



US 20140065658A1

(19) **United States**(12) **Patent Application Publication**
Bertholle et al.(10) **Pub. No.: US 2014/0065658 A1**(43) **Pub. Date: Mar. 6, 2014**(54) **METHOD FOR MONITORING A REACTION,
AND REACTION SYSTEM FOR
IMPLEMENTING SAME****Publication Classification**(51) **Int. Cl.**
C12Q 1/02 (2006.01)
(52) **U.S. Cl.**
CPC **C12Q 1/025** (2013.01)
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(FR)(21) Appl. No.: **14/003,002**(22) PCT Filed: **Feb. 1, 2012**(86) PCT No.: **PCT/IB12/50478**

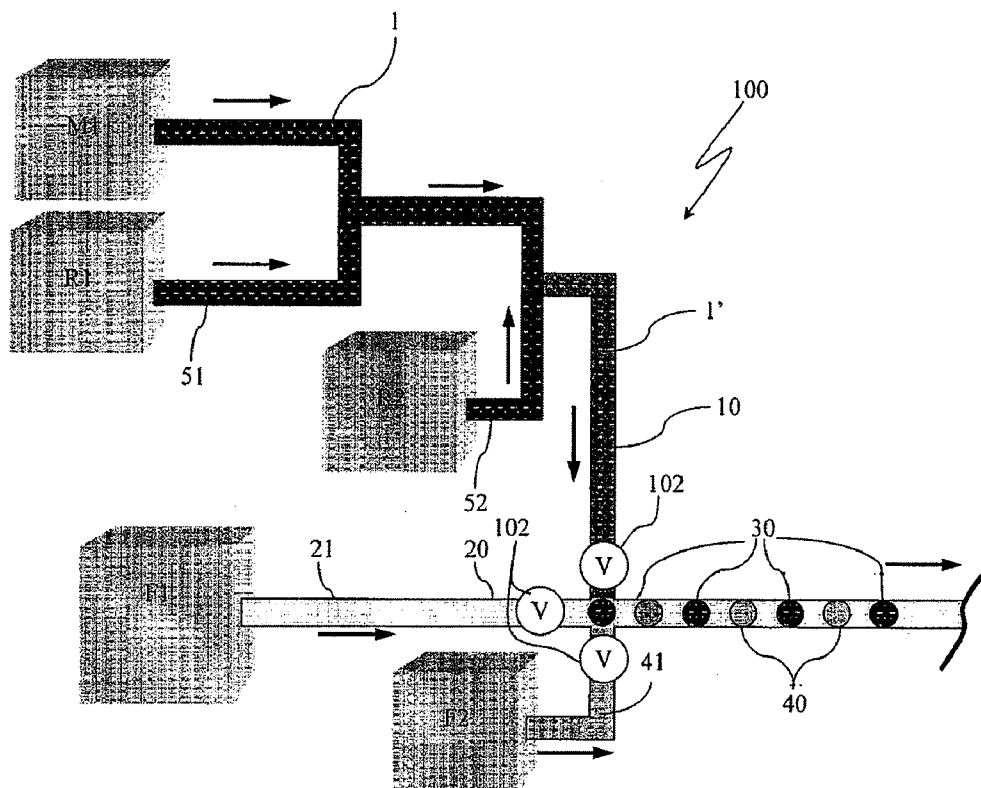
§ 371 (c)(1),

(2), (4) Date: **Nov. 14, 2013**(30) **Foreign Application Priority Data**

Mar. 4, 2011 (FR) 1100659

(57) **ABSTRACT**

The invention relates to a method for monitoring a reaction and to a reaction system which are inexpensive, compact, easy to implement, and enable the reaction medium to be fully supervised throughout the entire experiment. For this purpose, the invention relates to a reaction system, in particular for microorganism cultures, including: at least one vessel (M1) for the reaction medium (1, 1'), which is in fluid communication with an injection tube (10); at least one vessel (F1) for a carrier fluid (11) that is immiscible with the reaction medium (1, 1'), which is in fluid communication with a reaction tube (20); the injection tube (10) being mounted so as to lead into the reaction tube (20) such that individual drops (30) of the reaction medium can be injected into the reaction tube (20) and into the immiscible carrier fluid (11), so as to form a train of reaction chambers; at least one detector for monitoring a reaction; a means for classifying the reaction chambers; and at least one means for recirculating reaction chambers in front of at least one detector for monitoring a reaction.



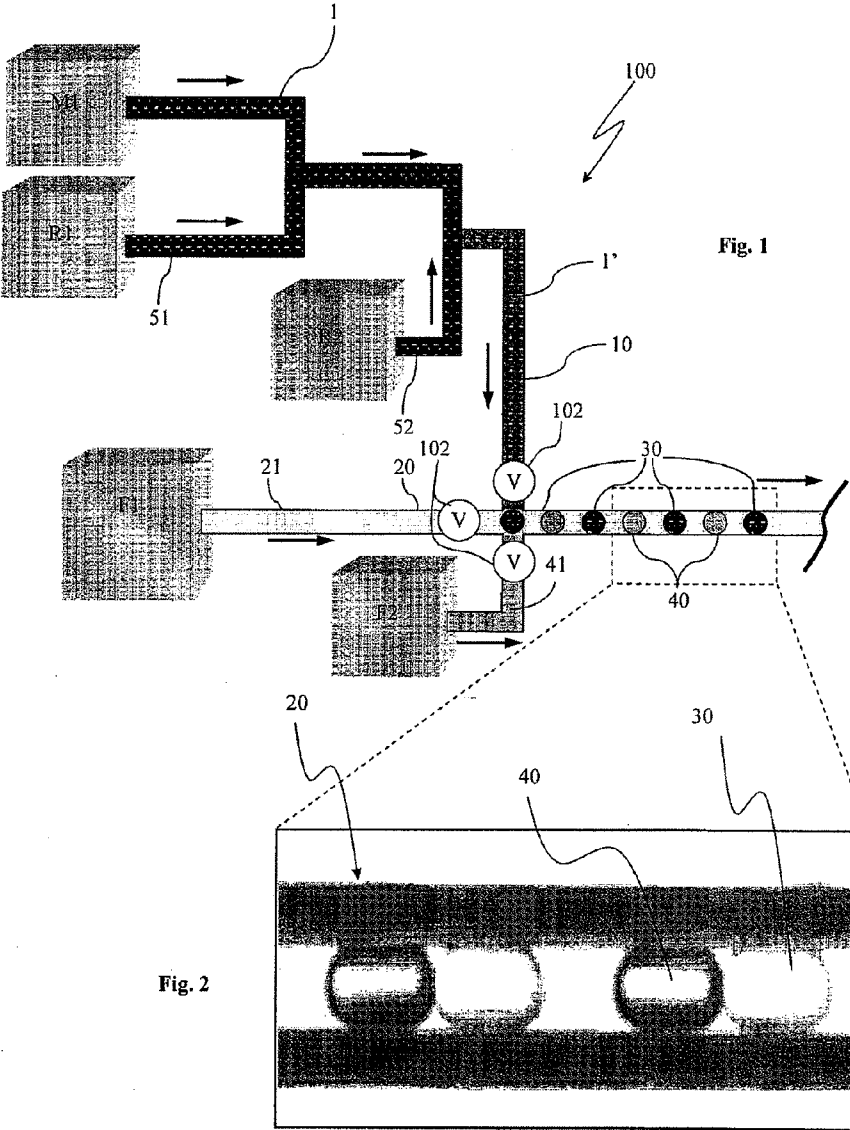


Fig. 3

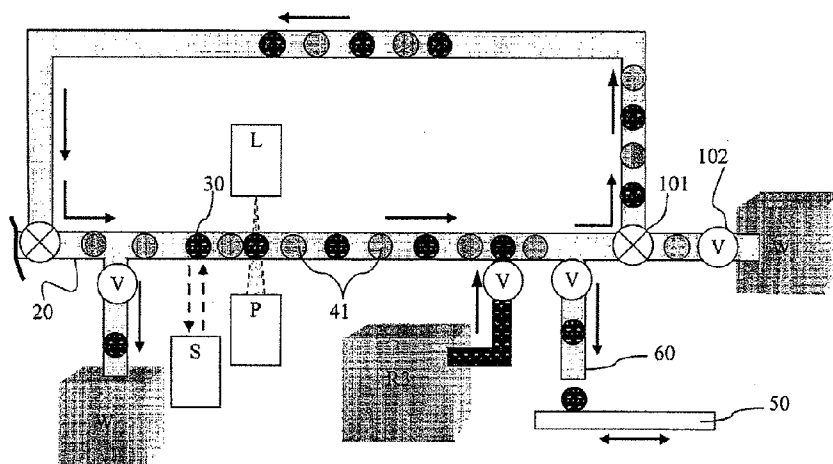
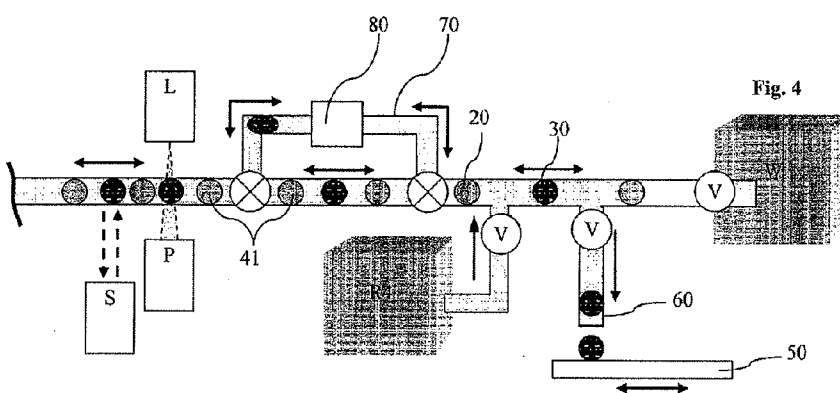
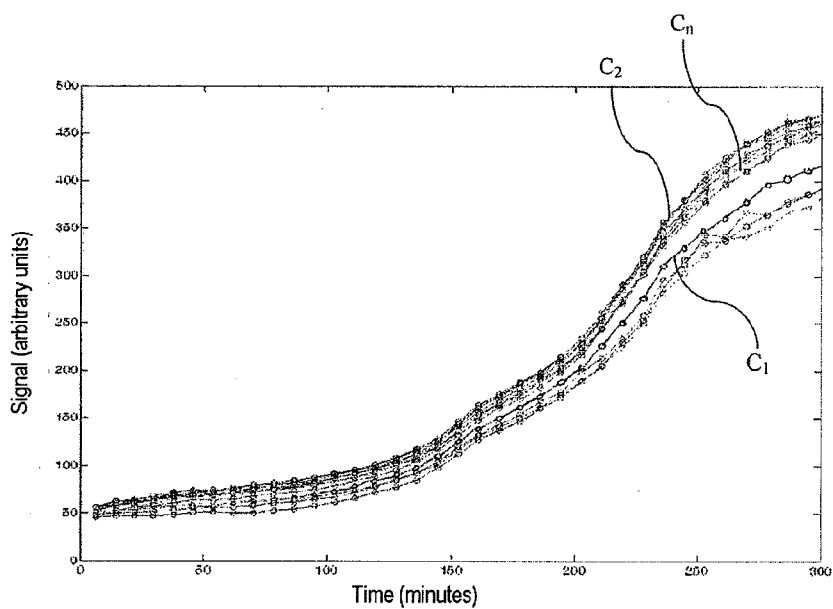
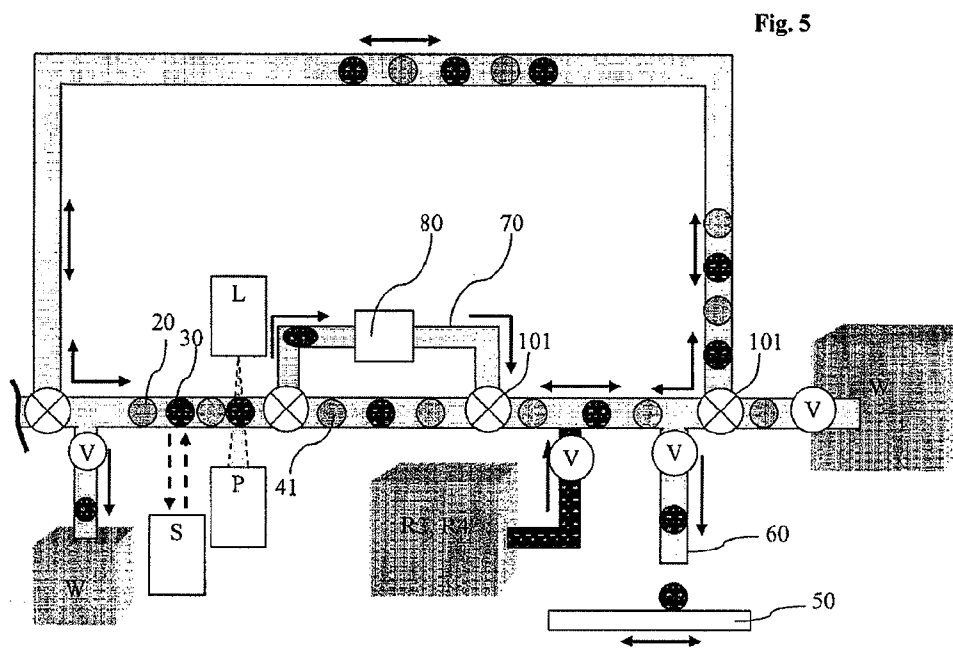


Fig. 4





METHOD FOR MONITORING A REACTION, AND REACTION SYSTEM FOR IMPLEMENTING SAME

[0001] The invention relates to a method for monitoring a reaction and to a reaction system for application thereof.

[0002] The investigation of microbiological entities, such as unicellular or multicellular microorganisms, requires being able to detect a population of these microorganisms in one or more reactors, as well as the development of these microorganisms over time. It is also necessary to be able to select easily and extract the populations of interest.

[0003] There are now machines called "plate readers", which are in the form of plates equipped with a plurality of wells (currently up to 1536 on an area of 127.76×85.48 mm) arranged as a two-dimensional matrix, and in which the microorganisms are cultured in a given culture medium.

[0004] The first drawback of this type of machine is the need for a system for scanning in two dimensions so as to make the well that we wish to fill or analyze coincide with the appropriate tool (filling device or measuring equipment). A device of this kind is expensive, bulky and must be very accurate to ensure good coincidence between each well and the equipment.

[0005] Another major drawback is the need to take considerable precautions during manipulation of the plate to avoid causing plate vibration or spillage and creating contamination between the wells. Now, constant stirring of the wells is required to keep the medium homogeneous and in the case of microorganisms to prevent the formation of biofilms. This means that the amount of biomass attained or detectable in a well is limited.

[0006] Another drawback is the difficulty of controlling the evaporation of the culture medium in the wells, in view of the small volume of liquid contained in each well. One solution proposed is to keep the plate under controlled atmosphere and/or regularly supplement each well with culture medium to make up for the evaporation.

[0007] Such methods are tedious and can influence the growth of the microorganisms, inducing a bias in the experiments and the measurements.

[0008] In the article "Controlled microfluidic interfaces" (Atencia and Beebe, Nature Review, 437, 648-655, 2005), it has already been proposed to produce a reaction system comprising:

[0009] several reservoirs of solutions of reagents fluidically connected to a capillary injection tube;

[0010] at least one reservoir of a carrier fluid that is immiscible with the solutions of reagents, fluidically connected to a capillary reaction tube, the capillary injection tube being mounted opening into the capillary reaction tube so that individual drops of reagents can be injected into the capillary reaction tube, into the immiscible carrier fluid, so as to form a plurality of reactors.

[0011] This system makes it possible to carry out a large number of experiments in succession, notably for studying the factors involved in the crystallization of proteins. Once the measurement has been carried out (measurement of X-ray diffraction), the drops are transported to the end of the reaction tube and removed.

[0012] Another application consists of carrying out the encapsulation of therapeutic agents. Once said encapsulation has been performed, the drops are recovered at the outlet of the reaction tube and are packaged for use.

[0013] This system solves many problems with plate readers.

[0014] However, this system does not allow monitoring of reaction kinetics, in particular monitoring of the temporal evolution of a culture of living cells as well as sorting them. The present invention aims to solve the above drawbacks and proposes a reaction system, in particular for culturing microorganisms, that is economical, compact, easy to use, and allows complete control of the culture medium throughout the experiment, and monitoring of the reaction kinetics, in particular of the temporal evolution of a culture of living cells and sorting thereof.

[0015] For this, the invention proposes making a capillary reaction system, notably for culturing microorganisms, comprising a means of referencing the drops for identifying them uniquely in the succession of drops, and at least one means for recirculating the reactors in front of at least one reaction monitoring sensor.

[0016] For this purpose, the invention relates to a reaction system, notably of cultures of microorganisms, comprising:

[0017] at least one reservoir of reaction mixture fluidically connected to a capillary injection tube,

[0018] at least one reservoir of a carrier fluid that is immiscible with the reaction mixture, fluidically connected to a capillary reaction tube,

[0019] the capillary injection tube being mounted opening into the capillary reaction tube so that individual drops of reaction mixture can be injected into the capillary reaction tube, into the immiscible carrier fluid, so as to form a succession of reactors,

[0020] at least one reaction monitoring detector.

[0021] The reaction system according to the invention comprises a means of referencing the reactors for identifying them uniquely in the succession of reactors, and at least one means for recirculating the reactors in front of at least one reaction monitoring detector.

[0022] According to other embodiments:

[0023] the recirculating means can comprise a loop for recirculating the reactors in front of the detector or detectors, said recirculating loop comprising a capillary that discharges upstream and downstream of the detector or detectors;

[0024] the recirculating means can comprise a recirculating means that is able to reverse the direction of circulation of the reactors;

[0025] the reaction mixture can be a culture medium of microorganisms, the capillary reaction tube then being a capillary culture tube, and the reactors being reactors for culture of microorganisms;

[0026] the reaction system can further comprise at least one reservoir of a so-called "separating" fluid, immiscible with the carrier fluid and immiscible with the reaction mixture, fluidically connected to the capillary reaction tube so that drops of separating fluid can be injected into the carrier fluid between two reactors;

[0027] the reaction system can further comprise at least one reagent reservoir fluidically connected to the capillary injection tube and/or to the capillary reaction tube, so that reagent can be mixed with the reaction mixture;

[0028] the carrier fluid and the separating fluid can be mutually immiscible oils, the reaction mixture being an aqueous medium that is immiscible with the aforementioned oils;

- [0029] the reaction system can further comprise at least one waste reservoir, connected fluidically to the capillary reaction tube;
- [0030] the reaction system can further comprise at least one detector, the capillary reaction tube comprising at least one portion that is transparent to a signal emitted and/or detected by the detector;
- [0031] the reaction system can further comprise a sampling capillary tube mounted opening into the capillary reaction tube so that at least one reactor can be sampled;
- [0032] the reaction system can further comprise at least one diverting capillary tube mounted opening into the capillary reaction tube so that at least one reactor can be diverted to a means for treatment of one or more reactors;
- [0033] the reaction system can further comprise a central control unit connected to the circulating means and capable of:
- [0034] controlling the injection of individual drops of reaction mixture into the capillary reaction tube, in the carrier fluid, imposing a velocity and a duration of circulation of the reaction medium, so as to form a plurality of reactors;
- [0035] controlling the circulation of the carrier fluid by imposing a velocity, duration and direction of circulation of the carrier fluid in the capillary reaction tube;
- [0036] counting the reactors in the carrier medium and storing the position of each reactor relative to a reference reactor;
- [0037] recirculating the reservoirs in the capillary reaction tube;
- [0038] the central control unit can be capable of controlling the injection of drops of separating fluid between two reactors;
- [0039] the central control unit can be capable of controlling the injection of at least one reagent in the reaction mixture for modifying its composition and/or its chemical and/or physical properties; and/or
- [0040] the central control unit can, moreover, be connected to the detector and is capable of storing at least one measurement performed by the detector or detectors.
- [0041] The invention also relates to a method for monitoring a reaction in a reaction mixture, comprising the following steps:
- [0042] a) filling a capillary reaction tube with a carrier medium that is immiscible with the reaction mixture;
- [0043] b) injecting, by means of a capillary injection tube, an individual drop of reaction mixture in the capillary reaction tube, into the immiscible carrier fluid;
- [0044] c) circulating the carrier fluid so that the drop of reaction mixture is moved relative to the capillary injection tube;
- [0045] e) repeating steps b) and c) to create an ordered succession of drops of reaction mixture in the carrier fluid to form a plurality of reactors;
- [0046] f) measuring at least one representative parameter of each reactor;
- [0047] g) recirculating at least one reactor to measure said at least one representative parameter over time.
- [0048] According to other embodiments:
- [0049] the method can comprise the following steps:
- [0050] a) filling a capillary culture tube with a carrier medium that is immiscible with the culture medium;
- [0051] b) injecting, by means of a capillary injection tube, an individual drop of culture medium in the capillary culture tube, into the immiscible carrier fluid;
- [0052] c) circulating the carrier fluid so that the drop of culture medium is moved relative to the capillary injection tube;
- [0053] e) repeating steps b) and c) to create an ordered succession of drops of culture medium in the carrier fluid to form a plurality of reactors for culture of microorganisms;
- [0054] f) measuring at least one parameter representative of each culture reactor, wherein said parameter can be representative of the quantity of microorganisms present in each reactor;
- [0055] g) recirculating at least one reactor to measure said at least one representative parameter over time.
- [0056] the method can further comprise after step c) and before step e), a step d) comprising injection, into the carrier fluid, of a drop of a so-called "separating" fluid that is immiscible with the carrier fluid and immiscible with the reaction mixture, so that at least one drop of separating fluid is interposed between two reactors and prevents their coalescence;
- [0057] measurement can be performed by an optical method such as measurement of absorbance, of diffusion or of fluorescence, or by an electrical measurement such as impedance; and/or
- [0058] the method can further comprise, after step e), a step f) of recovery of at least one reactor of interest by aspiration of said reactor of interest into a sampling capillary tube mounted opening into the capillary reaction tube.
- [0059] Other features of the invention will be formulated in the detailed description given hereunder, referring to the appended figures which show, respectively:
- [0060] FIG. 1, a schematic partial sectional view of a first functional part of the reaction system according to the invention;
- [0061] FIG. 2, an enlarged photograph of a partial section of a capillary reaction tube according to the invention;
- [0062] FIG. 3, a schematic partial sectional view of a second functional part of the reaction system according to the invention, according to a first embodiment;
- [0063] FIG. 4, a schematic partial sectional view of a second functional part of the reaction system according to the invention, according to a second embodiment;
- [0064] FIG. 5, a schematic partial sectional view of a second functional part of the reaction system according to the invention, according to a third embodiment; and
- [0065] FIG. 6, an example of curves of measurements for monitoring the growth of populations of microorganisms in a reaction system according to the invention.
- [0066] In the following detailed description, the reaction system described is a system for culture of microorganisms or of living biological cells. In this application, the reaction mixture is a medium for culture of microorganisms. The other reagents can be nutrients, solutions for modifying the pH, etc.
- [0067] However, the structure described can be used in other fields (chemical or experimental) for monitoring reactions over time.

[0068] In the following detailed description, a capillary tube is a fluidic tube on the millimeter scale, i.e. having an inside diameter of the order of a tenth of a millimeter to a millimeter, preferably between 0.5 and 1 mm. For example, for implementing the present invention it is possible to use connectors and capillary tubes for chromatography. A preferred embodiment uses tubes with a diameter of 0.5 millimeter, making it possible to obtain drops of culture medium of about 100 nL.

[0069] The invention proposes a method of culturing microorganisms in a culture medium comprising the following steps:

[0070] a) filling a capillary reaction tube with a carrier medium that is immiscible with the reaction mixture;

[0071] b) injecting, by means of a capillary injection tube, an individual drop of reaction mixture in the capillary reaction tube, into the immiscible carrier fluid;

[0072] c) circulating the carrier fluid so that the drop of reaction mixture is moved relative to the capillary injection tube;

[0073] e) repeating steps b) and c) to create an ordered succession of drops of reaction mixture in the carrier fluid to form a plurality of reactors;

[0074] f) measuring at least one representative parameter of each reactor or a signal resulting from the activity of said microorganisms;

[0075] g) recirculating at least one reactor in order to measure the representative parameter or parameters over time. This recirculation can be movements back and forth and/or successive passages of the succession of drops in front of the detector by the recirculating means, for measuring the quantity of microorganisms over time.

[0076] For implementing this method, the invention proposes a reaction system **100** for culture of microorganisms, a first functional part of which is illustrated in FIG. 1.

[0077] The culture reaction system **100** comprises one or more reservoir(s) **M1** of culture medium **1** fluidically connected to a capillary injection tube **10**. This fluidic connection is provided by T connectors.

[0078] The capillary injection tube **10** is mounted opening into a capillary culture tube **20** via a two-way valve **102**.

[0079] At least one reservoir **F1** of a carrier fluid **21** that is immiscible with the culture medium **1** is fluidically connected to the capillary culture tube **20** via a two-way valve **102**.

[0080] The culture reaction system **100** according to the invention also comprises at least one means of circulating the culture medium **1**, the carrier fluid **21** and any other fluid used in the reaction system **100** according to the invention.

[0081] This circulating means is capable of generating a flow in the various capillaries and of controlling the two-way valves **102** of the whole reaction system **100**.

[0082] Advantageously, the circulating means makes it possible to generate a flow in both directions within at least certain capillaries. In other words, it is capable of reversing the direction of circulation of the carrier fluid, and therefore of the reservoirs, in some of the capillaries.

[0083] The arrangement with the capillary injection tube **10** opening into the capillary culture tube **20** makes possible the injection, by the circulating means, of individual drops **30** of culture medium **1** in the capillary culture tube **20**, into the carrier fluid **21** that is immiscible with the culture medium **1**. Advantageously, the injection tube is mounted opening into

the culture tube via connectors, such as a T-junction or a four-way junction, equipped with one or more suitable valve(s).

[0084] The carrier fluid **21** is advantageously an oil, whereas the culture medium **1** is aqueous.

[0085] It is thus possible to produce monodispersed drops of inverted emulsion (water in oil) by controlling the flow rates (or the pressure) of the immiscible fluids. By imposing a velocity and a duration of circulation of the culture medium and/or of the carrier fluid, it is possible to accurately inject a defined volume of culture medium into the carrier fluid in the form of individual drops.

[0086] Each drop **30** constitutes a reactor for culture of microorganisms within the carrier fluid **21**.

[0087] The reaction system for cultures of microorganisms according to the invention advantageously comprises one or more reservoirs **R1**, **R2** of reagent **51**, **52** fluidically connected to the capillary injection tube **10** via T-connectors (see FIG. 1) and/or to the capillary culture tube **20** (see reservoir **R3** in FIG. 3 directly connected to the culture tube **20**), so that reagent **51**, **52** can be mixed with the culture medium **1**. This makes it possible to modify the composition and/or the chemical and/or physical properties of the culture medium, then referenced **1'**. For example, it is possible to enrich or deplete a reactor **30** of nutrients, modify the pH, inject labeling molecules, for example fluorescent, inject molecules whose stimulating or inhibitory capacity is to be tested on the microorganisms (for example antibiotics), etc.

[0088] It is thus possible to define the composition of the culture medium precisely by adjusting the flow rates of the fluids constituting the aqueous phase.

[0089] To prevent the risks of coalescence and difficulties with detection connected with the closeness of the reservoirs **30**, the invention advantageously proposes interposing another fluid that is immiscible with the culture medium **1**, **1'** and with the carrier fluid **21**.

[0090] Thus, after step c) and before step e), the invention envisages a step d) comprising injection, in the carrier fluid **21**, of a drop of a so-called "separating" fluid, immiscible with the carrier fluid and immiscible with the culture medium, so that at least one drop **40** of separating fluid is interposed between two culture reactors **30** and prevents their coalescence.

[0091] For this purpose, the reaction system of cultures of microorganisms according to the invention advantageously comprises at least one reservoir **F2** of a separating fluid **41** that is immiscible with the carrier fluid **21** and immiscible with the culture medium **1**, **1'**.

[0092] This reservoir **F2** is fluidically connected to the capillary culture tube **20** via a two-way valve **102** so that drops **40** of separating fluid can be injected into the carrier fluid **21** between two culture reactors **30**.

[0093] The carrier fluid **21** and the separating fluid **41** are preferably mutually immiscible oils, for example fluorinated oil as carrier fluid and mineral oil for the separating fluid, the culture medium **1**, **1'** being an aqueous medium that is immiscible with the aforementioned oils **21**, **41**.

[0094] The length of the capillary culture tube in which the reactors are formed, and the flow rates imposed, define the quantity of reactors that can be used per experiment and the time interval between each measurement. It is thus possible to work on several thousand reactors in parallel. This method of manipulating drops in one dimension makes it possible to preserve the identity of each drop in the course of an experi-

ment, and control their composition perfectly by avoiding any loss by evaporation or transfer.

[0095] According to a preferred embodiment, the method according to the invention comprises, after step e), a step f) of measuring one or more representative parameters of each culture reactor **30**, wherein said parameter can be representative, for example, of the quantity of microorganisms present in each reactor.

[0096] Measurement can be performed by an optical method such as measurements of absorbance, of diffusion or of fluorescence, or by an electrical measurement such as impedance.

[0097] A first embodiment of a second functional part of the reaction system according to the invention is illustrated in FIG. 3. This second functional part makes it possible to carry out the aforementioned steps of the method.

[0098] For this purpose, capillary culture tube **20**, at least, comprises at least one portion that is transparent to a signal emitted and/or captured by a detector S, or a detector L-P.

[0099] Detector S can be an electrical impedance sensor.

[0100] Detector L-P consists, in this example, of a laser L emitting optical excitation radiation, and a photodiode P sensitive to the radiation emitted by the reservoir **30** under excitation of the laser, which can be positioned on the axis or at an angle to the excitation radiation (in the case of dispersion of light, the light dispersed by the drop at 90° of the laser or any other angle can be observed).

[0101] The embodiment illustrated in FIG. 3 comprises a means for recirculating the reservoirs comprising a loop for recirculating the reactors in front of the detector or detectors S, L-P. This recirculating loop then comprises a capillary discharging upstream and downstream of the detector or detectors S, L-P. In this case the circulating means for the fluids (culture medium, carrier fluid) can function only in a single direction of circulation.

[0102] It is thus possible to monitor the growth of the microorganisms in each reservoir by mechanically displacing the carrier fluid, thus making each reactor pass repeatedly (recirculation of the reactors) in front of the detector or detectors S or L-P, in the same direction of circulation. This displacement is very easy to implement, and does not risk overturning the reactors, as with the plates of the prior art. Thus, the speed of displacement can be accelerated, the more so if there are drops of separating fluid **40** between each reactor **30**.

[0103] Alternatively, as illustrated in FIG. 4, or in combination, as illustrated in FIG. 5, the means for circulating the fluids can function bidirectionally, i.e. leading the fluids through the capillaries in one direction or in the opposite direction.

[0104] It is thus possible to monitor the growth of the microorganisms in each reservoir by mechanically displacing the carrier fluid back and forth, to recirculate each reactor in front of the detector or detectors S or L-P.

[0105] By combining a recirculating loop and a means for circulating the fluids functioning bidirectionally (FIG. 5), it is possible to reduce the time between two passages of one and the same reactor in front of the detector or detectors, optimizing the recirculation as a function of the distances upstream and downstream of the reservoir relative to the detectors. Thus, depending on the user's requirements and on the particular case, it will be advantageous to reverse the direction of circulation of the fluid to bring a reactor of interest in front of the detector or detectors S or L-P, or, conversely, to continue

circulating the carrier fluid in the same direction, to recirculate the reactor of interest via the recirculating loop.

[0106] Knowing the position of each reactor in the succession of reactors precisely, and knowing the chemical and/or physical characteristics of the culture medium, it is possible to analyze the influence of the composition of the culture medium on the growth of the microorganisms. Measurement curves C_1 , C_2 , C_n of the population of microorganisms in a plurality of reactors are shown in FIG. 6.

[0107] It is thus possible to measure the variation of the population of microorganisms in each successive reservoir over time by performing successive passages of the reservoirs, in the same direction of circulation (FIGS. 3 and 5) and/or by alternating the direction of circulation (FIGS. 4 and 5), in front of the detectors. Each curve represents an identified reactor and each point represents the passage of the reactor in question in front of the detector at a given time interval. Thus, each drop is identified, measured and parameterized.

[0108] A reservoir R4 of carrier fluid can be mounted opening into the culture capillary **20** for separating the drops before sorting them (FIG. 4). This reservoir R4 can of course be provided in combination with one or more reservoirs R3 of reagents such as that illustrated in FIGS. 3 and 5.

[0109] As illustrated in FIGS. 3 to 5, the microorganism culture sorter according to the invention preferably comprises at least one waste reservoir W, connected fluidically to the capillary culture tube **20** for removing the reactors after the experiment and valves **101-102** for orienting the drops.

[0110] The invention also permits easy selection and extraction of a culture reactor of interest. Thus, the invention proposes, after step e), a step f) of recovery of at least one culture reactor of interest by aspiration of said reactor of interest into a sampling capillary tube **60** mounted opening into the capillary culture tube **20**.

[0111] Advantageously, the sampling capillary tube allows the sampled reactor to be deposited on a culture substrate **65**, such as a layer of agar or in the wells of a microplate.

[0112] Thus, during detection, each reactor is tagged with its position in the succession, and a counting detector allows the reservoirs to be identified. By means of valves **102**, the reactor or reactors of interest are directed into the sampling capillary tube **60**, whereas the other reactors remain in the capillary culture tube **20**. The reactor or reactors of interest are recovered at the outlet of the sampling capillary tube **60**.

[0113] The reverse is also possible: the reactors of interest are kept in the capillary culture tube **20**, while the other reactors are collected and removed. Then only the reactors of interest for the experiment remain in the culture tube **20**.

[0114] Alternatively, or in combination, the invention advantageously envisages at least one diverting capillary tube **70** mounted opening into the capillary culture tube **20** so that at least one culture reactor **30** can be diverted to a treatment means **80** of one or more reactors **30**. This treatment means **80** can be a thermal regulating means that can heat or cool one or more reactors. Other treatment means can be provided such as the addition of culture medium or sampling of a portion of the reactor for making a chemostat (bioreactor in which organisms (bacteria, phytoplankton) grow in a controlled manner).

[0115] The diverting capillary tube **70** thus permits selective treatment of one or more reactors relative to the other reactors that remain in the culture tube **20**. It will be understood that several diverting tubes can be provided so that reactors **30** diverted selectively can be treated differently.

[0116] The invention is advantageously implemented by means of a central control unit connected to the circulating means and capable of:

- [0117] controlling the injection of individual drops of culture medium in the capillary culture tube, into the carrier fluid, imposing a velocity and a duration of circulation of the culture medium, so as to form a plurality of reactors 30 for culture of microorganisms;
- [0118] controlling the circulation of the carrier fluid by imposing a velocity, duration and direction of circulation of the carrier fluid in the capillary culture tube by controlling the valves;
- [0119] counting the culture reactors 30 in the carrier medium and storing the position of each reactor relative to a reference reactor 30;
- [0120] recirculating the reservoirs (30) in the capillary reaction tube;
- [0121] controlling the injection of drops 41 of separating fluid between two culture reactors 30;
- [0122] controlling the injection of at least one reagent 51, 52 into the culture medium 1, 1' for modifying its composition and/or its chemical and/or physical properties;
- [0123] controlling the sampling of at least one reactor of interest; and/or
- [0124] controlling the diverting of at least one reactor of interest to a treatment means, itself advantageously controlled by the central unit.

[0125] Advantageously, the central control unit is, in addition, connected to the detector S, L-P and is capable of storing at least one measurement performed by the detector.

[0126] Advantageously, the reaction system comprises a thermal regulating means of the reactors which is preferably arranged to allow thermal regulation in the whole reaction system. This thermal regulation can be homogeneous, i.e. roughly identical throughout the system, or heterogeneous, i.e. the temperature can be increased in certain places and decreased in other places of the system.

1. A reaction system, notably of cultures of microorganisms, comprising:

- at least one reservoir of reaction mixture fluidically connected to a capillary injection tube;
- at least one reservoir of a carrier fluid that is immiscible with the reaction mixture, fluidically connected to a capillary reaction tube,
- the capillary injection tube being mounted opening into the capillary reaction tube so that individual drops of reaction mixture are injectable into the capillary reaction tube, into the immiscible carrier fluid, so as to form a succession of reactors,
- at least one reaction monitoring detector,
- wherein the system comprises a means of referencing the reactors for identifying them uniquely in the succession of reactors, and at least one means for recirculating the reactors in front of at least one reaction monitoring detector.

2. The reaction system as claimed in claim 1, in which the recirculating means comprises a loop for recirculating the reactors in front of the detector or detectors, said recirculating loop comprising a capillary discharging upstream and downstream of the detector or detectors.

3. The reaction system as claimed in claim 1, in which the recirculating means comprises a recirculating means able to reverse the direction of circulation of the reactors.

4. The reaction system as claimed in claim 1, for culturing microorganisms, in which the reaction mixture is a medium for culturing microorganisms, the capillary reaction tube is a capillary culture tube, and the reactors are reactors for culture of microorganisms.

5. The reaction system as claimed in claim 1, further comprising at least one reservoir of a separating fluid that is immiscible with the carrier fluid and immiscible with the reaction mixture, fluidically connected to the capillary reaction tube so that drops of separating fluid can be injected into the carrier fluid between two reactors.

6. The reaction system as claimed in claim 1, further comprising at least one reservoir of reagent fluidically connected to the capillary injection tube and/or to the capillary reaction tube, so that reagent can be mixed with the reaction mixture.

7. The reaction system as claimed in claim 5, in which the carrier fluid and the separating fluid are mutually immiscible oils, the reaction mixture being an aqueous medium that is immiscible with the aforementioned oils.

8. The reaction system as claimed in claim 1, further comprising at least one waste reservoir connected fluidically to the capillary reaction tube.

9. The reaction system as claimed in claim 1, further comprising at least one detector, the capillary reaction tube comprising at least one portion that is transparent to a signal emitted and/or detected by the detector.

10. The reaction system as claimed in claim 1, further comprising a sampling capillary tube mounted opening into the capillary reaction tube so that at least one reactor can be taken.

11. The reaction system as claimed in claim 1, further comprising at least one diverting capillary tube mounted opening into the capillary reaction tube so that at least one reactor can be diverted to a means for treatment of one or more reactors.

12. The reaction system as claimed in claim 1, further comprising a central control unit connected to the circulating means and configured for:

- controlling the injection of individual drops of reaction mixture into the capillary reaction tube, into the carrier fluid, imposing a velocity and a duration of circulation of the reaction medium, so as to form a plurality of reactors;
- controlling the circulation of the carrier fluid by imposing a velocity, duration and direction of circulation of the carrier fluid in the capillary reaction tube;
- counting the reactors in the carrier medium and storing the position of each reactor relative to a reference reactor;
- recirculating the reservoirs in the capillary reaction tube.

13. The reaction system as claimed in claim 5, in which the central control unit is capable of controlling the injection of drops of separating fluid between two reactors.

14. The reaction system as claimed in claim 12, further comprising at least one reservoir of reagent fluidically connected to the capillary injection tube and/or to the capillary reaction tube so that reagent can be mixed with the reaction mixture, and in which the central control unit is capable of controlling the injection of at least one reagent into the reaction mixture for modifying its composition and/or its chemical and/or physical properties.

15. The reaction system as claimed in claim 1, in which the central control unit is in addition connected to the detector and is capable of storing at least one measurement performed by the detector or detectors.

16. A method of monitoring a reaction in a reaction mixture, wherein the method comprises the following steps:

- a) filling a capillary reaction tube with a carrier medium that is immiscible with the reaction mixture;
- b) injecting, by means of a capillary injection tube, an individual drop of reaction mixture in the capillary reaction tube, into the immiscible carrier fluid;
- c) circulating the carrier fluid so that the drop of reaction mixture is moved relative to the capillary injection tube;
- e) repeating steps b) and c) to create an ordered succession of drops of reaction mixture in the carrier fluid to form a plurality of reactors;
- f) measuring at least one representative parameter of each reactor;
- g) recirculating at least one reactor to measure said at least one representative parameter over time.

17. The method of monitoring a reaction in a reaction mixture as claimed in claim **16**, for the culture of microorganisms in a culture medium, comprising the following steps:

- a) filling a capillary culture tube with a carrier medium that is immiscible with the culture medium;
- b) injecting, by means of a capillary injection tube, an individual drop of culture medium in the capillary culture tube, into the immiscible carrier fluid;
- c) circulating the carrier fluid so that the drop of culture medium is moved relative to the capillary injection tube;

- e) repeating steps b) and c) to create an ordered succession of drops of culture medium in the carrier fluid to form a plurality of reactors for culture of microorganisms;
- f) measuring at least one representative parameter of each culture reactor, wherein said parameter can be representative of the quantity of microorganisms present in each reactor;
- g) recirculating at least one reactor to measure said at least one representative parameter over time.

18. The method of monitoring a reaction in a reaction mixture as claimed in claim **16**, further comprising, after step c) and before step e), a step d) comprising injection, into the carrier fluid, of a drop of a separating fluid, immiscible with the carrier fluid and immiscible with the reaction mixture, so that at least one drop of separating fluid is interposed between two reactors and prevents their coalescence.

19. The method of monitoring a reaction in a reaction mixture as claimed in claim **16**, in which measurement is carried out by an optical method selected from the group consisting of measurements of absorbance, of diffusion, and of fluorescence, or by an electrical measurement comprising measuring impedance.

20. The method of monitoring a reaction in a reaction mixture as claimed in claim **16**, further comprising, after step e), a step f) of recovery of at least one reactor of interest by aspiration of said reactor of interest into a sampling capillary tube mounted opening into the capillary reaction tube.

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