present disclosure, there is a method for measuring urine osmolality, the method comprising: receiving one or more urine samples disposed on a sampling device; measuring electrical resistance of a urine sample that is untreated; measuring electrical resistance of a urine sample that has been treated with a catalyst for hydrolysing urea; and determining the urine osmolality based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models for the sampling device.

According to a second aspect of the present disclosure, there is a measurement device for measuring urine osmolality, the measurement device comprising: a reader unit for receiving a sampling device comprising a first urine sample being an untreated urine sample and a second urine sample that has been treated by a catalyst for

hydrolysing urea; electrical connectors for electrically connecting to the sampling device and measuring electrical resistances of the untreated and treated urine samples; and a processor configured for determining the urine osmolality based on the measured electrical resistances of the untreated and treated urine samples and pre-calibrated electrical resistance models for the sampling device.

According to a third aspect of the present disclosure, there is a sampling device for collecting urine samples for measuring urine osmolality, the sampling device comprising: a first sample region for receiving a first urine sample being an untreated urine sample; a set of first electrodes electrically connected to the first sample region, the first electrodes arranged for measuring electrical resistance of the untreated urine sample; a second sample region for receiving a second urine sample, the second sample region comprising a catalyst for hydrolysing urea and thereby treat the second urine sample; a set of second electrodes electrically connected to the second sample region, the second electrodes arranged for measuring electrical resistance of the treated urine sample, wherein the urine osmolality is determinable based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models for the sampling device.

Methods and devices for measuring urine osmolality according to the present disclosure are thus disclosed herein. Various features, aspects, and advantages of the present disclosure will become more apparent from the following detailed description of the embodiments of the present disclosure, by way of non-limiting examples only, along with the accompanying drawings.

Brief Description of the Drawings

Figures 1A to 1C illustrate flowcharts of a method for measuring urine osmolality.

Figures 2A and 2B illustrate pre-calibrated electrical resistance models and steps for measuring urine osmolality.

Figure 3 illustrates a system for measuring urine osmolality.

Figures 4A and 4B illustrate flowcharts of calibration processes for the electrical resistance models.

Figures 5A and 5B illustrate a first calibration process for a first electrical resistance model.

Figures 6A and 6B illustrate a second calibration process for a second electrical resistance model.

Figures 7A to 7E illustrate results from validation tests of the system for measuring urine osmolality.

Figures 8A to 8C illustrate a sampling device and a measurement device for measuring urine osmolality.

Figures 9A to 9E illustrate another sampling device and measurement device for measuring urine osmolality and the pre-calibrated electrical resistance models for the sampling device.

Detailed Description

For purposes of brevity and clarity, descriptions of embodiments of the present disclosure are directed to methods and devices for measuring urine osmolality, in accordance with the drawings. While aspects of the present disclosure will be described in conjunction with the embodiments provided herein, it will be understood that they are not intended to limit the present disclosure to these embodiments. On the contrary, the present disclosure is intended to cover alternatives, modifications and equivalents to the embodiments described herein, which are included within the scope of the present disclosure as defined by the appended claims. Furthermore, in the following detailed description, specific details are set forth in order to provide a thorough understanding of the present disclosure. However, it will be recognized by an individual having ordinary skill in the art, i.e. a skilled person, that the present

disclosure may be practiced without specific details, and/or with multiple details arising from combinations of aspects of particular embodiments. In a number of instances, well-known systems, methods, procedures, and components have not been described in detail so as to not unnecessarily obscure aspects of the embodiments of the present disclosure.

In embodiments of the present disclosure, depiction of a given element or consideration or use of a particular element number in a particular figure or a reference thereto in corresponding descriptive material can encompass the same, an equivalent, or an analogous element or element number identified in another figure or descriptive material associated therewith.

References to “an embodiment / example”, “another embodiment / example”, “some embodiments / examples”, “some other embodiments / examples”, and so on, indicate that the embodiment(s) / example(s) so described may include a particular feature, structure, characteristic, property, element, or limitation, but that not every embodiment / example necessarily includes that particular feature, structure, characteristic, property, element or limitation. Furthermore, repeated use of the phrase “in an embodiment / example” or “in another embodiment / example” does not necessarily refer to the same embodiment / example.

The terms “comprising”, “including”, “having”, and the like do not exclude the presence of other features / elements / steps than those listed in an embodiment. Recitation of certain features / elements / steps in mutually different embodiments does not indicate that a combination of these features / elements / steps cannot be used in an embodiment.

As used herein, the terms “a” and “an” are defined as one or more than one. The use of “/” in a figure or associated text is understood to mean “and/or” unless otherwise indicated. The term “set” is defined as a non-empty finite organization of elements that mathematically exhibits a cardinality of at least one (e.g. a set as defined herein can correspond to a unit, singlet, or single-element set, or a multiple-element set), in accordance with known mathematical definitions. The recitation of a particular

numerical value or value range herein is understood to include or be a recitation of an approximate numerical value or value range.

In representative or exemplary embodiments of the present disclosure, there is a method 100 for measuring urine osmolality, as shown in Figure 1A. The method 100 comprises a step 110 of receiving one or more urine samples disposed on a sampling device. The sampling device may be any device that is configured for or capable of collecting urine samples. The method 100 comprises a step 120 of measuring electrical resistance of a urine sample that is untreated, and a step 130 of measuring electrical resistance of a urine sample that has been treated with a catalyst for hydrolysing urea. The method 100 comprises a step 140 of determining the urine osmolality based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models 200 for the sampling device.

In a normal urine sample, the urine composition may be divided into conductive ions and non-conductive solutes. The conductive ions (~44%) consist of sodium ions (~18%), potassium ions (~7%), chloride ions (~19%), and trace amounts of other dissolved ions. The non-conductive solutes (~56%) consist of predominantly urea (~55%) and remaining solutes (~1%) such as creatinine, inorganic sulphur, and other inorganic and organic compounds. The urine osmolality can be determined by the summation of the molarity of conductive ions and the molarity of non-conductive solutes. The urine osmolality can achieve an accuracy of up to approximately 99% by quantifying the conductive ions (~44%) and non-conductive urea (~55%) present in the urine sample.

However, as urea is non-conductive, the urea must be hydrolysed to produce conductive ions. Notably, urea hydrolysis is a chemical reaction which transforms the urea in urine into ammonia and carbon dioxide. By treating the urine sample with the catalyst, the catalyst is able to catalyse the hydrolysis of urea and convert the non-conductive urea to conductive ions (ammonia) for measurement of the electrical resistance. The catalyst may comprise an enzyme such as urease (or urea amidohydrolase) which is an enzyme found in a large variety of organisms including

Canavalia ensiformis (jack bean). Alternatively, the catalyst used may be synthesized by bacteria such as Helicobacter pylori, Staphylococcus, Klebsiella aerogenes and Sporosarcina pasteurii.

Figure 2A shows the pre-calibrated electrical resistance models 200 for determining the urine osmolality. The models 200 include a first electrical resistance model 210 calibrated from sodium chloride solutions, and a second electrical resistance model 220 calibrated from sodium chloride and urea solutions. The sodium chloride and urea solutions are solution mixtures comprising sodium chloride solutions and urea solutes. Further as shown in Figure 2B, the step 140 of determining the urine osmolality comprises a step 142 of determining a molarity of conductive ions in the untreated urine sample based on the measured electrical resistance of the untreated urine sample and the first electrical resistance model 210. The step 140 further comprises a step 144 of determining a molarity of urea in the treated urine sample before treatment based on the measured electrical resistance of the treated urine sample, the molarity of conductive ions in the untreated urine sample, and the second electrical resistance model 220. The step 140 further comprises a step 146 of determining the urine osmolality based on the molarity of conductive ions in the untreated urine sample and the molarity of urea in the treated urine sample before treatment.

The molarity of conductive ions determined in the step 142 represents the molarity of conductive ions in the untreated urine sample. This is because the electrical resistance property of conductive ions in urine is very similar to that of sodium chloride. The molarity of urea determined in the step 144 refers to the concentration of urea originally in the treated urine sample before treatment with the catalyst. The molarity of non-conductive urea is representative of the molarity of non-conductive solutes originally in the treated urine sample because urea is the dominant non-conductive solute. The urine osmolality can then be determined, in the step 146, from the total urine osmolarity which is the combination of the molarities of the conductive ions and urea in the urine.

In some embodiments, the untreated and treated urine samples are the same urine sample, and the electrical resistances are measured before and after treatment. With reference to Figure 1B, the method 100 includes a step 112 of receiving one urine

sample. For example, the sampling device has a single sample region for collecting the sole urine sample. The method 100 includes a step 122 of measuring the electrical resistance of the urine sample before treatment, a step 150 of treating the urine sample with the catalyst to hydrolyse urea in the urine sample, and a step 132 of measuring the electrical resistance of the urine sample after treatment.

The method 100 for measuring urine osmolality using the same urine sample may be performed using an integrated apparatus configured for sampling and measuring the electrical resistance of the urine sample. The integrated apparatus includes a single sample region, such as a chamber well, for collecting the urine sample. The sample region includes microelectrodes for measuring the electrical resistances of the urine sample before and after treatment. The integrated apparatus includes a catalyst administering device configured for administering the catalyst in the urine sample to treat the urine sample. Alternatively, the catalyst is formed as part of the sample region, such as a coating layer, and a reaction can be triggered to treat the urine sample. The integrated apparatus may include a temperature controller for incubating the urine sample in the sample region, such as at 60 °C which is the optimal working temperature for urease, before measuring the electrical resistances. The integrated apparatus includes a processor configured for determining the urine osmolality of the urine sample based on the measured electrical resistances and the pre-calibrated electrical resistance models 200 for the integrated apparatus.

In some embodiments, the untreated and treated urine samples are separate urine samples, and their electrical resistances are measured separately. With reference to Figure 1C, the method 100 comprises a step 114 of receiving a first urine sample being the untreated urine sample and a step 116 of receiving a second urine sample separately from the first urine sample. For example, the sampling device has separate sample regions for collecting the first and second urine samples separately. This prevents mixing and cross-contamination of the urine samples. The method 100 comprises a step 152 of treating urea in the second urine sample with the catalyst to hydrolyse urea in the second urine sample. The method comprises steps 124,134 of separately measuring the electrical resistances of the untreated and treated urine samples.

The method 100 for measuring urine osmolality using separate urine samples may be performed using a system 300 as shown in Figure 3. The system 300 includes a sampling device 310 for collecting the urine samples and a measurement device 320 for measuring the electrical resistance of the urine samples. The sampling device 310 includes a first sample region 312A and a second sample region 312B. 0.3 ml (or any other suitable sample volume) of each of the first and second urine samples are loaded onto the first and second sample regions 312A,312B, respectively, using a precision instrument such as a pipette. The second sample region 312B may be coated with the catalyst to treat the second urine sample. The sampling device 310 may further include a temperature controller for incubating the urine samples, particularly the second urine sample during treatment. Alternatively, the second urine sample is treated and incubated beforehand, and the treated urine sample is loaded onto the second sample region 312B.

Each of the first and second sample regions 312A,312B includes a printed circuit board (PCB) microchip with embedded microelectrodes for measuring the electrical resistances of the untreated and treated urine samples, respectively. The microelectrodes may have a finger length of 3.5 mm, a finger width of 1.5 mm, and a finger gap of 1.0 mm. The surface of the microelectrodes may be coated with a layer of non-conductive polymer, leaving only a circular opening of 10 mm in diameter for electrical connection to the measurement device 320 for measurement of the electrical resistance.

The measurement device 320 may be an impedance analyser with a built-in AC voltage source for measuring electrical resistance, which is the real part of impedance. A frequency sweep is executed wherein the output frequency is varied from 1 kHz to 1 MHz to measure the impedance responses to determine the electrical resistances. The system 300 further includes a relay switch 330 and a computing device 340. The sampling device 310 is electrically connected to the measurement device 320 via the relay switch 330 for sequentially measuring the electrical resistances of the untreated and treated urine samples. The computing device 340, such as a personal computer, laptop, or mobile device, then receives the measured electrical resistances and

processes them based on the pre-calibrated electrical resistance models 200 to determine the urine osmolality.

It will be appreciated that the design parameters of sample volume and the microelectrode finger dimensions can be changed for different sampling devices 310. It will be appreciated that any sampling device 310 can be used for measurement of urine osmolality, as long as the electrical resistance models 200 are calibrated for the specific design parameters of that sampling device 310.

An exemplary set of calibration processes 400 for the system 300 is shown in Figures 4A and 4B. The calibration processes 400 include a first calibration process 410 for calibrating the first electrical resistance model 210 using of sodium chloride solutions, and a second calibration process 420 for calibrating the second electrical resistance model 220 using of urea and sodium chloride solution mixtures.

For the first calibration process 410, several calibration samples of sodium chloride (NaCl) solutions of various concentrations or molarities ranging from 0.05 M to 0.5 M are used, this range representing the typical concentration of conductive ions in urine, are used. For example, there are six samples having NaCl molarities of 0.05 M, 0.10 M, 0.20 M, 0.30 M, 0.40 M, and 0.50 M.

As shown in Figure 4A, the first calibration process 410 includes a number of steps for each NaCl sample. In a step 411, the NaCl sample is diluted by 10 folds. In a step 412, 0.3 ml of the diluted NaCl sample is loaded onto the first sample region 312A. In a step 413, the temperature controller incubates the diluted NaCl sample at 60 °C for 2 minutes. In a step 414, the measurement device 320 performs a frequency sweep from 1 kHz to 1 MHz to measure the electrical resistance of the NaCl sample. The steps 411-414 are repeated for three times or any number of times using duplicates of each NaCl sample to determine the mean electrical resistance of each NaCl sample.

A graph 500 of the mean electrical resistances, R_{NaCl}, as a function of frequency for the six samples of sodium chloride solutions is shown in Figure 5A. The vertical error bars represent the standard deviations at the corresponding frequencies. In a step 415,

the optimal frequency is identified as 724 kHz. At this optimal frequency as shown in Figure 5A, the six graph lines have large gaps between each other while the standard deviations are the smallest. Therefore, the optimal frequency of 724 kHz is identified as the test frequency for measurement of the molarity of conductive ions in an untreated urine sample. It will be appreciated that the optimal frequency varies for different sampling devices 310 with different electrode designs.

In a step 416, the first electrical resistance model 210 is generated as shown in a graph 510 in Figure 5B. The graph 510 is a function of R_{NaCl} against NaCl molarity at the optimal frequency of 724 kHz. The vertical error bars represent the standard deviations at the corresponding NaCl molarities, while the solid line is the interpolated curve 512.

For the second calibration process 420, several calibration samples of urea and sodium chloride solution mixtures of various NaCl molarities ranging from 0.05 M to 0.5 M and various urea molarities ranging from 0.1 M to 0.5 M are used. All permutations of six NaCl molarities (0.05 M, 0.10 M, 0.20 M, 0.30 M, 0.40 M, and 0.50 M) and six urea molarities (0.10 M, 0.15 M, 0.20 M, 0.30 M, 0.40 M, and 0.50 M) are used, resulting in 36 mixture samples.

As shown in Figure 4B, the second calibration process 420 includes a number of steps for each mixture sample. In a step 421, the mixture sample is treated with the catalyst (urease) to convert non-conductive urea to conductive ions. In a step 422, the mixture sample is incubated in a water bath at 60 °C for 10 minutes to speed up the rate of urea hydrolysis. The incubation time of 10 minutes ensures sufficient change in the electrical resistance after treatment. The incubation time is fixed to control the amount of conductive ions released and can be changed to any specific incubation time, such as 2, 5, 10, or 15 minutes. In a step 423, after cooling the treated mixture sample to room temperature, the treated mixture sample is diluted by 10 folds. In a step 424, 0.3 ml the diluted treated mixture sample is loaded onto the second sample region 312B. In a step 425, the temperature controller incubates the diluted treated mixture sample at 60 °C for 2 minutes. In a step 426, the measurement device 320 performs a frequency sweep from 1 kHz to 1 MHz to measure the electrical resistance of the

treated mixture sample. The steps 421-426 are repeated for three times or any number of times using duplicates of each mixture sample to determine the mean electrical resistance of each treated mixture sample.

Graphs 600-605 of the mean electrical resistances, $R_{mixture}$, as a function of frequency for the 36 samples of urea and sodium chloride solution mixtures is shown in Figure 6A. The vertical error bars represent the standard deviations at the corresponding frequencies. At higher concentrations of urea, more conductive ions were released by the catalyst treatment, thus decreasing $R_{mixture}$ and shifting the electrical resistance lines downwards. In a step 427, the optimal frequency is identified as 316 kHz. At this optimal frequency as shown in Figure 6A, the six graph lines in each of the graphs 600-605 have large gaps between each other while the standard deviations are the smallest. Therefore, the optimal frequency of 316 kHz is identified as the test frequency for measurement of the molarity of urea in a treated urine sample. It will be appreciated that the optimal frequency varies for different sampling devices 310 with different electrode designs.

In a step 428, the second electrical resistance model 220 is generated as shown in a contour plot 610 in Figure 6B. Specifically, from the graphs 600-605, the values of $R_{mixture}$, NaCl molarity, and urea molarity for each of the 36 mixture samples at the optimal frequency of 316 kHz are extracted and transformed into the contour plot 610.

The urine osmolality of an unknown urine sample can be determined using the electrical resistance models 200 calibrated from the calibration processes 400 described above for the system 300. The unknown urine sample is separated into the first and second urine samples for the first and second sample regions 312A,312B, respectively.

With reference to the step 142, for the first urine sample which is untreated, 0.1 ml of it is first diluted with 0.9 ml of deionized water. 0.3 ml of the diluted untreated urine sample is pipetted to the first sample region 312A. The diluted untreated urine sample is incubated at 60 °C for 2 minutes. The measurement device 320 then measures the electrical resistance, R_{urine}, of the untreated urine sample. R_{urine} can be matched to the

corresponding NaCl molarity using the interpolated curve 512 in Figure 5B to determine the molarity of conductive ions, $[C]_{urine}$, in the untreated urine sample.

With reference to the step 144, for the second urine sample, 0.5 ml of it is first added with 0.1 ml of the catalyst (urease) to treat the second urine sample. The treated urine sample is incubated in a water bath at 60 °C for 10 minutes. 0.1 ml of the treated urine sample is diluted with 0.9 ml of deionized water. 0.3 ml of the diluted treated urine sample is pipetted to the second sample region 312B. The diluted treated urine sample is incubated at 60 °C for 2 minutes. The measurement device 320 then measures the electrical resistance, $R_{urine\_treatment}$, of the treated urine sample. R_{urine} and the molarity of conductive ions ($[C]_{urine}$) can be matched to the contour plot 610 in Figure 6B to determine the molarity of non-conductive urea, $[NC]_{urine}$, originally in the treated urine sample before treatment.

With reference to the step 146, the urine osmolality of the unknown urine sample can be determined based on the molarity of conductive ions ($[C]_{urine}$) and the molarity of non-conductive urea ($[NC]_{urine}$) using the equations below.

$$\text{Urine Osmolarity} = (2[C]_{urine} + [NC]_{urine}) \times 1000$$

$$\text{Urine Density} = (1000 + A_C \times [C]_{urine} + A_{NC} \times [NC]_{urine}) / 1000$$

$$\text{Urine Osmolality} = (\text{Urine Osmolarity}) / (\text{Urine Density})$$

The coefficient "A_C" denotes the molar mass of NaCl which is approximately 58.44 g/mol, and the coefficient "A_{NC}" denotes the molar mass of urea which is approximately 60.06 g/mol. For example, if $[C]_{urine}$ = 0.328 M and $[NC]_{urine}$ = 0.316 M, then the urine osmolarity is approximately 972 mOsm/L and the urine density is approximately 1.038 g/cm^3. Therefore, the urine osmolality is determined to be approximately 936 mOsm/kg.

A first validation test was conducted to investigate how the system 300 can measure urine osmolality accurately in a blinded manner. Urine samples were obtained from six healthy patients. Using the system 300, the urine osmolality of each urine sample was measured three times for (a) same day measurement at room temperature; (b) after

storing the urine sample at 4 °C for 48 hours; and (c) after storing the urine sample at -30 °C for 48 hours. For benchmark reference, the urine osmolality of each urine sample was also measured independently using a commercial freezing point osmometer. The table 700 in Figure 7A and the graph 710 in Figure 7B summarize the results from the first validation test. As shown in the table 700, the system 300 has an average measurement accuracy of 95.1±3.8% in comparison to the freezing point osmometer. Moreover, as shown in the graph 710, the storage temperature and condition of the urine samples do not affect the urine osmolality and are within acceptable margins of error.

A second validation test was conducted as part of a clinical trial of the system 300. Urine samples were obtained from four healthy patients who were instructed to collect the urine samples at timings of 0600, 1200, 1800, 0000, and 0300 hours. Like the first validation test, the urine osmolality of each urine sample was measured using the system 300 and the commercial freezing point osmometer. The table 720 in Figure 7C summarizes the results from the second validation test. For example, Sample 1-1 refers to the urine samples of patient number 1 collected at 0600 hours, and Sample 2-2 refers to the urine samples of patient number 2 collected at 1200 hours. The system 300 has an average measurement accuracy of 96.1±1.8% in comparison to the freezing point osmometer. The average measurement accuracies from both the first and second validation tests are thus in good agreement with each other.

As shown in Figure 7D, the graph 730 shows the urine osmolality profiles of the four patients throughout the day. The curves 731,732,733,734 represent the urine osmolality profiles of patient numbers 1 to 4, respectively. The suffixes “a” and “b” represent the urine osmolality profiles measured by the system 300 (solid lines) and the freezing point osmometer (dashed lines), respectively. The graph 730 thus monitors the urine at different times of the day and can serve as an adjunct to the bladder diary. As mentioned above, this can help clinicians to understand the patient’s body conditions and elucidate the underlying aetiology to guide treatment and administer appropriate medical therapy for nocturia. Additionally, the graph 740 in Figure 7E shows the values of urine osmolality measured using the system 300 against the urine osmolality values measured using the freezing point osmometer. The

linear correlation coefficient of the best fit line 742 between these two sets of urine osmolality values was calculated to be 0.9988, which corroborates the accuracy of the system 300 for measuring urine osmolality.

In some embodiments as shown in Figure 8A, there is a sampling device 800 for collecting urine samples and a measurement device 850 for measuring urine osmolality of the urine samples. The measurement device 850 includes a reader unit 852 for receiving the sampling device 810 comprising a first urine sample and a second urine sample that has been treated by a catalyst for hydrolysing urea. The first and second urine samples are thus the untreated and treated urine samples, respectively. Further as shown in Figure 8B, the measurement device 850 includes electrical connectors 854 for electrically connecting to the sampling device 800 and measuring electrical resistances of the untreated and treated urine samples. The electrical connectors 854 may be disposed at the reader unit 852. The measurement device 850 includes a processor configured for determining the urine osmolality based on the measured electrical resistances of the untreated and treated urine samples and the pre-calibrated electrical resistance models 200 for the sampling device 800. The measurement device 850 may include a temperature controller for incubating the urine samples in the reader unit 852 before measuring the electrical resistances, wherein treated urine sample may be incubated for a longer duration than the untreated urine sample. The measurement device 850 may include a display screen 856 for displaying information from the urine osmolality measurement, such as the urine osmolality value and incubation temperature. The display screen 856 may be a touchscreen capable of receiving touch inputs.

It will be appreciated that the pre-calibrated electrical resistance models 200 for the sampling device 800 may be different from those for the sampling device 310 of the system 300 described above because of different design parameters of the sampling devices 310,800. It will also be appreciated that various aspects of the system 300 described above will apply similarly or analogously to the sampling device 800 and measurement device 850 and vice versa and will not be further described for purpose of brevity.

As shown in Figure 8A, the sampling device 800 may be dipped into a container 802 containing the patient's urine, like a dipstick. The sampling device 800 collects the urine samples and is then inserted into the reader unit 852 of the measurement device 850. Further as shown in Figure 8C, the sampling device 800 comprises a first sample region 810A for receiving the first or untreated urine sample and a second sample region 810B for receiving the second urine sample. The second sample region 810B comprises the catalyst for hydrolysing urea and treat the second urine sample.

The sampling device 800 comprises a set of first electrodes 820A electrically connected to the first sample region 810A, the first electrodes 820A arranged for measuring electrical resistance of the untreated urine sample. The sampling device 800 comprises a set of second electrodes 820B electrically connected to the second sample region 810B, the second electrodes 820B arranged for measuring electrical resistance of the treated urine sample. The electrodes 820A,820B may be interdigitated microelectrodes made of metallic stripes. After insertion into the measurement device 850, the urine osmolality can be determined based on the measured electrical resistances of the treated and untreated urine samples and the pre-calibrated electrical resistance models 200 for the sampling device 800.

The sampling device 800 may comprise electrical contacts 830A,830B that are electrically connected to the first and second electrodes 820A,820B, respectively. The electrical contacts 830A,830B are electrically connectable to the electrical connectors 854 of the measurement device 850 upon insertion of the sampling device 800 therein. Alternatively, the electrical connectors 854 are directly connectable to the first and second electrodes 820A,820B.

The sampling device 800 may comprise a sample loading region 840 for receiving a bulk sample of urine (such as from the container of urine 802) and communicating the bulk urine sample separately to the first and second sample regions 810A,810B as the first and second urine samples, respectively. Notably, the first and second sample regions 810A,810B are arranged to collect the respective urine samples separately so that the untreated and treated urine samples do not mix with and contaminate each other. The sample loading region 840 may comprise a wicking element. When the

sampling device 800 is dipped into the bulk sample of urine, the sample loading region 840 absorbs the urine and communicates the urine to the first and second sample regions 810A,810B via capillary action. Alternatively, the urine samples are directly dispensed onto the first and second sample regions 810A,810B such as with a pipette.

In one embodiment, the sampling device 800 comprises microfluidic channels or microchannels for receiving the urine samples. Specifically, the first sample region 810A comprises a first microchannel for receiving the first urine sample, and the second sample region 810B comprises a second microchannel for receiving the second urine sample, wherein the catalyst is coated on the second microchannel. For example, during fabrication of the sampling device 800, 0.2 ml of the catalyst is coated on the second microchannel and dried overnight. The microchannels are dimensioned such that the urine samples can communicate from the sample loading region 840 via capillary action.

In one embodiment, the sampling device 800 comprises absorbent elements for receiving the urine samples. Specifically, the first sample region 810A comprises a first absorbent element for receiving the first urine sample, and the second sample region 810B comprises a second absorbent element for receiving the second urine sample, wherein the catalyst is impregnated in the second absorbent element. For example, during fabrication of the sampling device 800, the second absorbent element is soaked with 0.2 ml of the catalyst and dried at overnight. The absorbent elements are arranged to be fluidically communicative with the sample loading region 840 to absorb the urine samples therefrom. The absorbent elements may comprise absorbent pads made of a liquid absorbent material such as polyester felt. Alternatively, the absorbent elements may comprise liquid absorbent paper strips. The absorbent elements may include a dye reagent that changes colour upon reaction with urine.

Figure 9A shows another sampling device 900 for collecting urine samples for measuring urine osmolality. It will be appreciated that the pre-calibrated electrical resistance models 200 for the sampling device 900 may be different from those for the sampling devices 310,800 described above. It will also be appreciated that various

aspects of the sampling devices 310,800 described above will apply similarly or analogously to the sampling device 900 and vice versa and will not be further described for purpose of brevity.

The sampling device 900 comprises a substrate 905 which may be made of a printed circuit board (PCB). The sampling device 900 comprises a first sample region 910A for receiving the first or untreated urine sample and a second sample region 910B for receiving the second urine sample. The second sample region 910B comprises the catalyst for hydrolysing urea and treat the second urine sample. Specifically, the first sample region 910A comprises a first absorbent element 912A for receiving the first urine sample, and the second sample region 910B comprises a second absorbent element 912B for receiving the second urine sample, wherein the catalyst is impregnated in the second absorbent element 912B. For example, the catalyst is urease and during fabrication of the sampling device 900, the second absorbent element 912B is soaked in urease solution with specific activity of 1,500 to 5,000 units of urease diluted in 5 ml of deionized water, and then dried overnight. The absorbent elements 912A,912B may comprise absorbent pads made of a liquid absorbent material such as polyester felt.

The sampling device 900 comprises a set of first electrodes 920A disposed on the substrate 905 and electrically connected to the first sample region 910A, the first electrodes 920A arranged for measuring electrical resistance of the untreated urine sample. The sampling device 900 comprises a set of second electrodes 920B disposed on the substrate 905 and electrically connected to the second sample region 910B, the second electrodes 920B arranged for measuring electrical resistance of the treated urine sample. The electrodes 920A,920B may be interdigitated microelectrodes made of metallic stripes. The sampling device 900 comprises a set of first electrical contacts 930A electrically connected to the first electrodes 920A, and a set of second electrical contacts 930B electrically connected to the second electrodes 920B.

Figure 9B shows another measurement device 950 for receiving the sampling device 900. The measurement device 950 includes a reader unit 952 and a display screen

956. The electrical contacts 930A,930B are electrically connectable to the electrical connectors of the measurement device 950 upon insertion of the sampling device 900 therein. After insertion into the measurement device 850, the urine osmolality can be determined based on the measured electrical resistances of the treated and untreated urine samples and the pre-calibrated electrical resistance models 200 for the sampling device 900.

The sampling device 900 may include a cover element 940 and a double-sided adhesive foam 942. The cover element 940, such as a glass cover slip, is arranged to cover the first and second sample regions 910A,910B to prevent evaporation of the first and second urine samples. The adhesive foam 942 is used to bond the cover element 940 to the substrate 905, thus sandwiching and covering the and to sandwich the first and second sample regions 910A,910B. Additionally, the adhesive foam 942 separates the first and second sample regions 910A,910B from each other to prevent mixing and cross-contamination of the untreated and treated urine samples.

The set of first electrodes 920A includes a first pair of first electrodes 922A (A-A') for measuring the electrical resistance of the untreated urine sample, and a second pair of first electrodes 924A (C-C') for detecting that the untreated urine sample in the first sample region is sufficient. The untreated urine sample is sufficient if the first absorbent element 912A is fully wetted to form an electrical connection between the second pair of first electrodes 924A. The first pair of first electrodes 922A may have a finger gap of 2 mm. The set of first electrical contacts 930A includes a first pair of first electrical contacts 932A electrically connected to the first pair of first electrodes 922A, and a second pair of first electrical contacts 934A electrically connected to the second pair of first electrodes 924A.

The set of second electrodes 920B includes a first pair of second electrodes 922B (B-B') for measuring the electrical resistance of the treated urine sample, and a second pair of second electrodes 924B (D-D') for detecting that the treated urine sample in the second sample region is sufficient. The treated urine sample is sufficient if the second absorbent element 912B is fully wetted to form an electrical connection between the second pair of second electrodes 924B. The first pair of second

electrodes 922B may have a finger gap of 2 mm. The set of second electrical contacts 930B includes a first pair of second electrical contacts 932B electrically connected to the first pair of second electrodes 922B, and a second pair of second electrical contacts 934B electrically connected to the second pair of second electrodes 924B.

To collect urine samples using the sampling device 900, the sampling device 900 is first dipped into a bulk sample of urine for 5 to 10 seconds to load the urine samples by wetting the absorbent elements 912A,912B. The sampling device 900 with the untreated and treated urine samples is then inserted into the reader unit 952 of the measurement device 950, thereby establishing electrical connections between the electrical contacts 930A,930B and the electrical connectors.

Once the measurement device 950 detects that there is sufficient untreated urine sample at the first sample region 910A (via the first electrical contacts 934A and first electrodes 924A) and sufficient treated urine sample at the second sample region 910B (via the second electrical contacts 934B and second electrodes 924B), the temperature controller will increase and regulate the temperature to 60 °C, which is the optimal working temperature for urease, and incubate the urine samples on the sampling device 900.

After the untreated urine sample has been incubated for 2 minutes, the measurement device 950 measures the electrical resistance of the untreated urine sample to determine the molarity of conductive ions therein based on the first electrical resistance model 210 for the sampling device 900. After the treated urine sample has been incubated for 5 minutes, the measurement device 950 measures the electrical resistance of the treated urine sample to determine molarity of urea in the treated urine sample before treatment based on the molarity of conductive ions in the untreated urine sample and the second electrical resistance model 220 for the sampling device 900. Notably, the treated urine sample is incubated for a longer duration than the untreated urine sample to allow more time for the urea hydrolysis. It will be appreciated that the incubation duration for the treated urine sample may be different for other urease concentrations.

With reference to the first calibration process 410, the first electrical resistance model 210 for the sampling device 900 was calibrated using six calibration samples of sodium chloride solutions with NaCl molarities of 0.05 M, 0.10 M, 0.20 M, 0.30 M, 0.40 M, and 0.50 M. A frequency sweep from 1 kHz to 1 MHz was performed to measure the impedance responses and determine the real part of impedance, which is the electrical resistances, of the NaCl samples.

A graph 960 of the mean electrical resistances as a function of frequency for the six samples of sodium chloride solutions is shown in Figure 9C. The optimal frequency which minimizes error in concentration estimation was determined to be 871 kHz. With reference to Figure 9D, the first electrical resistance model 210 is shown as a graph 970 being a function of NaCl electrical resistance against NaCl molarity at the optimal frequency of 871 kHz. Notably, the coefficient of determination R^2 for the interpolated curve 972 was calculated to be 0.999, evidencing a near perfect fit between NaCl electrical resistance and NaCl molarity. The measurement device 950 measures the electrical resistance of the untreated urine sample at the first sample region 910A (via the first electrical contacts 932A and first electrodes 922A). The measurement device 950 then matches the measured electrical resistance to the corresponding NaCl molarity using the graph 970 to determine the molarity of conductive ions in the untreated urine sample.

With reference to the second calibration process 420, the second electrical resistance model 220 for the sampling device 900 was calibrated using 15 calibration samples of urea and sodium chloride solution mixtures. The 15 mixture samples consist of all permutations of three NaCl molarities (0.10 M, 0.30 M, and 0.50 M) and five urea molarities (0.10 M, 0.20 M, 0.30 M, 0.40 M, and 0.50 M). Instead of performing a frequency sweep, a frequency of 1 MHz was arbitrarily selected to measure the impedance responses and determine the electrical resistances of the mixture samples. However, it will be appreciated that the frequency sweep can be performed to determine the optimal frequency, as described in the second calibration process 420.

With reference to Figure 9E, the second electrical resistance model 220 is shown as a graph 980 being a function of electrical resistance against urea molarity at the

selected frequency of 1 MHz. The three interpolated curves 982,984,986 represent the three NaCl molarities (0.10 M, 0.30 M, and 0.50 M, respectively). Notably, the coefficients of determination R^2 for the interpolated curves 982,984,986 were calculated to be 0.976, 0.915, and 0.938, respectively, evidencing a strong relationship between electrical resistance of the mixture samples and urea molarities. The measurement device 950 measures the electrical resistance of the treated urine sample at the second sample region 910B (via the second electrical contacts 932B and second electrodes 922B). The measurement device 950 then matches the measured electrical resistance of the treated urine sample to the interpolated curve 982,984,986 corresponding to the molarity of conductive ions of the untreated urine sample and determines the corresponding molarity of urea originally in the treated urine sample before treatment.

Various embodiments herein describe devices and methods for measuring urine osmolality based on the electrical resistances and concentrations of conductive ions and non-conductive solutes (predominantly urea) in urine. These devices include the sampling devices 800,900 and measurement devices 850,950 which are compact, portable, and affordable. As such, patients can easily use the devices to monitor their urine osmolality measurements regularly throughout the day at the comfort of their home. These point-of-care devices obviate the need for frequent trips to specialized clinics for urine osmolarity measurements and reduces medical costs. The regular urine osmolality measurements facilitate the assessment of nocturia and nocturnal polyuria, and they supplement the bladder diaries to help clinicians elucidate the underlying aetiology and administer appropriate medical treatment. This improves the accuracy of diagnosis of nocturia and nocturnal polyuria, and allows for better management of such medical conditions through better personalised treatments and avoidance of unnecessary medications. This mitigates the risk of emergency visits to hospitals due to drug toxicity effects from unnecessary medications. Nocturia patients can more quickly have their medical conditions accurately diagnosed and resolved, resulting in overall reduction in healthcare costs.

In the foregoing detailed description, embodiments of the present disclosure in relation to methods and devices for measuring urine osmolality are described with reference

to the provided figures. The description of the various embodiments herein is not intended to call out or be limited only to specific or particular representations of the present disclosure, but merely to illustrate non-limiting examples of the present disclosure. The present disclosure serves to address at least one of the mentioned problems and issues associated with the prior art. Although only some embodiments of the present disclosure are disclosed herein, it will be apparent to a person having ordinary skill in the art in view of this disclosure that a variety of changes and/or modifications can be made to the disclosed embodiments without departing from the scope of the present disclosure. Therefore, the scope of the disclosure as well as the scope of the following claims is not limited to embodiments described herein.

Claims

1. A method for measuring urine osmolality, the method comprising:

receiving one or more urine samples disposed on a sampling device;

measuring electrical resistance of a urine sample that is untreated;

measuring electrical resistance of a urine sample that has been treated with a catalyst for hydrolysing urea; and

determining the urine osmolality based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models for the sampling device.

2. The method according to claim 1, comprising:

receiving a first urine sample being the untreated urine sample;

receiving a second urine sample separately from the first urine sample;

treating the second urine sample with the catalyst to hydrolyse urea in the second urine sample; and

separately measuring the electrical resistances of the untreated and treated urine samples.

3. The method according to claim 1, comprising:

receiving one urine sample;

measuring the electrical resistance of the urine sample before treatment;

treating the urine sample with the catalyst to hydrolyse urea in the urine sample;

measuring the electrical resistance of the urine sample after treatment.

4. The method according to any one of claims 1 to 3, wherein determining the urine osmolality comprises:

determining a molarity of conductive ions in the untreated urine sample based on the measured electrical resistance thereof and a first electrical resistance model calibrated from sodium chloride solutions;

determining a molarity of urea in the treated urine sample before treatment based on the measured electrical resistance thereof, the molarity of

conductive ions in the untreated urine sample, and a second electrical resistance model calibrated from sodium chloride and urea solutions; and

determining the urine osmolality based on the molarity of conductive ions in the untreated urine sample and the molarity of urea in the treated urine sample before treatment.

5. The method according to any one of claims 1 to 4, comprising incubating the urine samples before measuring the electrical resistances.

6. The method according to claim 5, wherein the urine sample treated with the catalyst is incubated for a longer duration than the untreated urine sample.

7. The method according to any one of claims 1 to 6, wherein the catalyst comprises urease.

8. A measurement device for measuring urine osmolality, the measurement device comprising:

a reader unit for receiving a sampling device comprising a first urine sample being an untreated urine sample and a second urine sample that has been treated by a catalyst for hydrolysing urea;

electrical connectors for electrically connecting to the sampling device and measuring electrical resistances of the untreated and treated urine samples; and

a processor configured for determining the urine osmolality based on the measured electrical resistances of the untreated and treated urine samples and pre-calibrated electrical resistance models for the sampling device.

9. The measurement device according to claim 8, wherein determining the urine osmolality comprises:

determining a molarity of conductive ions in the untreated urine sample based on the measured electrical resistance thereof and a first electrical resistance model calibrated from sodium chloride solutions;

determining a molarity of urea in the treated urine sample before treatment based on the measured electrical resistance thereof, the molarity of conductive ions in the untreated urine sample, and a second electrical resistance model calibrated from sodium chloride and urea solutions; and

determining the urine osmolality based on the molarity of conductive ions in the untreated urine sample and the molarity of urea in the treated urine sample before treatment.

10. The measurement device according to claim 8 or 9, further comprising a temperature controller for incubating the urine samples in the reader unit before measuring the electrical resistances.

11. The measurement device according to claim 10, wherein the treated urine is incubated for a longer duration than the untreated urine sample.

12. The measurement device according to any one of claims 8 to 11, wherein the catalyst comprises urease.

13. A sampling device for collecting urine samples for measuring urine osmolality, the sampling device comprising:

a first sample region for receiving a first urine sample being an untreated urine sample;

a set of first electrodes electrically connected to the first sample region, the first electrodes arranged for measuring electrical resistance of the untreated urine sample;

a second sample region for receiving a second urine sample, the second sample region comprising a catalyst for hydrolysing urea and thereby treat the second urine sample; and

a set of second electrodes electrically connected to the second sample region, the second electrodes arranged for measuring electrical resistance of the treated urine sample,

wherein the urine osmolality is determinable based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models for the sampling device.

14. The sampling device according to claim 13, wherein

the first sample region comprises a first microchannel for receiving the first urine sample; and

the second sample region comprises a second microchannel for receiving the second urine sample, wherein the catalyst is coated on the second microchannel.

15. The sampling device according to claim 13, wherein

the first sample region comprises a first absorbent element for receiving the first urine sample; and

the second sample region comprises a second absorbent element for receiving the second urine sample, wherein the catalyst is impregnated in the second absorbent element.

16. The sampling device according to any one of claims 13 to 15, further comprising a sample loading region for receiving a bulk sample of urine and communicating the bulk urine sample separately to the first and second sample regions as the first and second urine samples, respectively.

17. The sampling device according to claim 16, wherein the sample loading region comprises a wicking element.

18. The sampling device according to any one of claims 13 to 17, further comprising a cover element for covering the first and second sample regions to prevent evaporation of the first and second urine samples.

19. The sampling device according to any one of claims 13 to 18, wherein the catalyst comprises urease.

20. The sampling device sampling device according to any one of claims 13 to 19, wherein

the set of first electrodes comprises:

a first pair of first electrodes for measuring the electrical resistance of the untreated urine sample;

a second pair of first electrodes for detecting that the untreated urine sample in the first sample region is sufficient; and

the set of second electrodes comprises:

a first pair of second electrodes for measuring the electrical resistance of the treated urine sample; and

a second pair of second electrodes for detecting that the treated urine sample in the second sample region is sufficient.

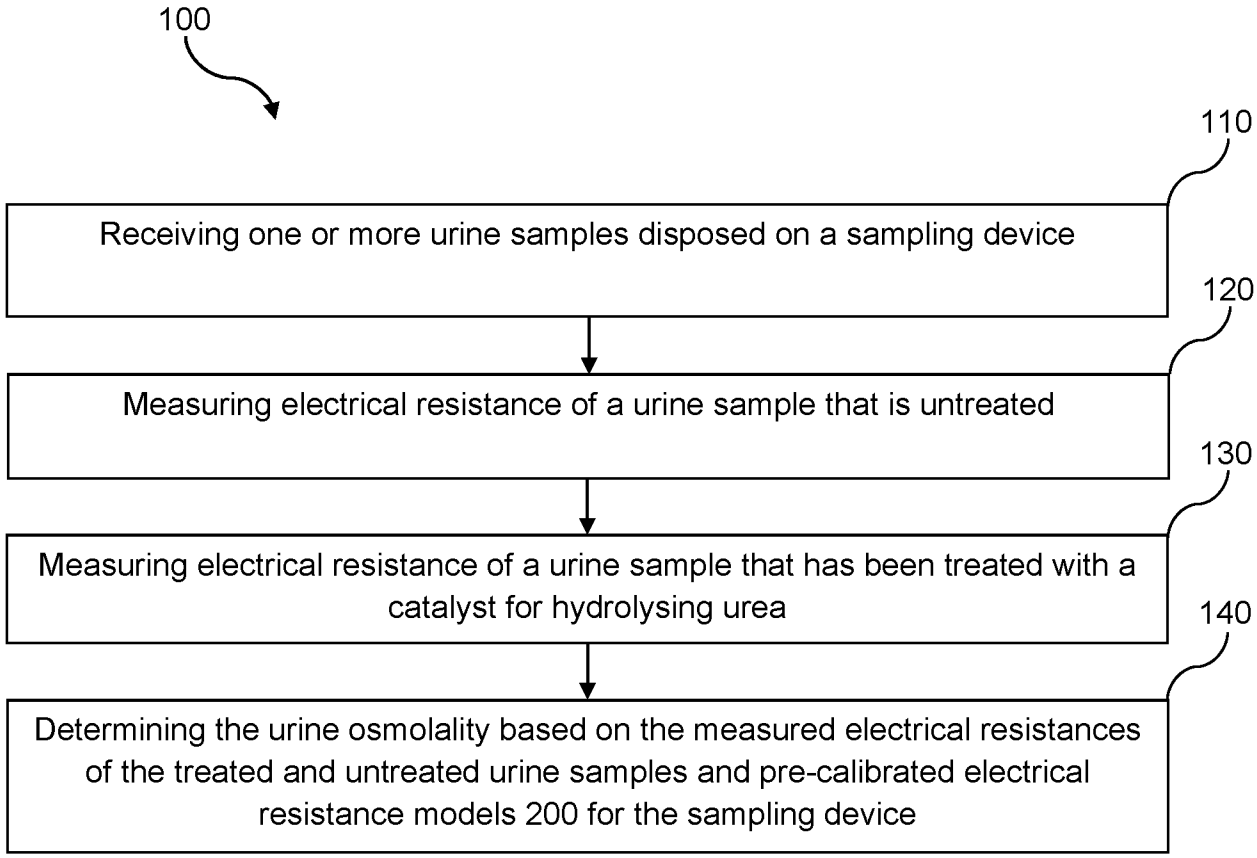

100
110
Receiving one or more urine samples disposed on a sampling device
120
Measuring electrical resistance of a urine sample that is untreated
130
Measuring electrical resistance of a urine sample that has been treated with a catalyst for hydrolysing urea
140
Determining the urine osmolality based on the measured electrical resistances of the treated and untreated urine samples and pre-calibrated electrical resistance models 200 for the sampling device

Figure 1A

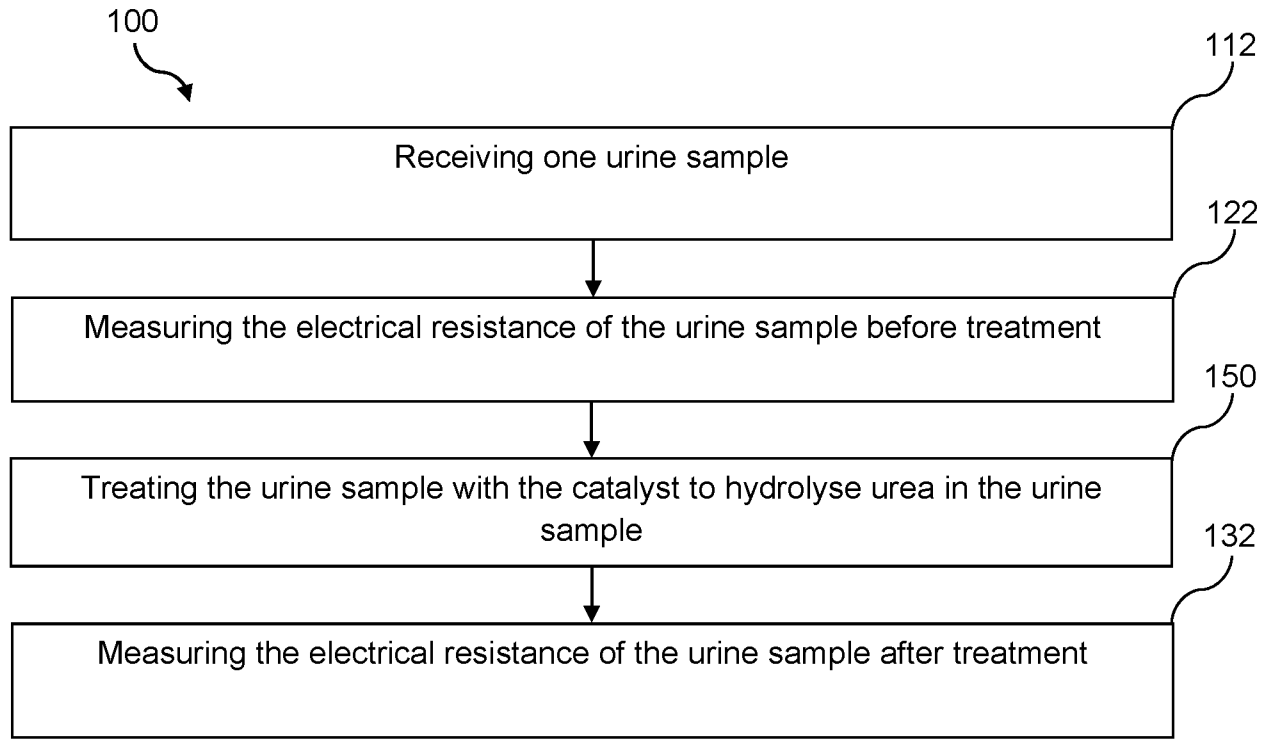


Figure 1B

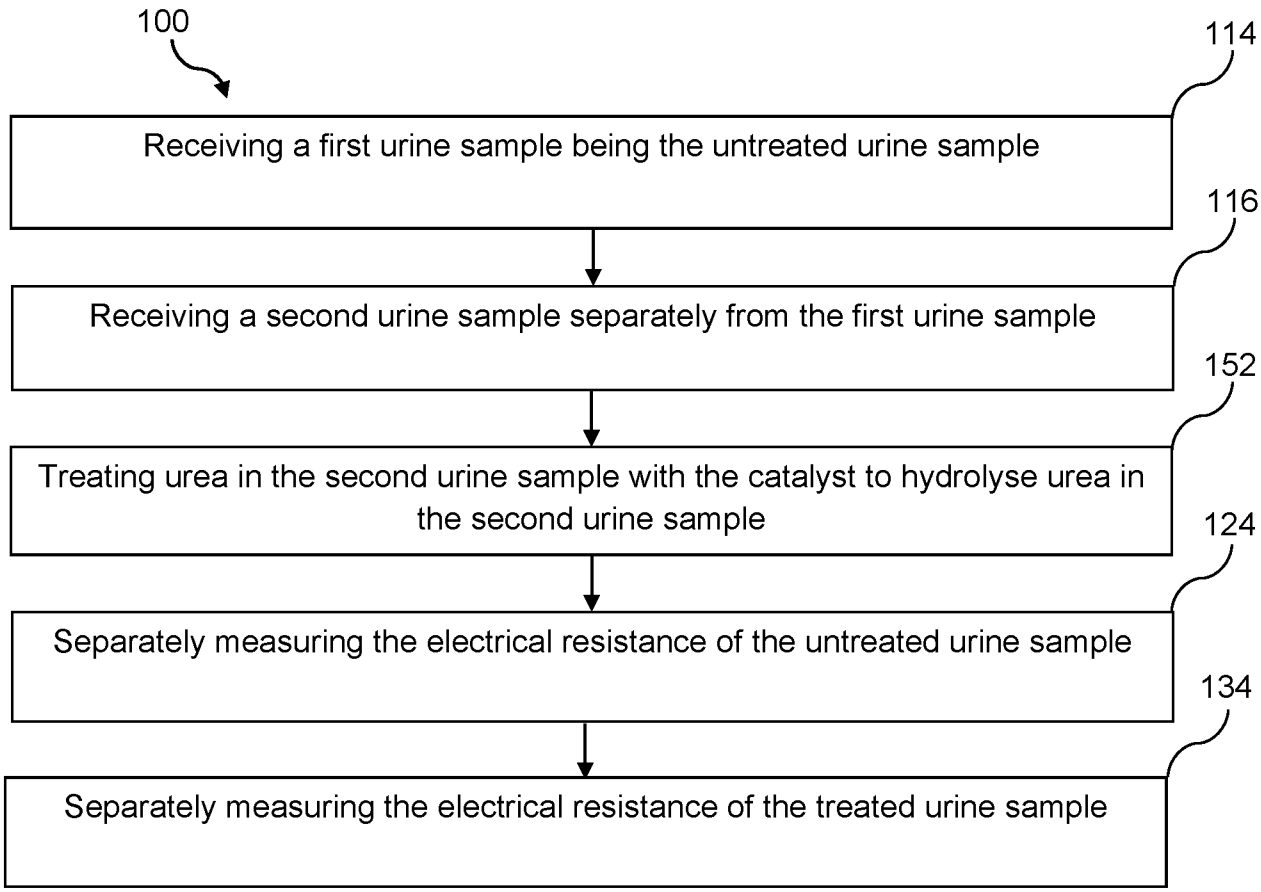


Figure 1C

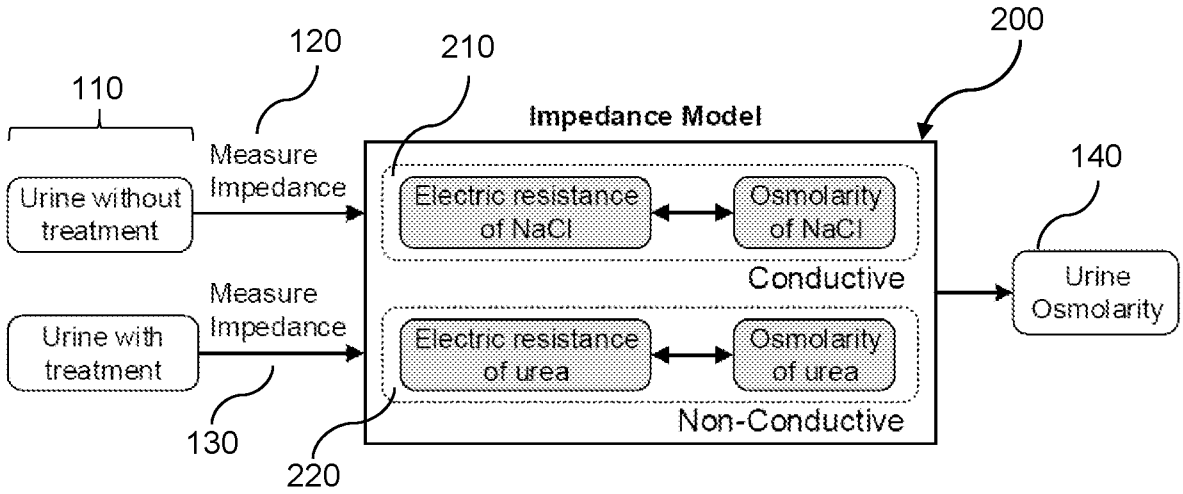


Figure 2A

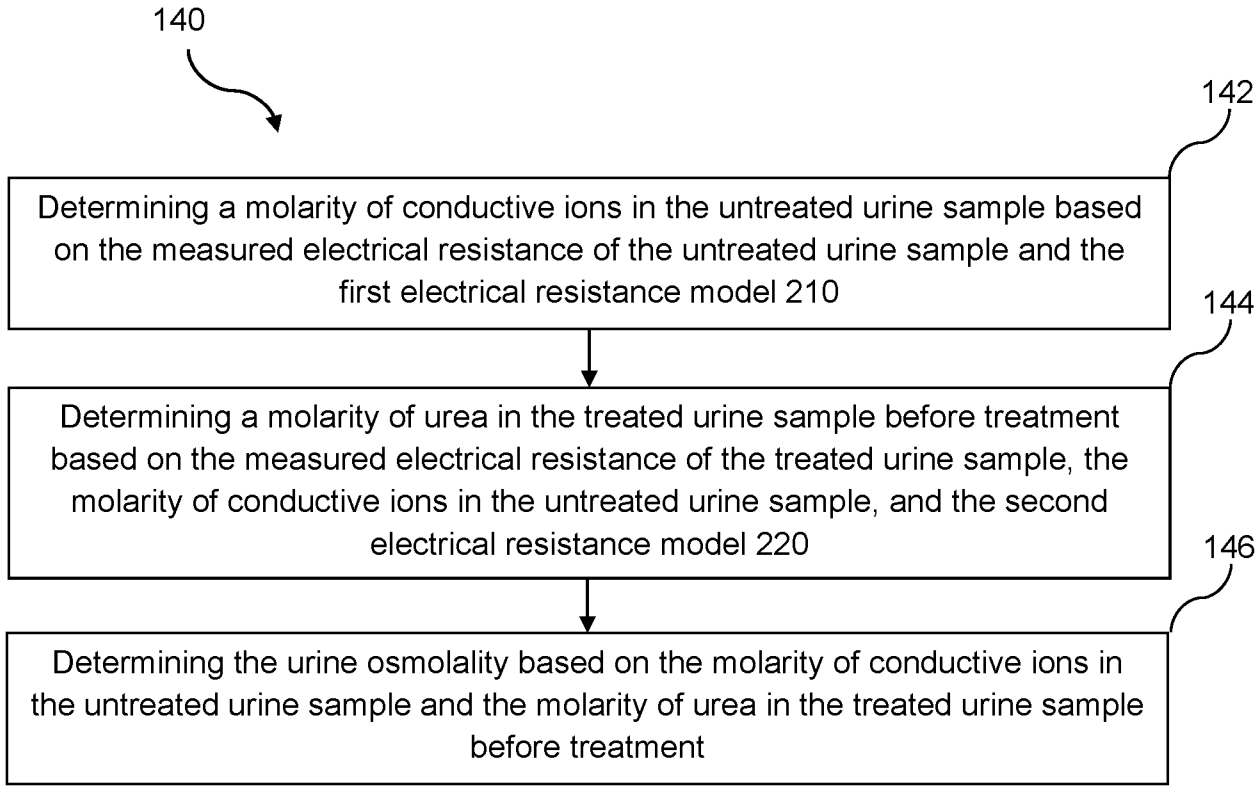


Figure 2B

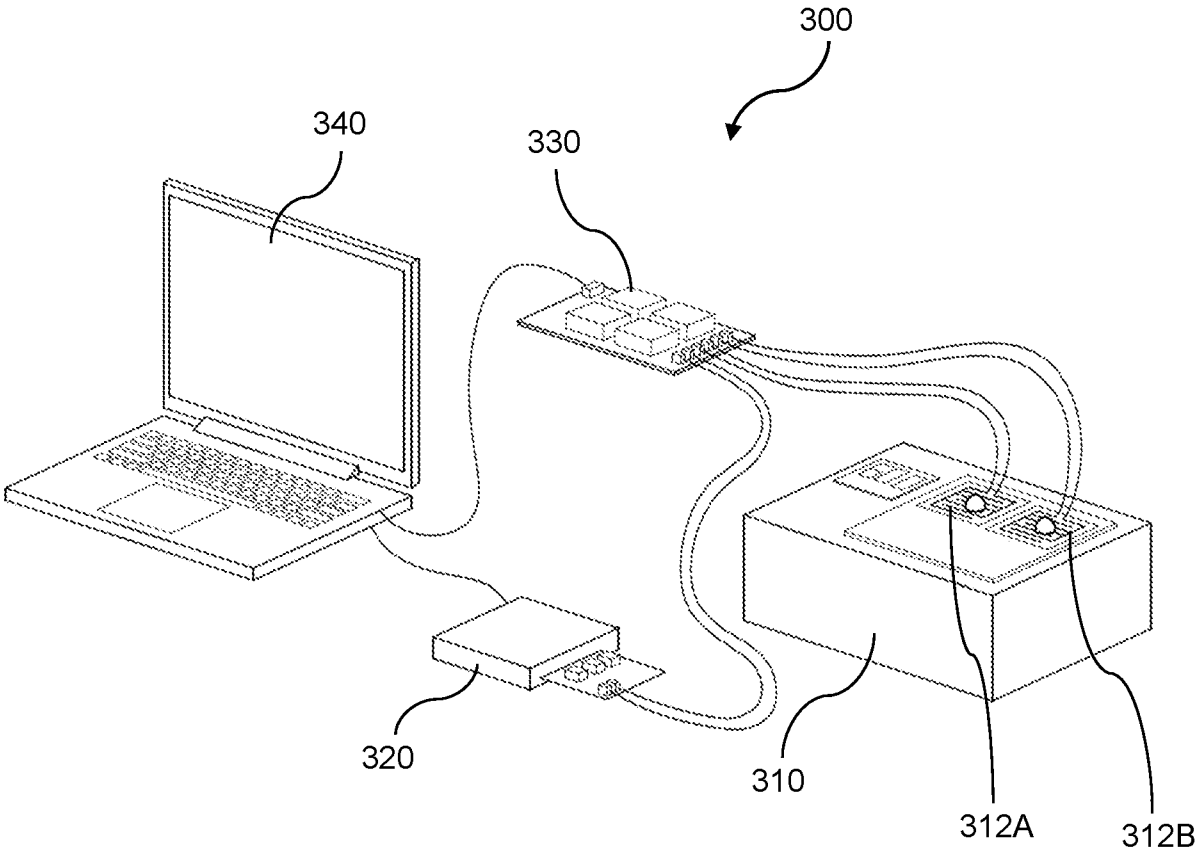


Figure 3

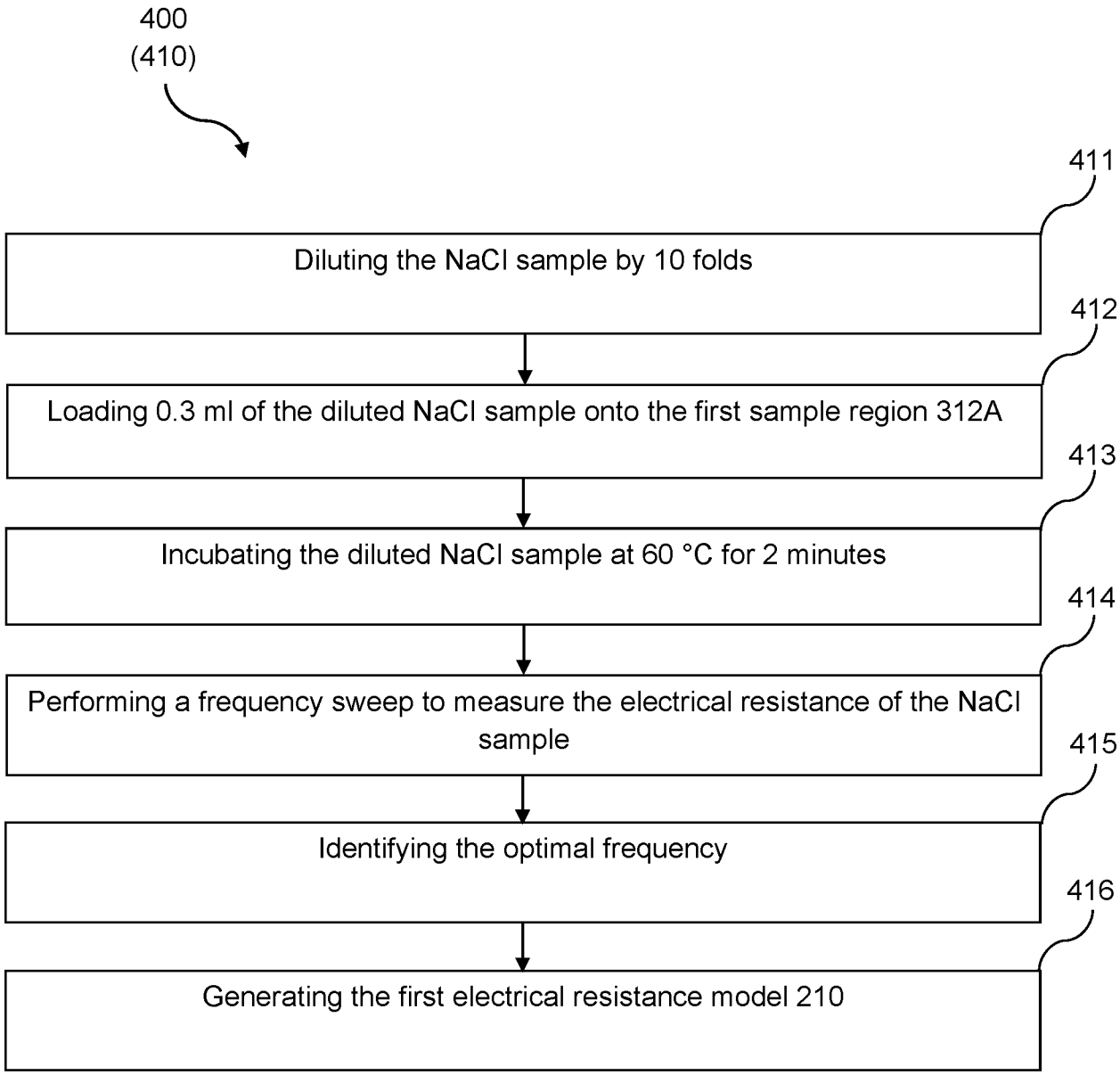

400
(410)
411
Diluting the NaCl sample by 10 folds
412
Loading 0.3 ml of the diluted NaCl sample onto the first sample region 312A
413
Incubating the diluted NaCl sample at 60 °C for 2 minutes
414
Performing a frequency sweep to measure the electrical resistance of the NaCl sample
415
Identifying the optimal frequency
416
Generating the first electrical resistance model 210

Figure 4A

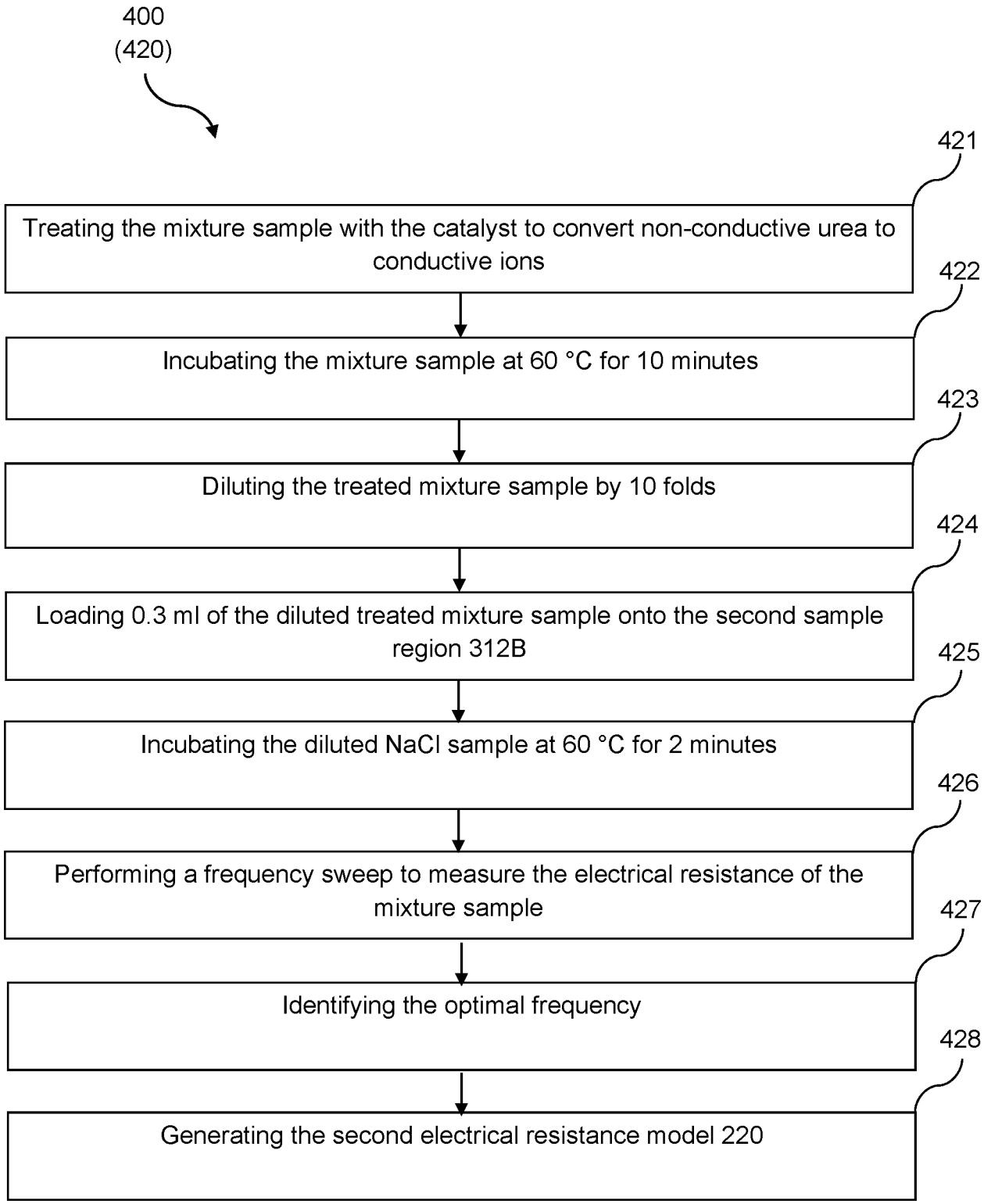

400
(420)
421
Treating the mixture sample with the catalyst to convert non-conductive urea to conductive ions
422
Incubating the mixture sample at 60 °C for 10 minutes
423
Diluting the treated mixture sample by 10 folds
424
Loading 0.3 ml of the diluted treated mixture sample onto the second sample region 312B
425
Incubating the diluted NaCl sample at 60 °C for 2 minutes
426
Performing a frequency sweep to measure the electrical resistance of the mixture sample
427
Identifying the optimal frequency
428
Generating the second electrical resistance model 220

Figure 4B

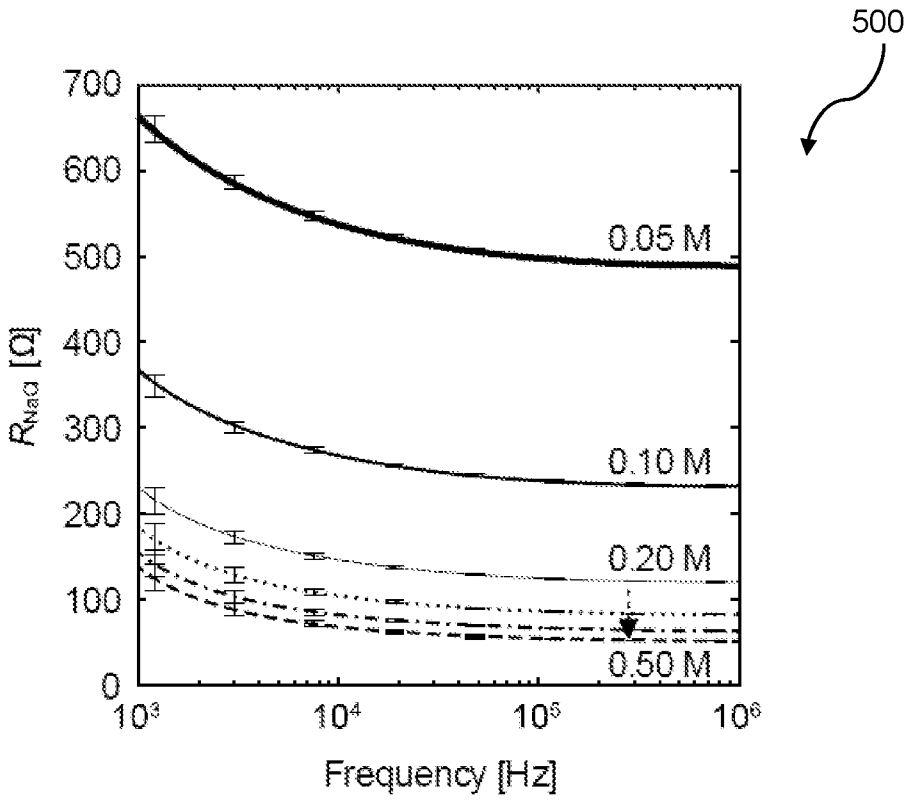


Figure 5A

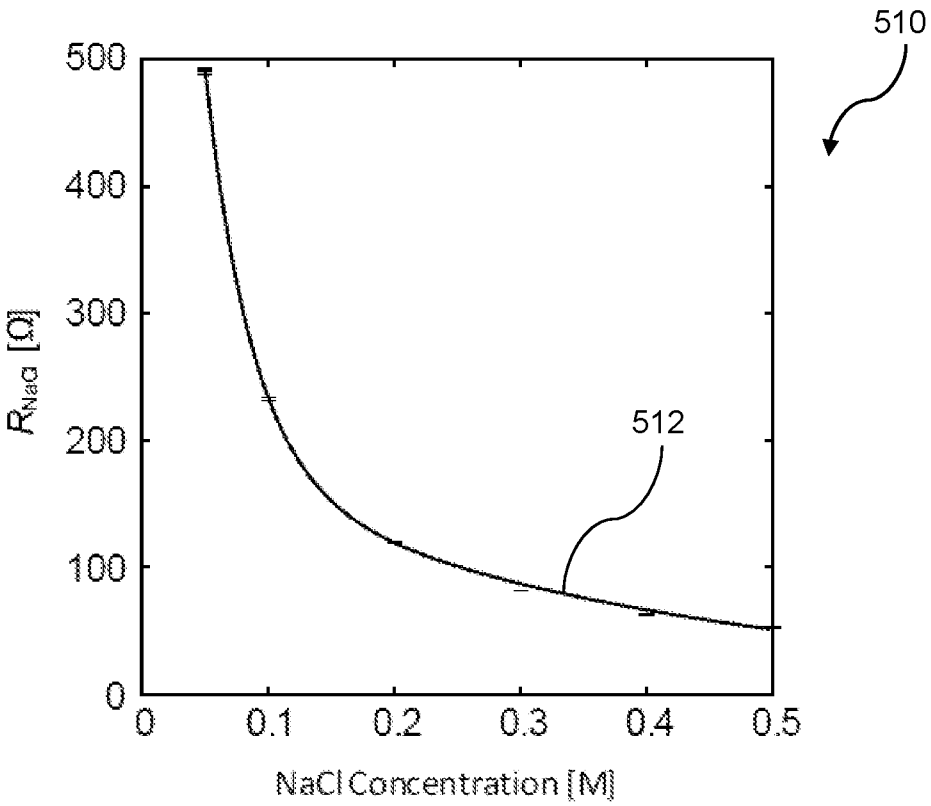


Figure 5B

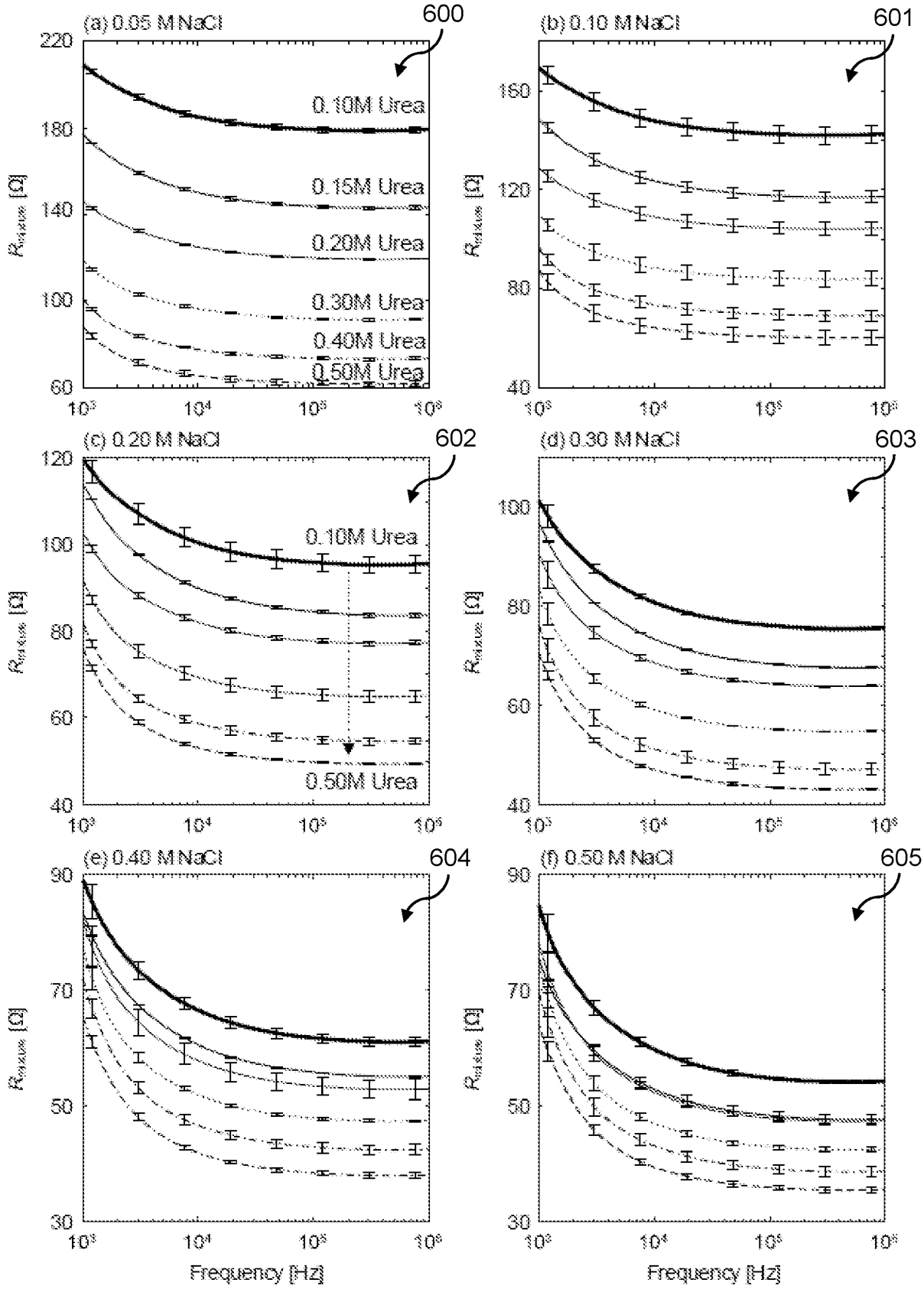

(a) 0.05 M NaCl
600
0.10M Urea
0.15M Urea
0.20M Urea
0.30M Urea
0.40M Urea
0.50M Urea
(b) 0.10 M NaCl
601
(c) 0.20 M NaCl
602
(d) 0.30 M NaCl
603
(e) 0.40 M NaCl
604
(f) 0.50 M NaCl
605
Frequency [Hz]

Figure 6A

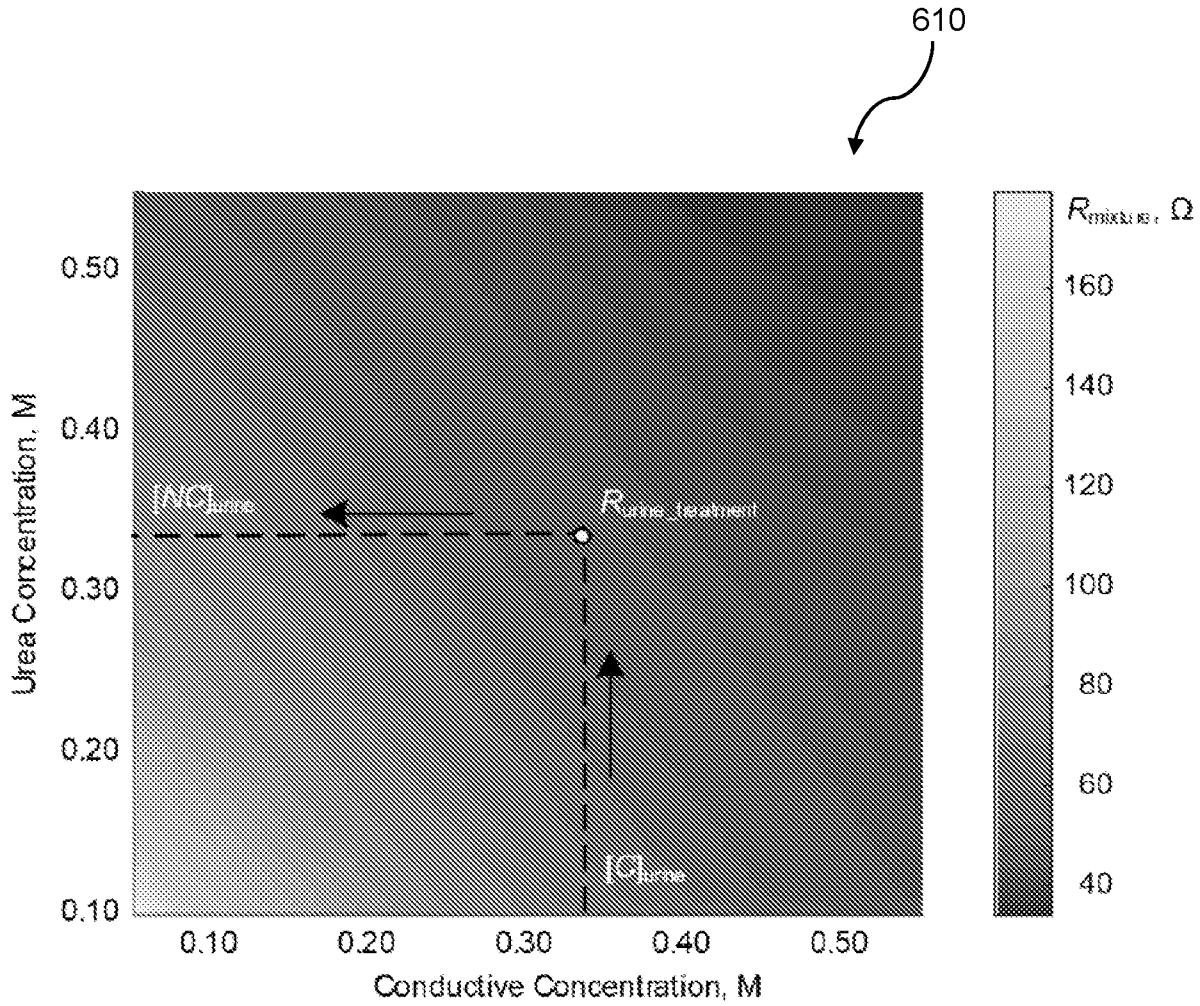

610
Urea Concentration, M
0.50
0.40
0.30
0.20
0.10
0.10
0.20
0.30
0.40
0.50
Conductive Concentration, M
$[NC]_{urine}$
$R_{urine\_treatment}$
$[C]_{urine}$
$R_{mixture}$, Ω
160
140
120
100
80
60
40

Figure 6B

700

Urine Sample	Urine Osmolality measured by Freezing Point Osmometer (mOsm/kg)	Urine Osmolality measured by System 300 (mOsm/kg)			Accuracy (%)
		Room Temperature	4 °C for 48 hours	-30 °C for 48 hours	
Sample 1	736	743	728	750	99.3
Sample 2	501	533	536	548	92.3
Sample 3	364	382	380	380	95.4
Sample 4	317	325	326	322	97.6
Sample 5	311	344	347	343	89.0
Sample 6	425	440	433	440	97.0

Figure 7A

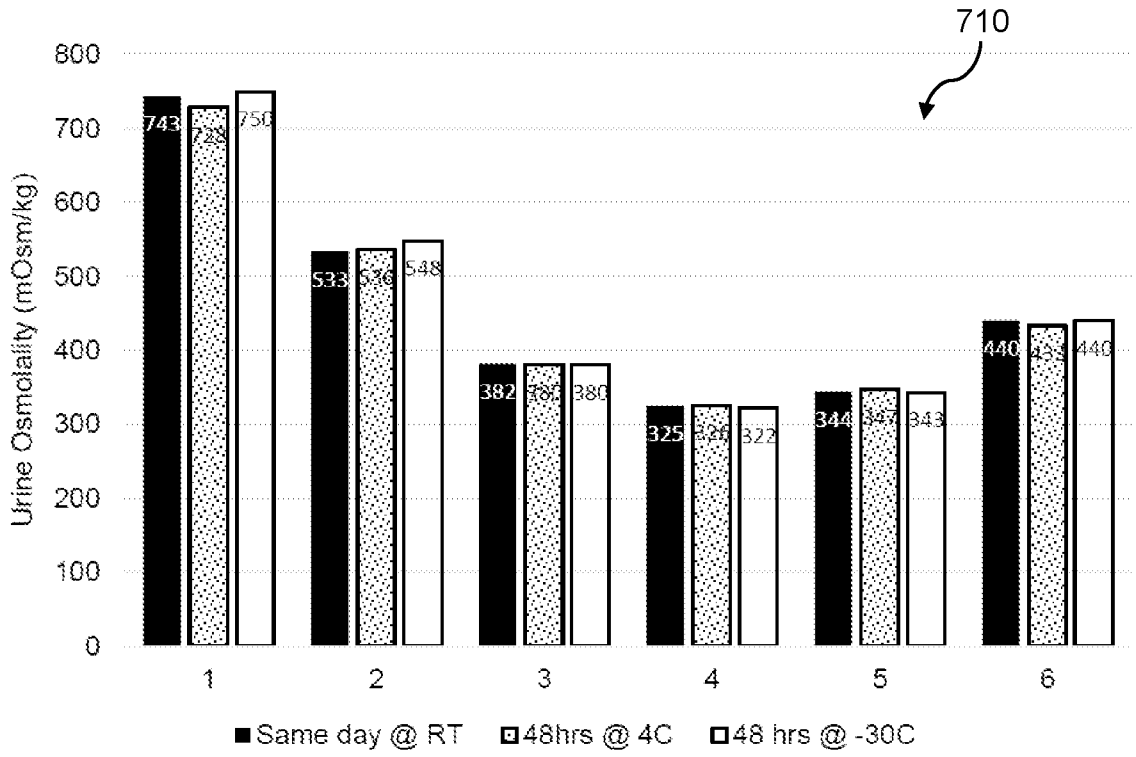
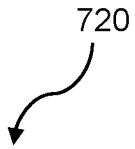


Figure 7B



Urine Sample	Urine Osmolality measured by System 300 (mOsm/kg)					Urine Osmolality measured by Freezing Point Osmometer (mOsm/kg)	Accuracy (%)
	Room Temperature	4 °C for 48 hours	-30 °C for 48 hours	Average	Standard Deviation		
Sample 1-1	840	866	843	850	14	889	95.6
Sample 1-2	868	865	855	862	7	901	95.7
Sample 1-3	846	864	860	857	10	896	95.6
Sample 1-4	844	844	861	850	10	885	96.0
Sample 1-5	888	880	884	884	4	901	98.1
Sample 2-1	351	352	350	351	1	354	99.2
Sample 2-2	490	488	488	489	1	522	93.6
Sample 2-3	583	577	565	575	9	596	96.5
Sample 2-4	494	495	494	494	1	522	94.6
Sample 2-5	489	492	484	488	4	505	96.7
Sample 3-1	393	398	398	397	3	400	99.2
Sample 3-2	537	537	541	538	3	561	95.9
Sample 3-3	814	823	817	818	5	864	94.7
Sample 3-4	694	704	717	705	12	732	96.3
Sample 3-5	575	575	580	577	3	580	99.5
Sample 4-1	157	161	156	158	3	163	96.9
Sample 4-2	677	675	688	680	7	714	95.2
Sample 4-3	948	959	955	954	6	1007	94.7
Sample 4-4	808	804	814	809	5	869	93.1
Sample 4-5	558	556	557	557	1	593	93.9

Figure 7C

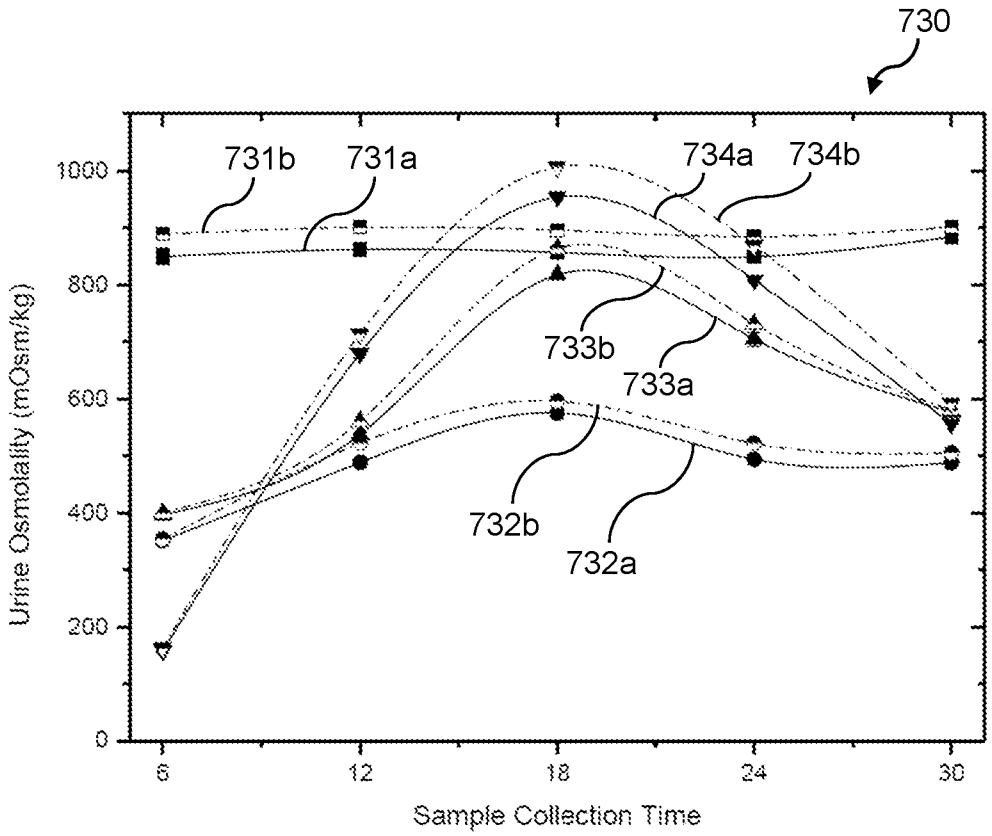


Figure 7D

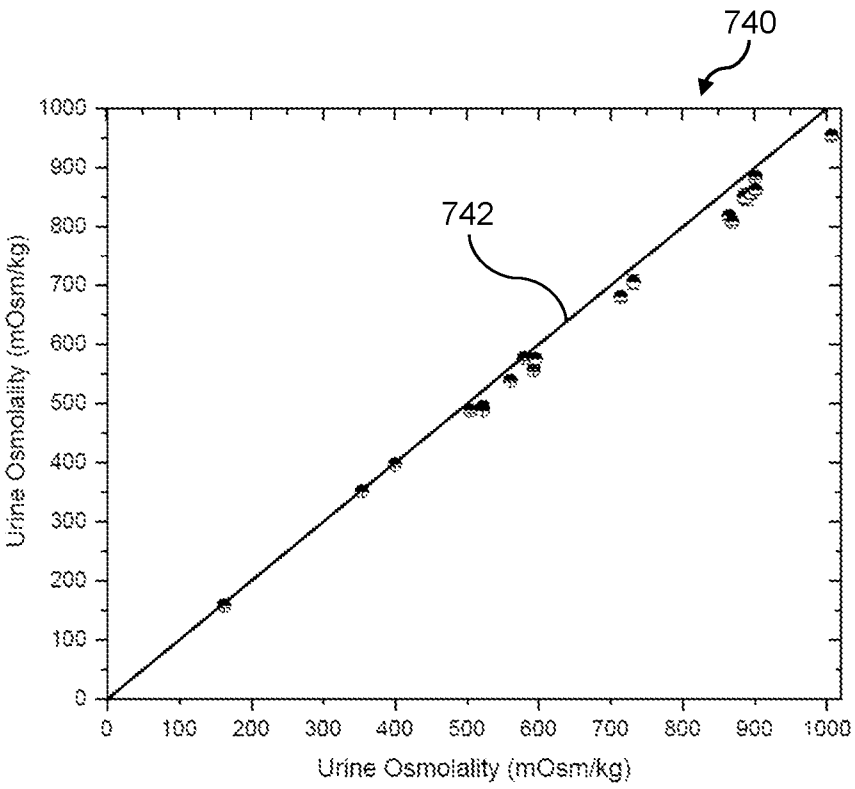


Figure 7E

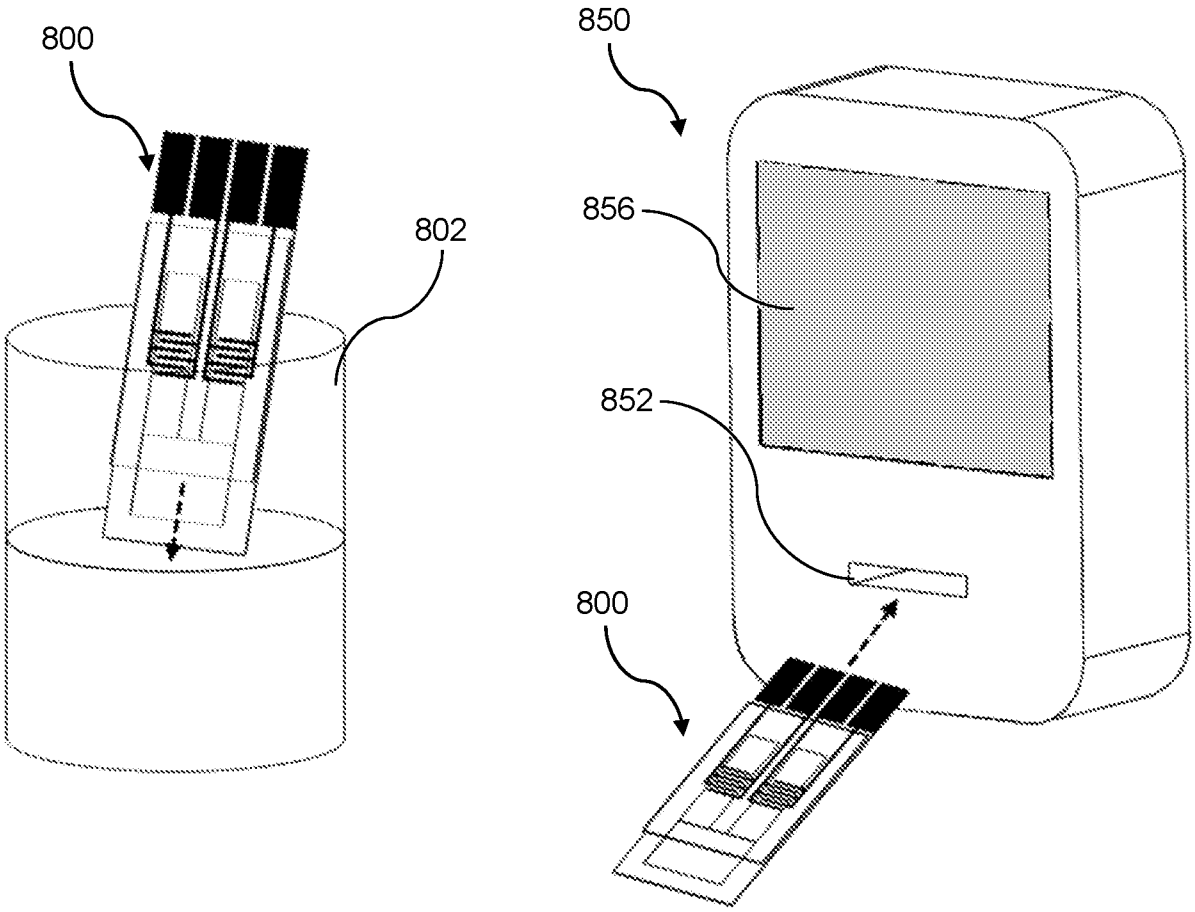


Figure 8A

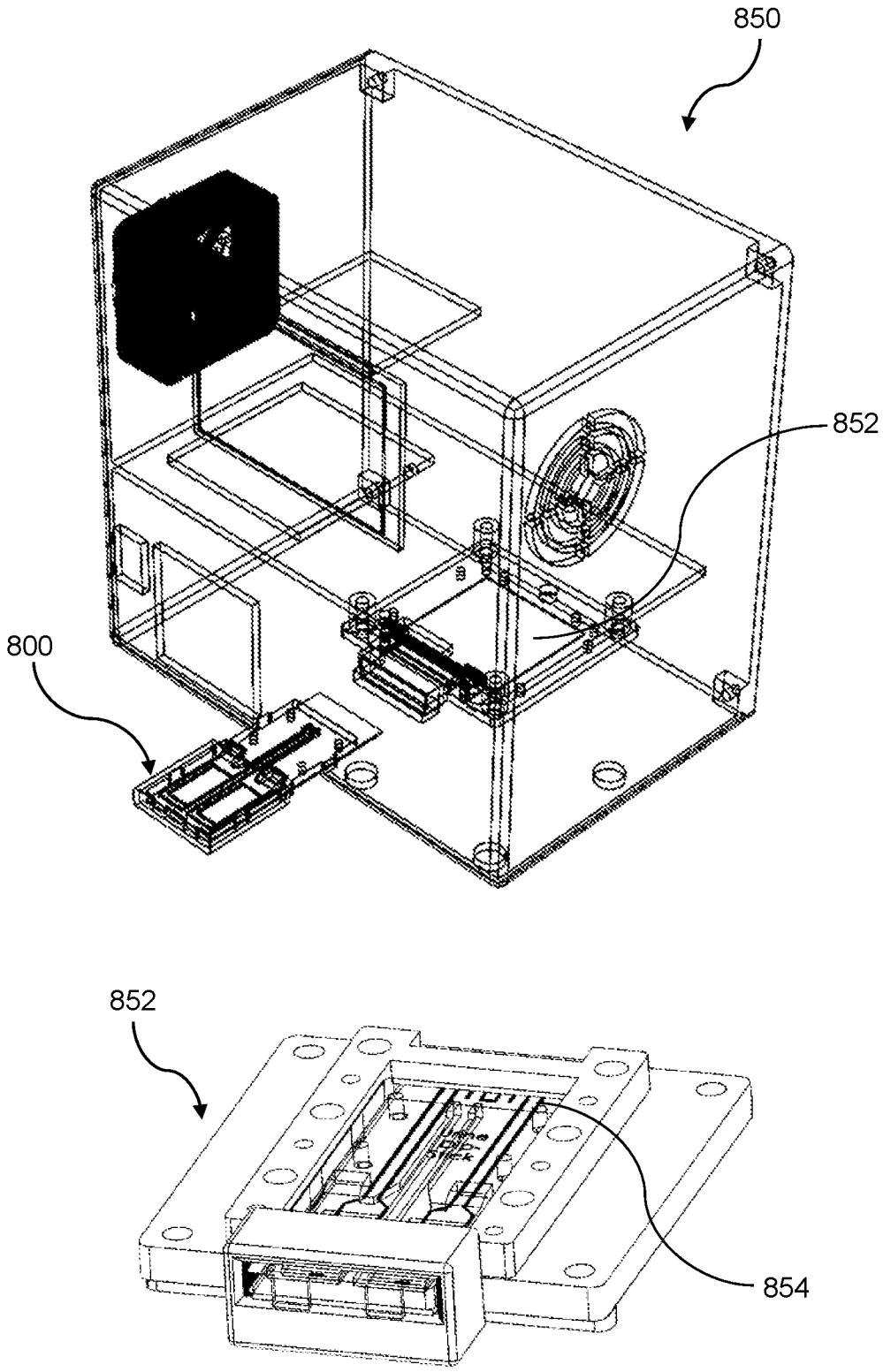


Figure 8B

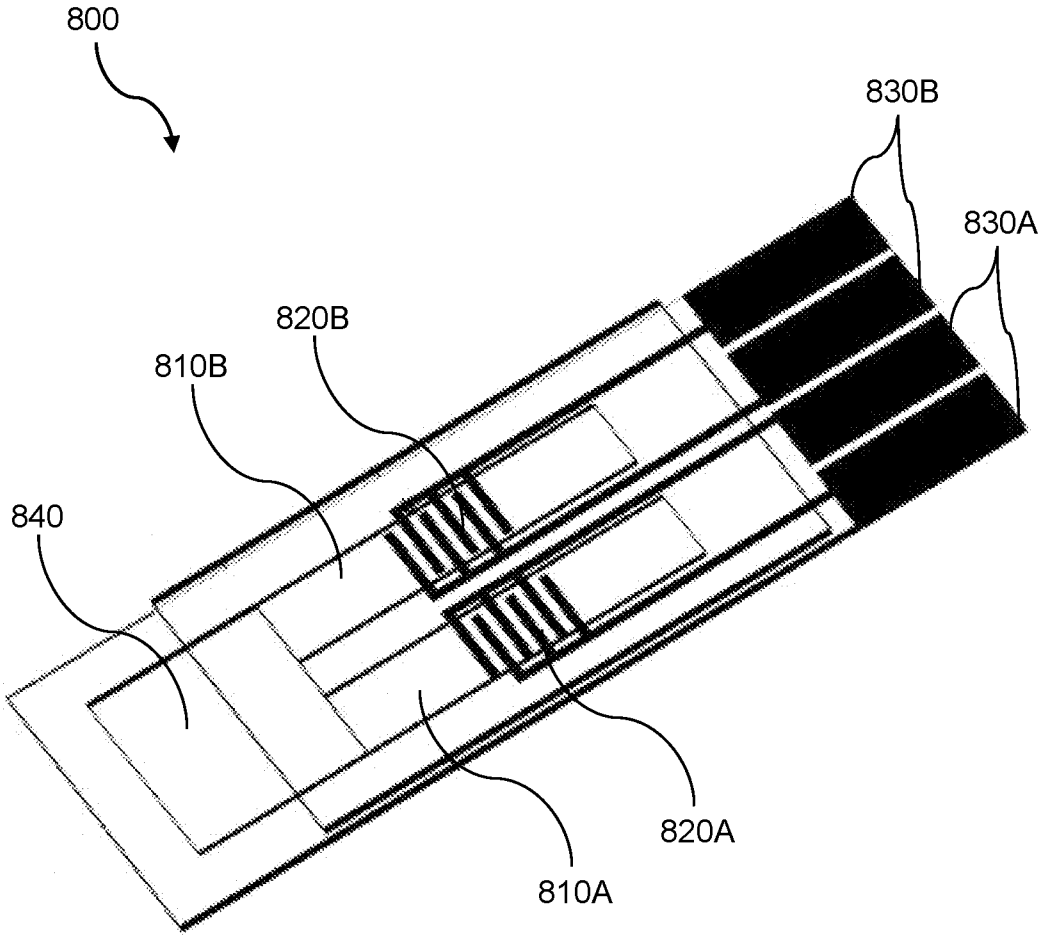


Figure 8C

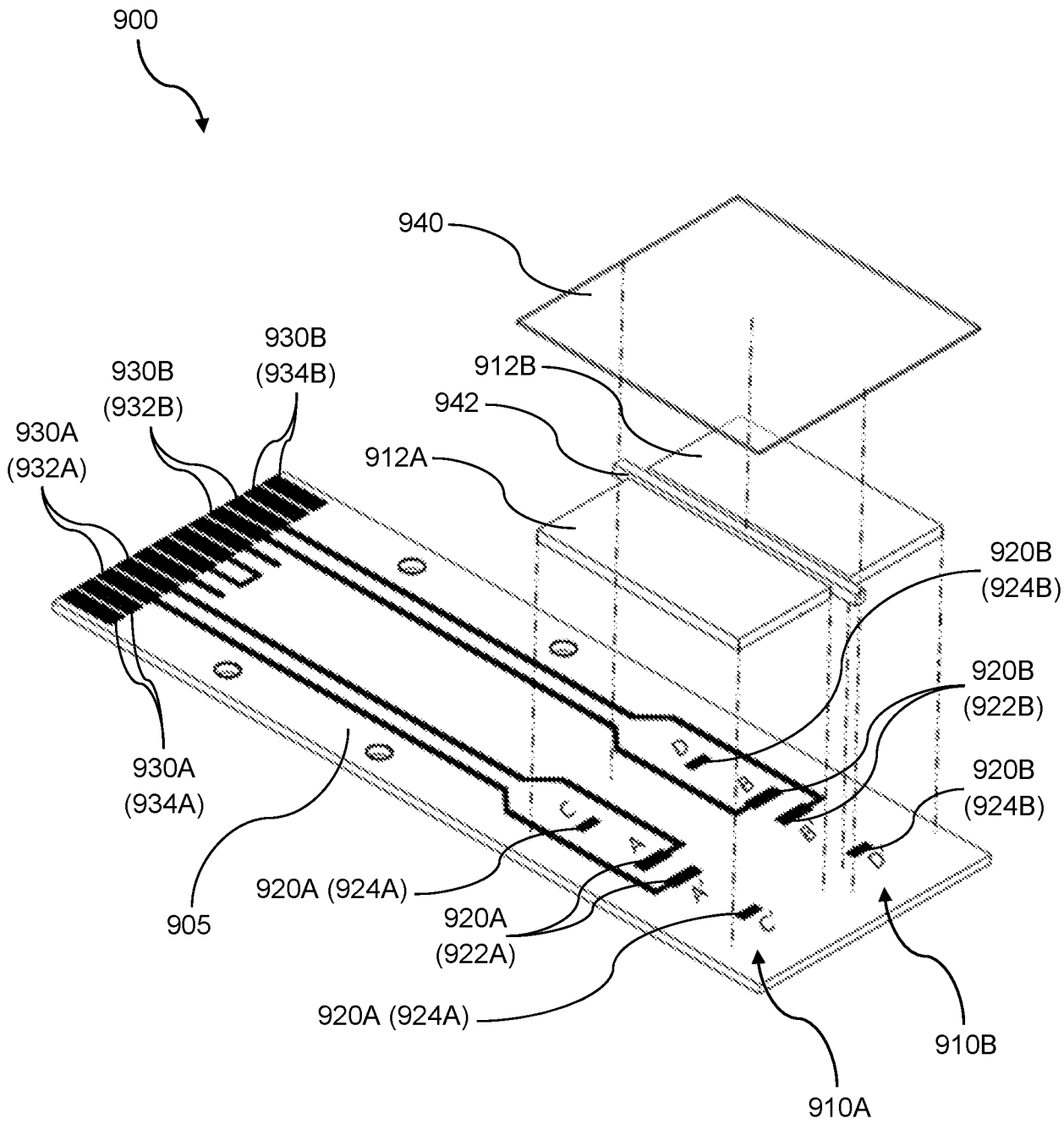

900
940
930B
(934B)
930B
(932B)
912B
942
930A
(932A)
912A
920B
(924B)
920B
(922B)
930A
(934A)
920B
(924B)
905
920A (924A)
920A
(922A)
920A (924A)
910B
910A

Figure 9A

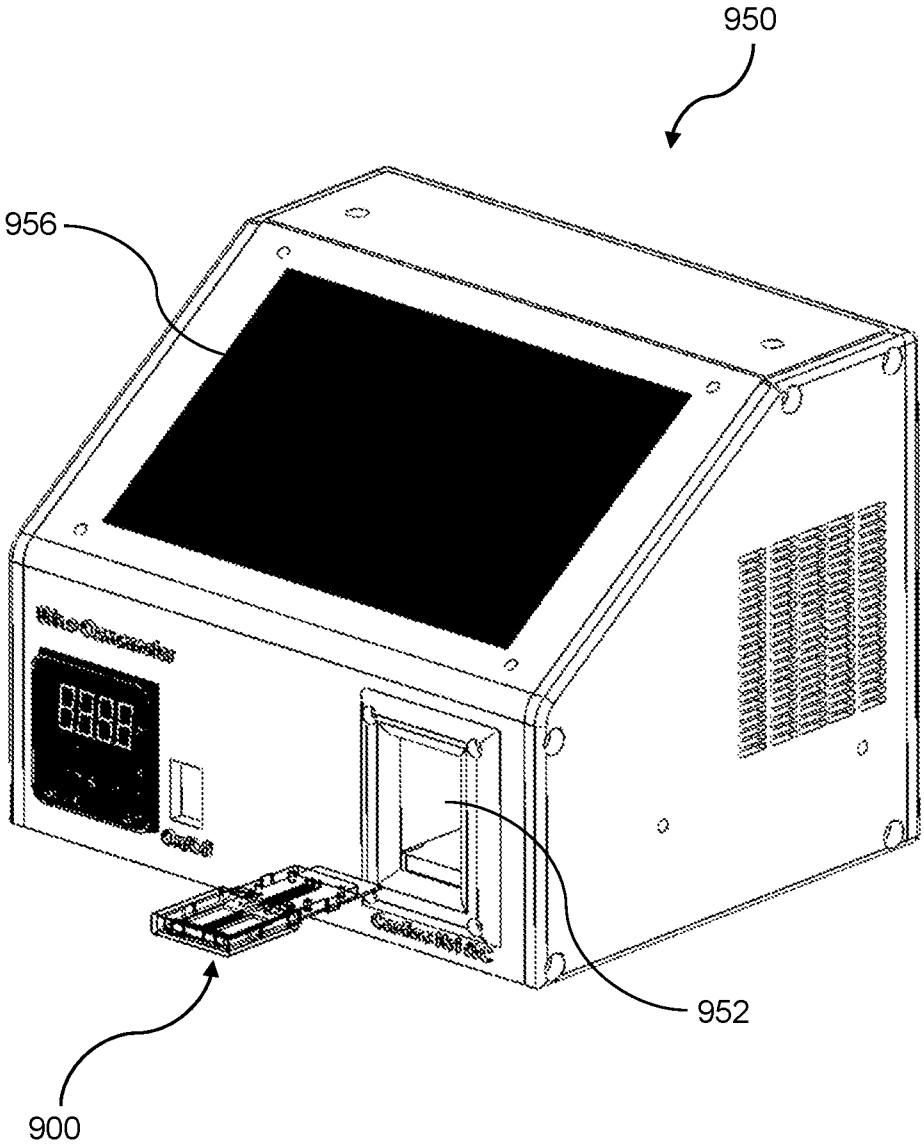


Figure 9B

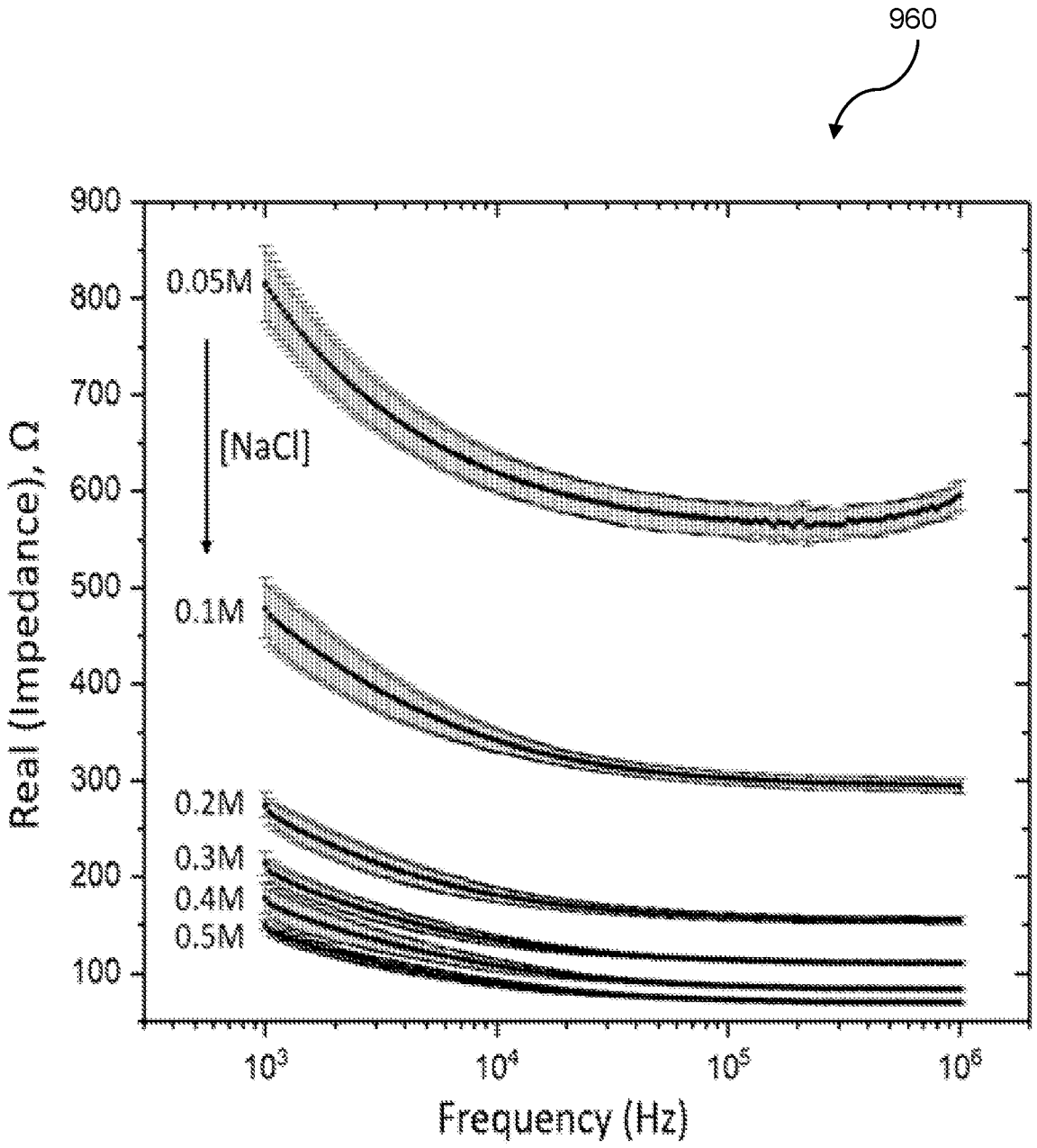

960
900
800
700
600
500
400
300
200
100
Real (Impedance), Ω
0.05M
[NaCl]
0.1M
0.2M
0.3M
0.4M
0.5M
10^3
10^4
10^5
10^6
Frequency (Hz)

Figure 9C

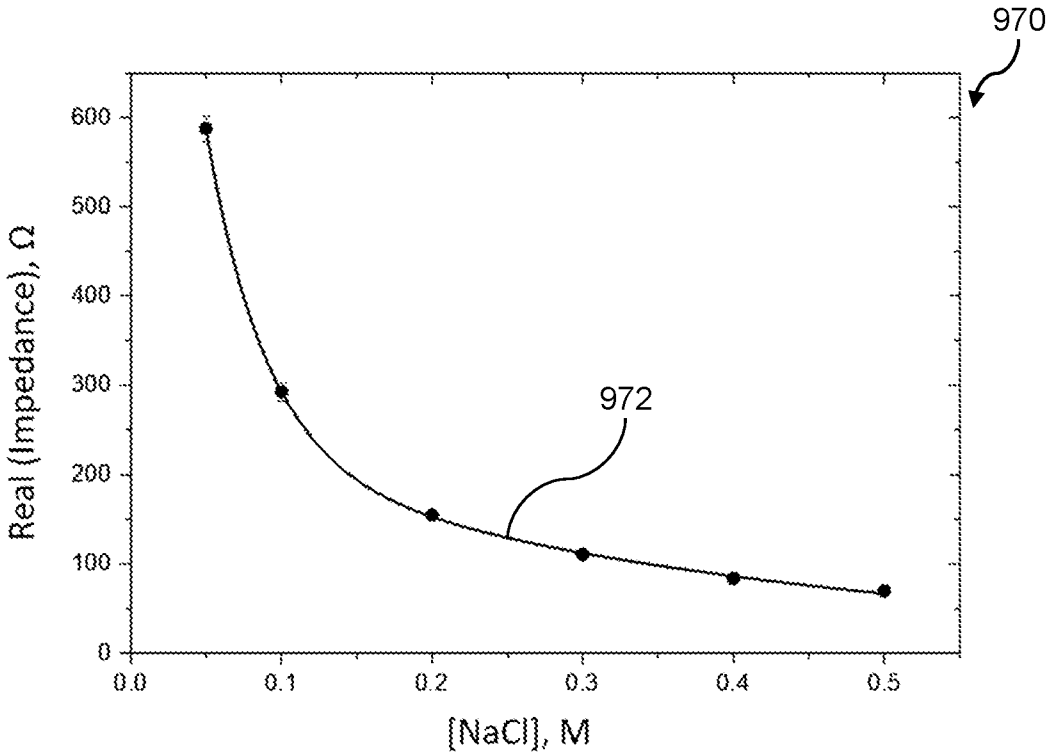


Figure 9D

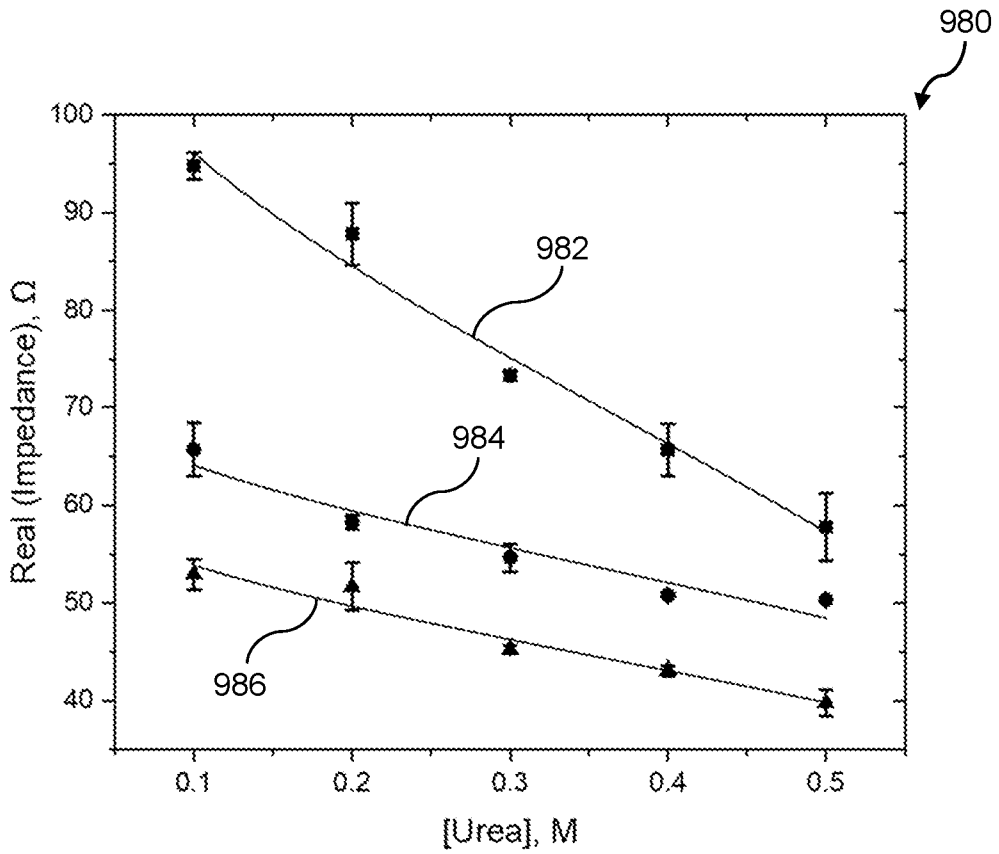


Figure 9E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050398

A. CLASSIFICATION OF SUBJECT MATTER

G01N 33/493 (2006.01) G01N 33/62 (2006.01) C12Q 1/58 (2006.01) B01L 3/00 (2006.01)

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N, C12Q, B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

FAMPAT/CAplus/BIOSIS/EMBASE/MEDLINE: urine osmolality, electrical resistance, impedance, electrical conductance, current, urease, urea hydrolysis, catalyst, enzyme, region, channel and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/045647 A1 (GENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH) 7 March 2019 fig. 1, 4-6; pg. 12, ln. 11-21; pg. 21, ln. 10-15; pg. 22, ln. 10 – pg. 24, ln. 20; pg. 25, ln. 6-12	1-20
X	EP 0121385 A1 (CAMBRIDGE LIFE SCIENCES PLC) 10 October 1984 fig. 2; examples 1, 3; table 1	13-20
X	SOLDATKIN O. O. ET AL., Application of enzyme/zeolite sensor for urea analysis in serum. *Materials Science and Engineering C*, 22 May 2014, Vol. 42, pages 155-160 [Retrieved on 2021-08-31] <DOI: 10.1016/J.MSEC.2014.05.028> sections 2.4, 2.5	13-20
A	US 4108727 A (STISO S. N. ET AL.) 22 August 1978 example 7	-

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31/08/2021 *(day/month/year)*	*02/09/2021* *(day/month/year)*

Name and mailing address of the ISA/SG	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SG2021/050398

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019/045647 A1	07/03/2019	NONE	
EP 0121385 A1	10/10/1984	WO 84/03945 A1 ZA 842205 B	11/10/1984 31/10/1984
US 4108727 A	22/08/1978	GB 1562700 A CA 1074221 A	12/03/1980 25/03/1980