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(54) Method for controlling an acoustic cell

(57) The present invention is related to an iterative method for controlling an acoustic cell (1) separating dispersed particles in a liquid medium, said acoustic cell (1) comprising two opposed plates (5) delimiting a resonating cavity filled with said liquid medium, at least one of the opposed surfaces (4) comprising a piezoelectric transducer (4) coupled to an electrical power generator for producing ultrasonic waves in said resonating cavity, said method comprising the steps of:
a. applying an ultrasonic sound field by applying a periodic electrical potential of initial resonant frequency fi and initial power Pi to said piezoelectric transducer (5);
b. measuring the cosine of the resulting phase shift phi (cos(phi)) between the electric current and the electric potential applied to the transducer (5);
c. if the cos(phi) is lower than a predetermined threshold, increasing the power Pi, else decreasing the power Pi;
d. determining the sign of the gradient of cos(phi) as a function of the frequency;
e. varying the frequency in the gradient direction thereby maximising cos(phi);
f. getting to step (b).

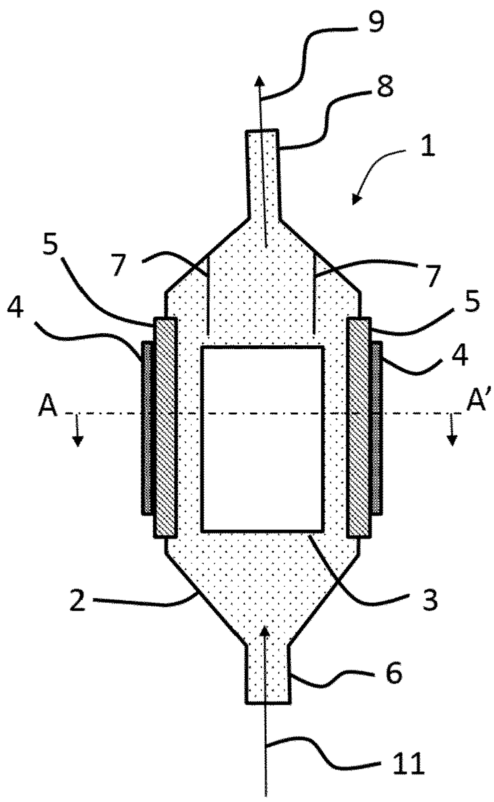

Fig. 1

A-A' cross section

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Description

Field of the Invention

[0001] The present invention is related to a method for regulating the power and frequency of an acoustic field applied to an acoustic cell. More particularly, the present invention is related to the regulation of the control parameters used in an acoustic cell for separating particles such as biological cells in a liquid medium.

[0002] The present invention is also related to an acoustic cell to be controlled by the method of the invention.

Background

[0003] In biotechnologies, separating particles from a liquid medium has been the subject of research for a long time. At first, classical mechanical filters were used, but such kind of methods suffers several drawbacks. For example, the pressure and flow is limited by mechanical stress applied to the cells, or cell adhesion may occur on the filtering medium.

[0004] A second strategy is based upon centrifugation. In that case, the developed systems are mechanically complex, and it is difficult to produce disposable parts that can provide continuous separation by centrifugation.

[0005] Therefore, acoustic separation was developed, to solve some of those problems. In such separation methods, an acoustic field is applied to a resonant cavity, with the acoustic wave nodes and antinodes planes parallel to the direction of the liquid flow to be filtered. When a fluid comprising particles heavier than the surrounding medium pass through such acoustic field, the particles are trapped in the antinodes planes and accumulate in those planes. The particles can then be collected by periodically stopping the acoustic field and reversing the flow or let the particles sediment by gravity to a collecting tank. This can be performed by a backflush procedure wherein the acoustic cell is emptied by injecting a gas from above, the particles being collected along with the liquid flushed from the cell. In such system, the separation cell consist in a resonating cavity, comprising to opposed parallel plane surfaces, at least one of them being coupled to a piezoelectric transducer for producing the acoustic field. Document EP0633049 discloses such an acoustic cell, and the corresponding filtering method.

[0006] In order to obtain optimum filtering in such a system, it is of key importance to have resonating conditions. Document EP0633049 describes how to calculate the theoretical resonance frequencies of typical cavities, but, such frequencies are usually not perfectly stable. For example, small dimensional variation of the plate distance, particle density, and fluid temperature are known to have an important impact on the sound speed and therefore on the resonance frequency.

[0007] Therefore, the frequency is usually adapted in a closed loop regulation, by maximising the power transfer to the fluid. In order to make such frequency adjustment, the power needs to be sufficient at any time, so that the signal arising from the coupling with the filtered fluid is sufficient. Therefore, in such frequency tracking method, the power is permanently maintained higher than what is really needed for maintaining resonance conditions.

Aims of the invention

[0008] An aim of the invention is to provide a method for continuously regulating both frequency and power applied to the piezoelectric transducer(s) of an acoustic cell wherein the injected power is minimised, and the resonance conditions are optimised.

[0009] More particularly, the method of the invention aims to provide a regulating method of both power and frequency applied to an acoustic cell adapted to continuously filter particles from a fluid having varying physical properties such as sound speed, compressibility and density.

[0010] An aim of the invention is to provide a regulating method sufficiently robust to be used for controlling disposable acoustic cells having broad dimensional tolerances.

Summary of the Invention

[0011] The present invention is related to an iterative method for controlling an acoustic cell separating dispersed particles in a liquid medium, said acoustic cell comprising two opposed plates delimiting a resonating cavity filled with said liquid medium, at least one of the opposed surfaces comprising a piezoelectric transducer coupled to an electrical power generator for producing ultrasonic waves in said resonating cavity, said method comprising the steps of:

a) applying an ultrasonic acoustic field by applying a periodic electrical potential of frequency fi and power Pi to said piezoelectric transducer ;
b) measuring the cosine of the resulting phase shift phi (cos(phi)) between the electric current and the electric potential applied to the transducer;
c) if the cos(phi) is lower than a predetermined threshold, increasing the power Pi, else decreasing the power Pi;
d) determining the sign of the gradient of cos(phi) as a function of the frequency;
e) varying (increasing or decreasing) the frequency in the gradient direction thereby maximising cos(phi);
f) getting to step (b).

[0012] Preferred embodiments of the present invention disclose at least one or a suitable combination of the following features:

- the method comprising an initialisation step wherein the power is gradually increased until cos(phi) decreases below a predetermined initial value;
- the method comprising an initial frequency tracking step, wherein initial resonant frequency is determined;
- the initial frequency tracking is performed by a dichotomic search method;
- a lag time is inserted after any variation of the power or frequency before the cos(phi) measurement to let the system equilibrate before said measurement;
- the lag time is larger than 1ms, preferably 10ms, more preferably about 100ms.

[0013] The present invention is also related to a disposable acoustic cell for separating particles dispersed in a liquid medium, said acoustic cell comprising a polymeric housing and two opposed plates, said polymeric housing and said opposed plates defining an enclosure for receiving a liquid comprising particles to be separated from said liquid by an acoustic wave field, a piezoelectric transducer being fixed on at least one of said opposing plates for applying the acoustic wave field between said plates.

[0014] Preferred embodiments of the disposable acoustic cell of the invention disclose at least one or a suitable combination of the following features

- the opposed plates have a Knopp hardness HK 0.1/20 of 300 or more, preferably 480 or more;
- the distance between the opposed plates has a tolerance of more than 0.05mm;
- the side walls joining the opposed plates comprises acoustic absorbing means for inhibiting acoustic reflexion on said side walls;
- the means for inhibiting acoustic reflexion on said side walls comprises an elastomeric polymer such as a silicone rubber coated on said side walls;
- the polymer housing have vicat softening temperature according to ISO 306 is higher than 121°C;
- a piezoelectric transducer is fixed on both opposed plates;
- the opposed plates have a density higher than 1,1, preferably 1.5, more preferably higher then 2.

Figures

[0015] Fig. 1 represents a side view of an example of acoustic cell according to the invention.

[0016] Fig. 2 represents a top view of a cross section along the A-A' plane of the acoustic cell of fig.1

[0017] Fig. 3 represents a schematic view of the regulating system of the invention.

Figure Keys

[0018]

1: acoustic cell
2: polymeric housing
3: viewing window
4: piezoelectric transducer
5: opposed plates
6: liquid inlet
7: upper wall, (means for inhibiting convection flow)
8: liquid outlet
9: outflow
10: absorbing layer
11: inflow

Detailed Description of the Invention

[0019] The present invention is related to a method for controlling the acoustic power and frequency injected in an acoustic cell. As represented in fig. 1 and 2, the acoustic cell comprises two opposed plates 5 defining a resonant cavity. An acoustic field is applied to the cavity by means of at least one piezoelectric 4 transducer fixed on the external surface of at least one of the opposed plates 5. When only one piezoelectric transducer 4 is used, the plate without transducer act as a mirror. Preferably, a piezoelectric transducer is fixed on both plates. This allows the use of larger cells for a given injected power by each piezoelectric transducer, thereby reducing local heat dissipation.

[0020] In order to obtain an optimal coupling between the piezoelectric transducer and the liquid to be filtered, it is preferred that the plates have Knopp hardness HK 0.1/20 higher than 300, preferably higher than 480, and a density higher than the liquid density. This can be for example silicate glass, preferably borosilicate glass.

[0021] Preferably the lateral sides of the acoustic cells comprises transparent viewing windows 3, for visual inspection of the filtering process (i.e. particles/cells agregation). An acoustic absorbing medium 10 is advantageously coated on those viewing window, in order to avoid complex reflexions on the windows, perturbing the resonant acoustic field. Silicone rubber is particularly adapted as absorbing medium.

[0022] In order to minimise heat dissipation at the different interfaces (piezo/plate and plate/liquid interfaces), the inner dimensions of the cell, and the thickness of the plate are selected so that they are multiples of half of the wavelength of the injected sound. Unfortunately, the properties of the liquid medium are varying around average values for example due to local temperature increase, particles density and composition of the liquid.

[0023] Furthermore, in biotechnologies (i.e. when filtering the cells from a cell culture) in order to avoid cross contamination between different batches, or different types of cell culture, it is desirable to use sterilized acoustic cells, preferably disposable. When disposable, the dimensional tolerances are usually much broader than the tolerance obtained on expensive non disposable cells. Additionally, when non disposable cells are used the system can be calibrated once, reusing initially measured resonance frequency in subsequent uses. This is not realistically feasible in the case of disposable acoustic cells.

[0024] Therefore, it is difficult to define the resonance frequency upfront, and this is even more difficult in the case of disposable acoustic cells. In prior art regulation methods, an initial acoustic power is applied to the transducer at a frequency close to the theoretical resonance frequency, and then the frequency is varied until resonance is obtained. The frequency is then slowly adapted to the changing parameters (temperature, particles density ...). Unfortunately, in order to have a sufficient initial signal the injected power has to be increased at a level above the optimum power needed to sustain the resonance conditions. This has the drawback of increasing temperature, potentially degrading the cells to be filtered, and also increase the power consumption. The temperature variation and gradient also induces instabilities in the resonant acoustic field and induces convection flows degrading the filtration performance.

[0025] The method of the invention does not only adapt the frequency to the resonance conditions, but also minimise the power injected in the liquid medium.

[0026] The load being capacitive, the maximum transmitted power occurs when the phase shift phi between the applied electrical potential and the resulting electrical current is minimum. A convenient measurement of said phase shift phi is the measurement of the cosine of phi (cos(phi)), cos(phi) being maximum at resonance.

[0027] In the present invention, both the power and the frequency being simultaneously regulated for maximising only one parameter, it is difficult to use standard analogic method such as PID regulation modules. Therefore, the method of the invention is preferably controlled by a numerical processor controlling the frequency of a wave generator and the gain of an amplifier (power control) downstream of the wave generator, the piezoelectric transducer being connected to the output of the amplifier, as represented in Fig. 3.

[0028] Preferably, in an initial step, an initial frequency is used to generate an acoustic field in the acoustic cell, and the gain of the amplifier is slowly increased until cos(phi) reaches a predetermined value. This step permits to obtain a sufficient signal to begin the tracking of the resonance frequency even in the case of badly known dimensions of the acoustic cell (disposable acoustic cell).

[0029] Then, the frequency is iteratively varied to increase cos(phi) and the power is decreased, so that in stable conditions, the resonance is maintained at the minimum feasible power input.

[0030] After the initial step, the variation of the power and frequency is performed according to the following sequential steps:

a. measuring the cosine of the resulting phase shift phi (cos(phi)) between the electric current and the electric potential applied to the transducer (5);
b. if the cos(phi) is lower than a predetermined threshold, increasing the power Pi, else decreasing the power Pi;
c. determining the sign of the gradient of cos(phi) as a function of the frequency;
d. varying the frequency in the gradient direction thereby maximising cos(phi);
e. getting to step (b).

[0031] The determination of the direction of the gradient of cos(phi) can for example be determined by performing the minimum possible decrement of frequency, then measuring cos(phi), if cos(phi) has increased, this means that the gradient is negative and the frequency is decreased before getting back to step b, else, performing a double increment of the frequency, if cos(phi) has increased, it means that the gradient is positive, and the frequency is increased before getting back to step b. If cos(phi) has not increased in both directions (increment or decrement) the gradient is considered as being zero, and the frequency is maintained at its previous value before getting to step b.

[0032] Sequences without acoustic field are used at periodical time in order to collect the particles agglutinated at the wave antinodes, the particles sedimenting when the acoustic field is stopped. Those stopping sequences are also used to perform a subsequent optimisation of the control parameters.

[0033] Advantageously, the initial frequency applied to the transducers is determined by a dichotomic numerical method. In such a method, a minimum and a maximum frequency (fmin and fmax) are initially determined. This can be for example an arbitrary frequency +/- the frequency variation leading to an increment/decrement of nx by $\lambda/4$, n being the resonance mode, and λ being the wavelength. Variation of the frequency by more than such value would lead to jump from one resonance mode to another resonance mode, and would induce instabilities in the frequency tracking. So, at first, the direction of the gradient of cos(phi) is determined at f=(fmin+fmax)/2 and

- if gradient(cos(phi)) at f is positive then, fmin is replaced by the previous value of (fmin+fmax)/2
- if gradient(cos(phi)) at f is negative then, fmax is replaced by the previous value of (fmin+fmax)/2

until fmin=fmax, when that condition is reached, the frequency is iteratively adapted only by the minimum possible increment/decrement (corresponding to the discrete interval between two possible values of the numerical system) at each iteration, for tracking the modifications of the frequency of resonance. This last frequency tracking is simultaneously performed along with power adaptation, as described hereabove.

[0034] Advantageously, a lag time of at least 1 ms, preferably 10ms, more preferably 100ms is used to let the system equilibrate after any frequency or power changes, before cos(phi) measurements.

[0035] The method of the invention has been tested on disposable acoustic cells of the type represented in fig. 1 and 2. The plates defining the resonant cavity where separated by 34mm. The plates themselves where made of glass plates of 1,2mm thickness. The plates dimensions where 41mm height and 31mm width.

[0036] The wave generator was operated between 2,18 and 2.3MHz, the power control of the gain of the amplifier was performed by a step by step potentiometer, the power varying from 0 to 15W. The predetermined threshold of step b was 0,3538 and was identical to the predetermined value used in the initial step (see initial step hereabove).

[0037] Typical operating cycle time is about 45s, separated by 5s lag time between each operating cycles.

[0038] The system has shown robust behaviour in finding resonance conditions in disposable acoustic cells and in changing conditions, giving rise to better filtering conditions.

Claims

1. Iterative method for controlling an acoustic cell (1) separating dispersed particles in a liquid medium, said acoustic cell (1) comprising two opposed plates (5) delimiting a resonating cavity filled with said liquid medium, at least one of the opposed surfaces (4) comprising a piezoelectric transducer (4) coupled to an electrical power generator for producing ultrasonic waves in said resonating cavity, said method comprising the steps of:

   a. applying an ultrasonic sound field by applying a periodic electrical potential of initial resonant frequency fi and initial power Pi to said piezoelectric transducer (5);
   b. measuring the cosine of the resulting phase shift phi (cos(phi)) between the electric current and the electric potential applied to the transducer (5);
   c. if the cos(phi) is lower than a predetermined threshold, increasing the power Pi, else decreasing the power Pi;
   d. determining the sign of the gradient of cos(phi) as a function of the frequency;
   e. varying the frequency in the gradient direction thereby maximising cos(phi);
   f. getting to step (b).

2. The iterative method according claim 1 comprising an initialisation step for determining the initial power wherein the power is gradually increased until cos(phi) decreases below a predetermined initial value.

3. The iterative method according to any of the previous claims comprising an initial frequency tracking step, wherein the initial resonant frequency is determined.

4. The iterative method according to claim 3 wherein the initial frequency tracking is performed by a dichotomic search method.

5. The iterative method according to any of the previous claims wherein a lag time is inserted after any variation of the power or frequency before the cos(phi) measurement to let the system equilibrate before said measurement.

6. The iterative method according to claim 4 wherein the lag time is larger than 10ms, preferably about 100ms.

7. Disposable acoustic cell for separating dispersed particles in a liquid medium, said acoustic cell comprising a polymeric housing and two opposed plates, said polymeric housing and said opposed plates defining an enclosure for receiving a liquid comprising particles to be separated from said liquid by an acoustic wave field, a piezoelectric transducer being fixed on at least one of said opposing plates for applying the acoustic wave field between said plates.

8. Disposable acoustic cell according to claim 7 wherein the opposed plates have a Knopp hardness HK 0.1/20 of 300 or more.

9. Disposable acoustic cell according to claim 7 or 8 wherein the distance between the opposed plates has a tolerance of more than 0.05mm.

10. Disposable acoustic cell according to any of claims 7 to 9 wherein the side walls joining the opposed plates comprises acoustic absorbing means for inhibiting acoustic reflexion on said side walls.

11. Disposable acoustic cell according to claim 10 wherein the means for inhibiting acoustic reflexion on said side walls comprises an elastomeric polymer coated on said side walls.

12. Disposable acoustic cell according to any of claims 7 to 11 wherein the polymer housing have vicat softening temperature according to ISO 306 under 1kg is higher than 121°C.

13. Disposable acoustic cell according to any of claims 7 to 12 wherein a piezoelectric transducer is fixed on both opposed plates.

14. Disposable acoustic cell according to any of claims 7 to 13 wherein the opposed plates have a density higher than 1,1.

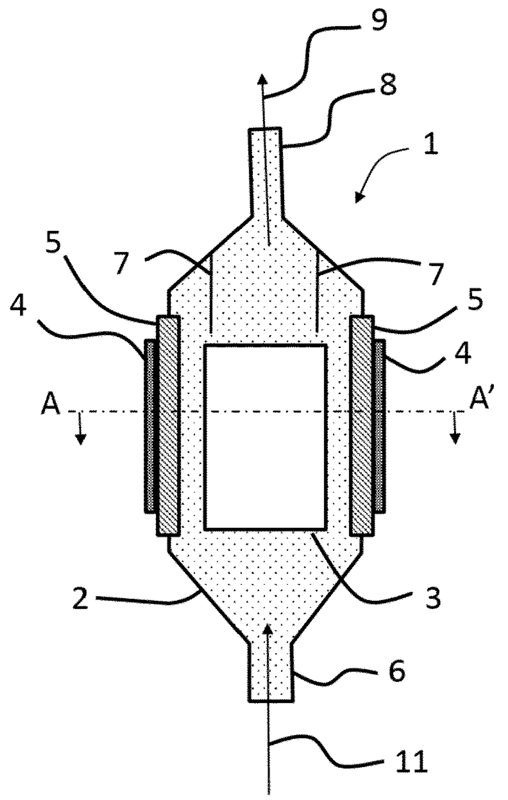

Fig. 1

A-A' cross section

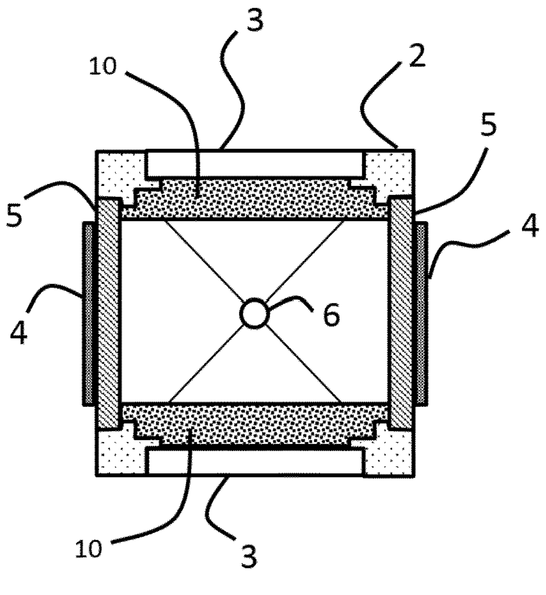

Fig. 2

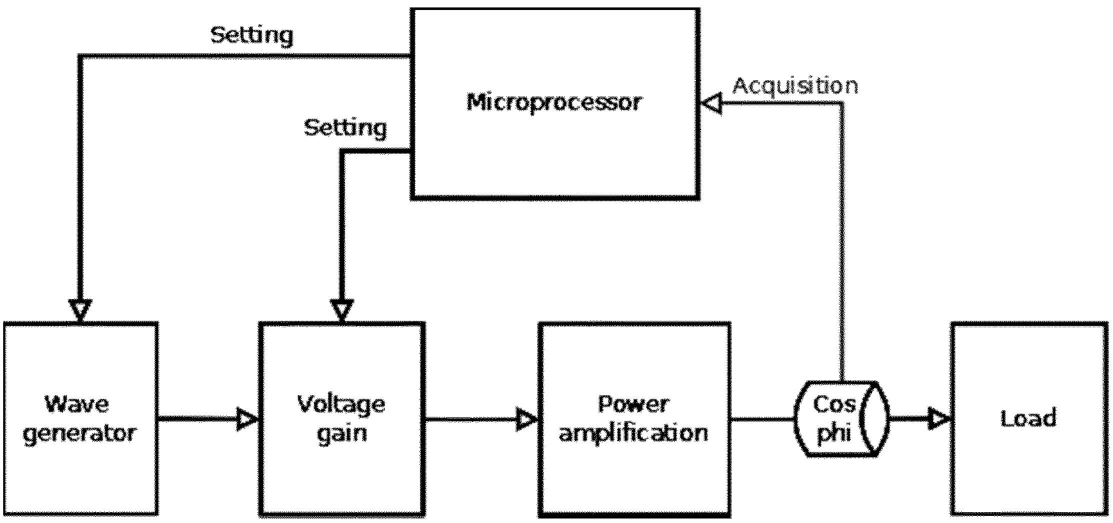
Setting
Microprocessor
Acquisition
Setting
Wave generator
Voltage gain
Power amplification
Cos phi
Load

Fig. 3

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EUROPEAN SEARCH REPORT

Application Number
EP 13 16 4759

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	US 5 711 888 A (TRAMPLER FELIX [AT] ET AL) 27 January 1998 (1998-01-27) * abstract * * column 3, lines 25-31 * * column 9, lines 16-22 * * column 27, lines 19-23 * * figure 1 * -----	1-6	INV. B06B1/02
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A	US 2011/254519 A1 (HASEGAWA HIROSHI [JP] ET AL) 20 October 2011 (2011-10-20) * the whole document * -----	1-4	

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~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
The Hague	26 September 2013	Mirkovic, Olinka

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

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Application Number
EP 13 16 4759

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-6

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

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LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 13 16 4759

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-6

   minimising the injected power, and optimising resonance conditions, by measuring the cosine of the phase shift between the electric current and the electric potential applied to the transducer, and adjusting power and frequency according to the measured value

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2. claims: 7-14

   obtaining a better coupling between the transducer and the liquid to be filtered, by using a material having a Knopp hardness HK 0.1/20 of 300 or more, to make the opposed plates of the acoustic cell

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 13 16 4759

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26-09-2013

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

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- EP 0633049 A **[0005] [0006]**