

(11) (21) (C) **2,024,232**  
(22) 1990/08/29  
(43) 1991/03/01  
(45) 2000/02/01

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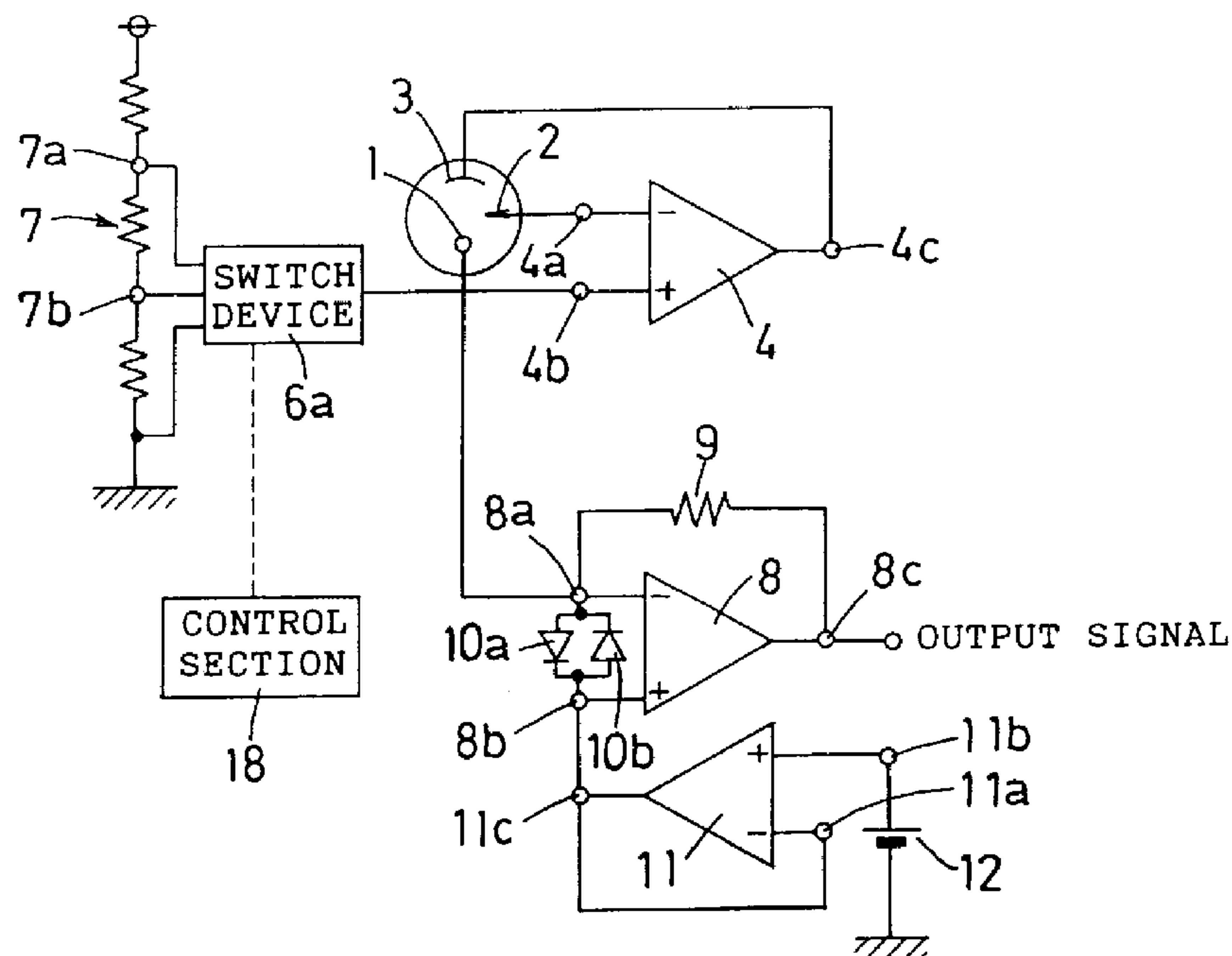
(73) Daikin Industries, Ltd., JP

(51) Int.Cl.<sup>6</sup> G01N 27/327

(30) 1989/08/30 (223613/1989) JP

(54) **METHODE ET DISPOSITIF POUR REMETTRE SOUS TENSION  
L'ELECTRODE D'UN BIOSENSEUR**

(54) **METHOD AND APPARATUS FOR REVIVING AN ELECTRODE  
OF A BIOSENSOR**



(57) After a reverse bias is applied between a working electrode and a counter electrode or a reference electrode, a forward bias higher than a forward measurement bias is applied between the working electrode and the counter electrode or the reference electrode before the forward measurement bias is applied. This reduces a time period before an actual measuring operation is possible.

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Abstract of the Disclosure

After a reverse bias is applied between a working  
electrode and a counter electrode or a reference  
5 electrode, a forward bias higher than a forward  
measurement bias is applied between the working  
electrode and the counter electrode or the reference  
electrode before the forward measurement bias is  
applied. This reduces a time period before an actual  
10 measuring operation is possible.

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Method and Apparatus for Reviving An Electrode of A  
Biosensor

Background of the Invention

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The present invention relates to methods and  
apparatus for reviving an electrode of a biosensor, and  
more particularly to methods and apparatus for reviving  
an electrode of a biosensor by supplying a bias having a  
10 different polarity from the measurement bias polarity to  
the electrode before a measuring operation is started.

It is known that a physiologically active  
substance is capable of selectively detecting a very  
15 complicated organic compound, protein or the like with  
high sensitivity. With attention directed to this  
characteristic, research has been made in various  
biosensors.

A typical biosensor having an electrode unit and  
20 a physiologically active substance fixed thereon is  
proposed. The biosensor is used for detecting the  
existence of an object substance, the relative or active  
quantity of the object substance and the like based on  
an electrical signal output from the electrode unit  
25 corresponding to the biological reaction of the object

substance, under the condition that a predetermined forward bias is applied to the electrode unit. For example, the electrode unit has a working electrode made of platinum and a counter electrode made of silver. An enzyme-immobilized membrane is fixed onto the electrode unit. When the object substance is to be measured, hydrogen peroxide is generated through an enzyme reaction of the object substance. Then the generated hydrogen peroxide reaches the surface of the electrode unit through a hydrogen peroxide penetration membrane. The electrode unit outputs an electrical signal corresponding to the quantity of hydrogen peroxide that reaches it. The existence of the object substance, the relative or active quantity of the object substance and the like are detected based on the electrical signal. Concretely, the working electrode has a forward bias of 0.6 volts applied with respect to the counter electrode.

In the biosensor described above, an interfering layer such as an oxidized layer and the like which interferes with electrical signals is generated on the working electrode, and the activity of the working electrode is lowered as the object substance measuring operation is continued with the forward bias being applied to the electrode unit. It is proposed that a reverse bias is accordingly applied to the electrode



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unit (the working electrode has a reverse bias of about -  
0.6 volts applied with respect to the counter electrode,  
corresponding to the concrete example) after one or more  
measuring is performed, within the time period in which  
5 the measurment is not performed, so as to remove the  
interfering layer. Then the activity of the working  
electrode is revived. The level of the output signal  
from the electrode unit is raised to the original level.

( Refer to Japanese Patent Laid Open Sho 60-155959 ).

10 Lowered measuring sensitivity is recovered by  
applying the predetermined reverse bias voltage to the  
electrode unit within the time period in which the  
measurment is not performed, as is described above, then  
measuring with high sensitivity can be performed again.

15 In the reviving apparatus described above, a  
constant-voltage for reviving ( reverse bias ) is  
applied between the working electrode and the counter  
electrode. The oxydized layer on the working electrode  
is reduced, hydrogen, hydrogen ions and the like are  
20 accordingly generated. When a constant-voltage for  
measurement ( forward bias ) is applied between the  
working electrode and the counter electrode, a diffusion  
current flows depending upon the generated hydrogen,  
hydrogen ions and the like.

25 As a result, the electrical signal provided for

measuring is affected by lowering, by the diffusion current, so as to remarkably lower measuring accuracy just after the constant-voltage for measurement is applied between the working electrode and the counter electrode. When the measurement is performed after the diffusion current is sufficiently lowered, sufficient measuring accuracy is obtained, but a remarkably long waiting time period ( for example, 1-2 minutes ) is needed.

The same disadvantages as above arises for a biosensor having a reference electrode in addition to the working electrode and the counter electrode.

#### Summary of the Invention

It is an object of the present invention to shorten the time period between performing a reviving operation for an electrode unit to when it is possible to start a measuring operation for an object substance.

This present invention first applies a predetermined reverse bias to a working electrode for a predetermined time period, then, applies forward bias higher than a forward measurement bias to the working electrode for a predetermined time period, then, applies

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the forward measurement bias to the working electrode.

In this reviving method, an interfering layer on the working electrode which interferes with the turning on of electricity is reduced and the activity of the working electrode is revived by applying the reverse bias to the working electrode. Substances generated through reduction of the interfering layer are moved to one of the electrodes at high speed by applying the forward bias higher than the forward measurement bias to the working electrode. The substances are rapidly consumed, accordingly, when the forward bias is applied to the working electrode. As a result, a time period between performing a reviving operation for an electrode unit to when it is possible to start a measuring operation for an object substance with a predetermined accuracy maintained, is remarkably shortened.

The time period for applying the higher bias to the working electrode may be nearly equal to the time period for applying the reverse bias to the working electrode.

It is preferred that the predetermined reverse bias is a reverse bias which is gradually increased until its absolute value reaches a predetermined value. Damage of a membrane fixed on the surface of the electrode unit, effected by current is remarkably



reduced.

It is also preferred that the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a higher predetermined value than the forward bias for measuring. Damage of the membrane fixed on the surface of the electrode unit, effected by current is remarkably reduced.

It is further preferred that the predetermined reverse bias is a reverse bias which is gradually increased until its absolute value reaches a predetermined value, and the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a predetermined value higher than the forward measurement bias. Damage of the membrane fixed on the surface of the electrode unit, effected by current is remarkably reduced.

This present invention comprises;

reviving voltage applying means for applying voltage for reviving to a working electrode;

measurement voltage applying means for applying voltage for measuring to the working electrode;

higher voltage applying means for applying a higher voltage than the voltage for measuring to the working electrode;

selection means for sequentially selecting a



condition under which to apply a voltage for reviving to the working electrode from the reviving voltage applying means, a condition under which to apply a higher voltage to the working electrode from the higher voltage

5 applying means, and a condition under which to apply a voltage for measuring to the working electrode from the measurement voltage applying means, when measuring an operation is to be performed.

10 In this reviving apparatus, the condition of applying voltage for reviving to the working electrode by the reviving voltage applying means and the condition of applying the higher voltage to the working electrode by the higher voltage applying means are selected in this order by the selection means, before an actual  
15 measuring operation is started. First, the interfering layer on the surface of the working electrode is removed. After the interfering layer has been removed, substances generated through removal of the interfering layer are moved to one of the electrodes at high speed  
20 by applying the higher forward bias to the working electrode. The substances are rapidly consumed when the forward bias is applied to the working electrode. As a result, after a short time period from when a reviving operation for an electrode unit has passed, a measuring  
25 operation for an object substance can be started with a

predetermined accuracy maintained.

It is preferred that the reviving apparatus further comprises a first time constant means for applying a predetermined time constant to the reviving  
5 voltage. Damage of a membrane fixed on a surface of an electrode unit, effected by current is remarkably reduced.

It is also preferred that the reviving apparatus further comprises a second time constant means for  
10 applying a predetermined time constant to the higher voltage. Damage of a membrane fixed on a surface of an electrode unit, effected by current is remarkably reduced.

It is further preferred that the reviving  
15 apparatus further comprises a first time constant means for applying a predetermined time constant to the reviving voltage, and a second time constant means for applying a predetermined time constant to the higher  
voltage. Damage of a membrane fixed on a surface of an  
20 electrode unit, effected by current is remarkably reduced.

More specifically, the interfering layer can easily be removed by a reduction operation because the  
reviving operation is an operation to remove the  
25 interfering layer formed on the working electrode, and



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the interfering layer is generated by oxidization. When the interfering layer is removed, hydrogen, hydrogen ions and the like are inevitably generated through removal of the interfering layer. The generated substances diffuse when the voltage for measuring is applied to the working electrode. As a result, concentration measuring of an object substance with high accuracy is performed only after the diffusion current is sufficiently lowered. Concretely, when the forward measurement bias is determined to be 0.75 volts and the reverse bias for reviving is determined to be -1 volt, the diffusion current is sufficiently lowered only after 1-2 minutes after removal of the interfering layer. The disadvantage of having to wait a long time period until actual measuring can be started, arises.

On the contrary, in the present invention, substances generated through removal of the interfering layer are moved to one of the electrodes at high speed because the higher voltage is applied to the working electrode before the measurement voltage is applied to the working electrode. The substances are sufficiently close to one of the electrodes, accordingly, when the measurement voltage is applied to the working electrode, thereby the substances are rapidly consumed when the measurement voltage is applied to the working electrode.



As a result, a time period between removal of the interfering layer to when it is possible to start the concentration measuring of an object substance with high accuracy is remarkably shortened.

5           Figures 4 are diagrams useful in understanding the operation described above. Figs. 4(A1) to fig. 4(A3) correspond to a conventional case, while figs. 4(B1) to fig. 4(B3) correspond to this present invention.

10           As is illustrated in figs. 4(A1) and 4(B1), the same quantity of generated substances exist between the working electrode and the reference electrode when the interfering layer is removed. Then, in the conventional case, only a fairly small moving force toward the  
15           working electrode acts on the generated substances as is illustrated in fig. 4(A2), thereby the time period for consuming a predetermined quantity of the generated substances is lengthened. That is, the generated substances are not so close to the working electrode as  
20           is illustrated in fig. 4(A3) after a predetermined time period has passed, thereby a long time period is needed for most of the generated substances to reach the working electrode and be consumed. On the contrary, in  
25           this present invention, a fairly large moving force toward the working electrode acts on the generated

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substances as is illustrated in fig. 4(B2), thereby the generated substances are fairly close to the working electrode when a time period equal to the above described time period has passed, as is illustrated in  
5 fig. 4(B3). Thereafter, the same moving force as in the conventional case acts on the generated substances. A time period for consuming a predetermined quantity of the generated substances is reduced because the generated substances are already close to the working  
10 electrode. As a result, the time period between removal of the interfering layer to when it is possible to start actual measuring is remarkably shortened. A biosensor having three electrodes is illustrated in figs. 4. A biosensor having two electrodes, excluding the reference  
15 electrode, is similar to the biosensor having three electrodes.

These and other objectives, features and advantages of the present invention will be more readily understood upon consideration of the present invention,  
20 taken in conjunction with the accompanying drawings.

#### Brief Description of the Drawings

Figure 1 is an electronic circuit diagram of an  
25 electrode reviving apparatus in accordance with a first

embodiment of the present invention;

Figure 2 is a vertical sectional view of the center portion of an electrode unit;

Figures 3(A) and 3(B) are diagrams showing  
5 variations of bias voltage and current when the electrode unit is revived;

Figures 4(A1), 4(A2), 4(A3), 4(B1), 4(B2), and 4(B3) are diagrams showing movement of substances generated through reviving of the electrode unit;

10 Figure 5 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a second embodiment of the present invention;

Figure 6 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a third  
15 embodiment of the present invention;

Figures 7(A) and 7(B) are diagrams showing variations of bias voltage and current when the electrode unit is revived;

Figure 8 is an electronic circuit diagram of an  
20 electrode reviving apparatus in accordance with a fourth embodiment of the present invention.

#### Detailed Description of the Preferred Embodiments

25 Fig. 1 is an electronic circuit diagram of an



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electrode reviving apparatus in accordance with a first embodiment of the present invention.

5 The apparatus revives an electrode unit having three electrodes, such as a working electrode 1 made of platinum, a reference electrode 2 and a counter electrode 3, both made of silver.

10 The reference electrode 2 and the counter electrode 3 are connected to an inverting input terminal 4a and an output terminal 4c of an operational amplifier 4, respectively. A non-inverting input terminal 4b of the operational amplifier 4 is selectively connected to a high voltage tap 7a, a low voltage tap 7b or ground of a voltage divider 7 having resistances by means of a switch device 6a. An inverting input terminal 8a of a  
15 current/voltage converting operational amplifier 8 for providing measurement signal is connected to the working electrode 1. A current/voltage converting resistance 9 is connected between an output terminal 8c and the inverting input terminal 8a of the current/voltage  
20 converting operational amplifier 8. Diodes 10a and 10b are connected in parallel and in reverse polarity with respect to one another between the inverting input terminal 8a and a non-inverting input terminal 8b of the current/voltage converting operational amplifier 8. A  
25 DC power source 12 for measuring is connected to a non-

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inverting input terminal 11b of a buffer amplifier 11.  
An output terminal 11c of the buffer amplifier 11 is  
connected directly to an inverting input terminal 11a of  
the buffer amplifier 11. The output terminal 11c of the  
5 buffer amplifier 11 is connected to the non-inverting  
input terminal 8b of the current/voltage converting  
operational amplifier 8. The DC power source 12 is used  
for applying a forward bias of 0.75 volts to the working  
electrode 1. The high voltage tap 7a and the low  
10 voltage tap 7b are used for applying biases of -1 volt  
and 1 volt respectively, to the working electrode 1. A  
control section 18, provided as a selection means, is  
used to control the operation of the switch device 6a.

Fig. 2 is a vertical sectional view of the  
15 center portion of an electrode unit to which the  
reviving apparatus is applied.

The working electrode 1 is provided at a  
predetermined position in an electrode unit body 13.  
The ring shaped reference electrode 2 and the ring  
20 shaped counter electrode 3, both electrodes 2 and 3  
surrounding the periphery of the working electrode 1,  
are provided in the electrode unit body 13 in this  
order. The electrode unit body 13 has a convex surface  
on the side on which the working electrode 1, the  
25 reference electrode 2 and the counter electrode 3 are



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provided. A hydrogen peroxide selective penetration  
membrane 14, a glucose oxidase immobilized membrane  
(hereinafter referred to as GOD immobilized membrane) 15  
and a diffusion-limiting membrane 16 made of polyvinyl  
acetate and the like are provided in this order to fit  
the convex surface of the electrode unit body 13.

5  
Terminals 17 for supplying output signals are provided  
in the electrode unit body 13. The terminals 17 are  
connected to the working electrode 1, the reference  
10 electrode 2 and the counter electrode 3, respectively.

The operation of the sensor for measuring  
glucose concentrations having the arrangement described  
above is as follows.

When measuring of glucose concentrations is  
15 carried out, the non-inverting input terminal 4b of the  
operational amplifier 4 is connected to the high voltage  
tap 7a of the voltage divider 7 by operating the switch  
device 6a. Then, a constant voltage for reviving (for  
example the constant voltage of -1 volt) is applied  
20 between the working electrode 1 and the reference  
electrode 2 (Refer to a region R1 in figs. 3(A) and  
3(B)).

In this condition, current flows to reduce  
interfering substances which are formed on a surface of  
25 the working electrode 1. The interfering substances are



completely removed and activity of the working electrode 1 is revived by continuing to apply the constant voltage for reviving between the electrodes 1 and 2 for a fairly short time period (for example a time period of about 4  
5 seconds). When the interfering substances are completely removed, hydrogen, hydrogen ions and the like are disposed between the working electrode 1 and the reference electrode 2.

Thereafter, the non-inverting input terminal 4b  
10 of the operational amplifier 4 is connected to the low voltage tap 7b of the voltage divider 7 by operating the switch device 6a. Then, a higher voltage (for example the higher voltage of 1 volt) higher than a measurement voltage is applied between the working electrode 1 and  
15 the reference electrode 2 ( Refer to a region R2 in figs. 3(A) and 3(B)).

In this condition, a large moving force acts on the floating hydrogen, hydrogen ions and the like to move them toward the working electrode 1. Most  
20 hydrogen, hydrogen ions and the like are moved close to the working electrode 1 by applying a high voltage between the working electrode 1 and the reference electrode 2 for a fairly short time period (for example, a time period of about 5 seconds).

25           Thereafter, the non-inverting input terminal 4b

of the operational amplifier 4 is connected to ground of the voltage divider 7 by operating the switch device 6a. Then, a predetermined voltage (for example a voltage of 0.75 volts) is applied as a forward bias to the working electrode 1 on the basis of the reference electrode 2. The hydrogen, hydrogen ions and the like are consumed within a short time period, then glucose concentrations may be measured. The time period between removal of interfering substances to when measuring is permitted 1-2 minutes in conventional reviving apparatus, while the time period is reduced to about 30-45 seconds in this embodiment.

After reviving is finished, a signal corresponding to the concentration of glucose is output as follows by dropping an object solution onto the electrode unit.

The dropped object solution is guided to the GOD immobilized membrane 15 with limited penetration by the glucose to some degree, by the diffusion-limiting membrane 16. Then, the following reaction takes place:

GOD



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Hydrogen peroxide, the quantity of which corresponds to concentration of existing glucose, is accordingly generated. The generated hydrogen peroxide is guided to the surface of the working electrode 1 which is revived to have sufficient activity, through the hydrogen peroxide selective penetration membrane 14. The forward bias is kept applied to the working electrode 1. An oxydation reaction is carried out on the surface of the working electrode 1 and current corresponding to the amount of hydrogen peroxide flows in through the working electrode 1. The current is applied to the inverting input terminal 8a of the current/voltage converting operational amplifier 8, then a voltage signal is output from the output terminal 8c of the current/voltage converting operational amplifier 8. The voltage signal is generated by adding an offset voltage caused by the forward bias and a voltage signal being proportional to the current.

Thereafter, only the voltage signal proportional to the current is extracted, then the extracted voltage



signal is differentiated to obtain a first-order  
differential value, then a peak value of the first-order  
differential value is detected. Finally, a glucose  
concentration detection signal with high accuracy is  
5 obtained by performing the necessary operations.

#### Second Embodiment

Fig. 5 is an electronic circuit diagram of an  
10 electrode reviving apparatus in accordance with a second  
embodiment of the present invention.

Different points from the first embodiment are  
as follows,

(1) an electrode unit having two electrodes,  
15 one is the working electrode 1 made of platinum while  
another, the counter electrode 3 made of silver, is used  
for being revived, and

(2) the counter electrode 3 is directly  
connected to the switch device 6a by omitting the  
20 operational amplifier 4.

In this embodiment, reviving for an electrode  
unit having two electrodes can be performed. Also, the  
time period between removal of an interfering substances  
to when it is possible to start actual measuring can be  
25 shortened.

### Third Embodiment

Fig. 6 is an electronic circuit diagram of an  
5 electrode reviving apparatus in accordance with a third  
embodiment of the present invention.

Different points from the first embodiment are  
as follows,

(1) the non-inverting input terminal 4b of the  
10 operational amplifier 4 is connected to ground through a  
condenser 5,

(2) the non-inverting input terminal 4b is  
selectively connected to the high voltage tap 7a and the  
low voltage tap 7b of the voltage divider 7 through a  
15 resistance 5a and the switch device 6a.

In this embodiment, bias voltages are increased  
in absolute value (refer to fig. 7(A)) based on a time  
constant (for example, a time constant of 0.5 seconds).  
The time constant is determined based on the resistance  
20 5a and the condenser 5. As a result, current  
undershoots and overshoots are remarkably suppressed as  
is illustrated in fig. 7(B). That is, an excessive  
current is securely prevented from flowing. Damage to a  
membrane or membranes fixed on the surface of the  
25 electrode unit, effected by current is remarkably

reduced, accordingly. As a result, the life of a membrane or membranes is extended up to about one year while the life of a membrane or membranes applied in the conventional reviving apparatus is about one month. The  
5 life is a time period when the penetration ratio of the hydrogen peroxide selective penetration membrane increases by 10 %.

#### Fourth Embodiment

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Fig. 8 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a fourth embodiment of the present invention.

Different points from the third embodiment are  
15 as follows,

(1) an electrode unit having two electrodes, one is the working electrode 1 made of platinum while another, the counter electrode 3 made of silver, is used for being revived, and

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(2) the counter electrode 3 is directly connected to the switch device 6a by omitting the operational amplifier 4.

In this embodiment, reviving for an electrode unit having two electrodes can be performed. Also, the  
25 time period between removal of interfering substances to



when it is possible to start actual measuring can be shortened. Furthermore, damage to a membrane or membranes fixed on the surface of the electrode unit, effected by current is remarkably reduced.

5           This invention is not limited to the foregoing embodiments. Preferably, the voltage for reviving and higher voltage are changed. Preferably, the time period for applying voltage is changed corresponding to the voltage value. Preferably, the reviving method and  
10   apparatus are applicable to apparatus for measuring concentrations of substances other than glucose. Preferably, a programmable power source which varies the output voltage under control by a microcomputer, is employed instead of the time constant circuit comprising  
15   the resistance 5a and the condenser 5.

          The terms and expressions which have been employed here are used as terms of description and not of limitations, and there is no intention, in the use of such terms and expressions of excluding equivalents of  
20   the features shown and described, or portions thereof, it being recognized that various modifications are possible within the scope of the invention as claimed.

## CLAIMS

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1. A method for reviving an electrode unit of a biosensor which includes a working electrode and a counter electrode, and which measures a concentration of an object substance based upon an electrical signal generated between the working electrode and the counter electrode when a predetermined forward measurement bias is applied to the working electrode on which a physiologically active substance is placed, the electrical signal being generated based upon a biological reaction of the object substance, said method comprising the steps of;

(1) applying a predetermined reverse bias to the working electrode for a time period which is in seconds order;  
and

(2) applying a higher forward bias than the forward measurement bias to the working electrode for a time period which is in seconds order before the forward measurement bias is applied to the function electrode.

2. A method as set forth in claim 1, wherein the predetermined reverse bias is a reverse bias which is exponentially increased until its absolute value reaches a predetermined value.

3. A method as set forth in claim 1, wherein the higher forward bias is a forward bias which is exponentially increased until its absolute value reaches a predetermined value which is higher than the forward measurement bias.

**B**

4. A method as set forth in claim 1, wherein the predetermined reverse bias is a reverse bias which is exponentially increased until its absolute value reaches a predetermined value, and the higher forward bias is a forward bias which is exponentially increased until its absolute value reaches a predetermined value which is higher than the forward measurement bias.

5. An apparatus for reviving an electrode unit of a biosensor which includes a working electrode and a counter electrode, and which measures a concentration of an object substance based upon an electrical signal generated between said working electrode and said counter electrode when a predetermined forward measurement bias is applied to said working electrode on which a physiologically active substance is placed, said electrical signal being generated based upon a biological reaction of said object substance, said apparatus comprising;

reviving voltage applying means for applying a reviving voltage to said working electrode;

measurement voltage applying means for applying a measurement voltage to said working electrode;

higher voltage applying means for applying a voltage higher than the measurement voltage to said working electrode; and

selection means for sequentially selecting a condition under which to apply a reviving voltage to said working electrode from said reviving voltage applying means, a condition under which to apply a higher voltage to said working electrode from said



higher voltage applying means, and a condition under which to apply a measurement voltage to said working electrode from said measurement voltage applying means, when a measuring operation is to be performed.

6. An apparatus as set forth in claim 6, further comprising a first time constant means for controlling a reviving voltage supplied by said reviving voltage applying means according to a predetermined time constant.

7. An apparatus as set forth in claim 6, further comprising a second time constant means for controlling a higher voltage supplied by said higher voltage applying means according to a predetermined time constant.

8. An apparatus as set forth in claim 6, further comprising a first time constant means for controlling a reviving voltage applied by said reviving voltage applying means according to a predetermined time constant, and a second time constant means for controlling a higher voltage applied by said higher voltage applying means according to a predetermined time constant.

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Fig. 1

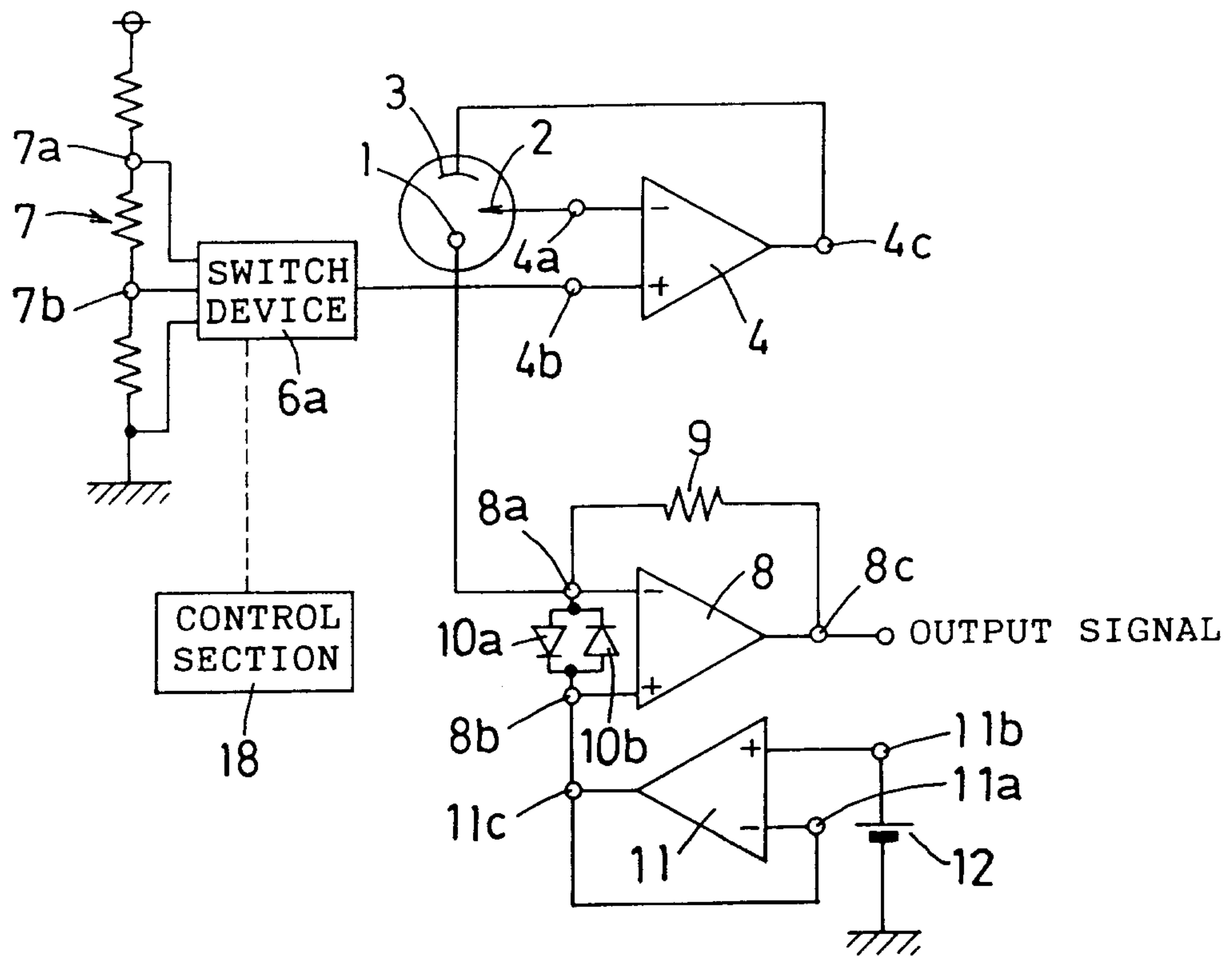
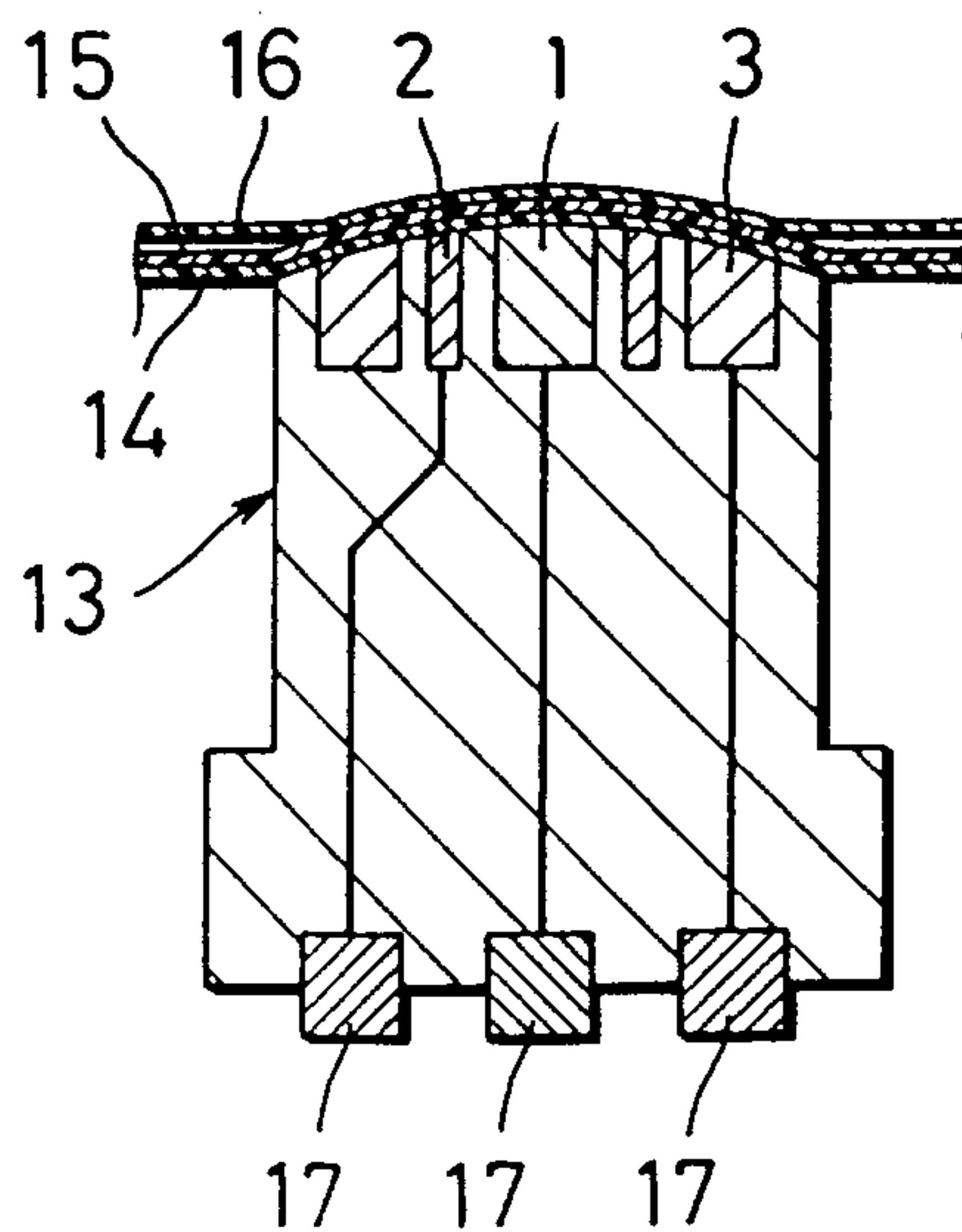


Fig. 2



by Rogers, Bereskin & Parr

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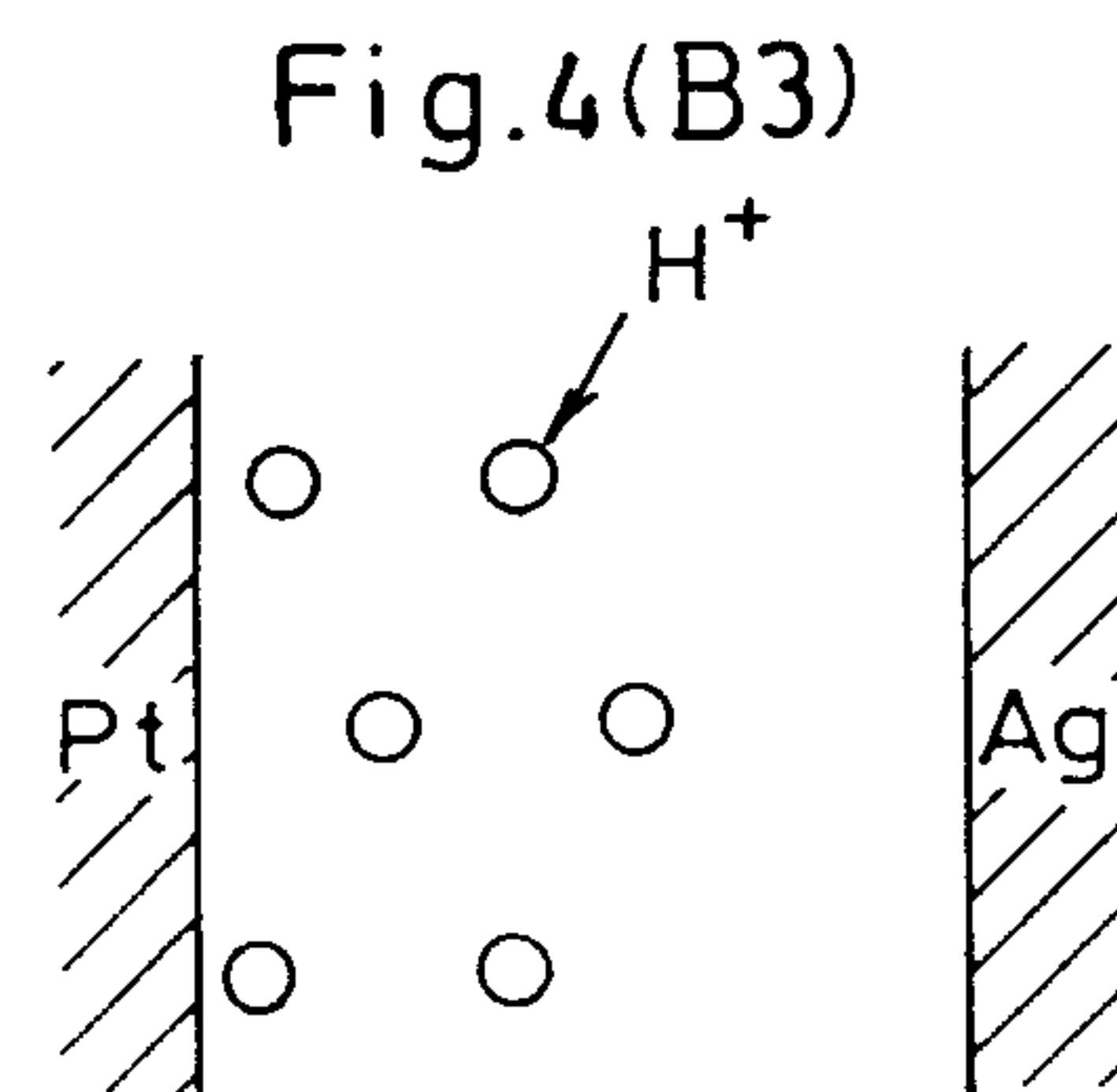
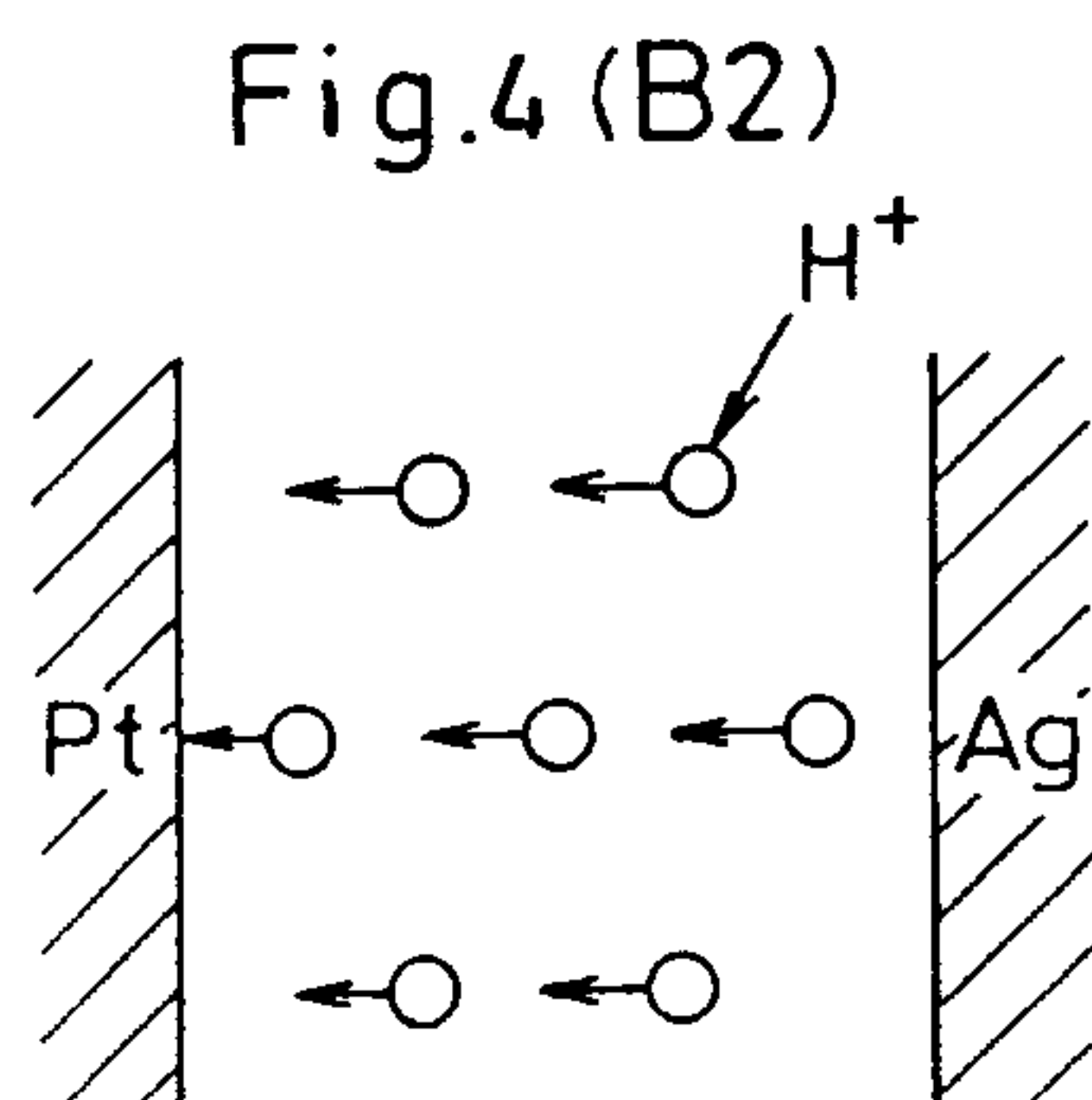
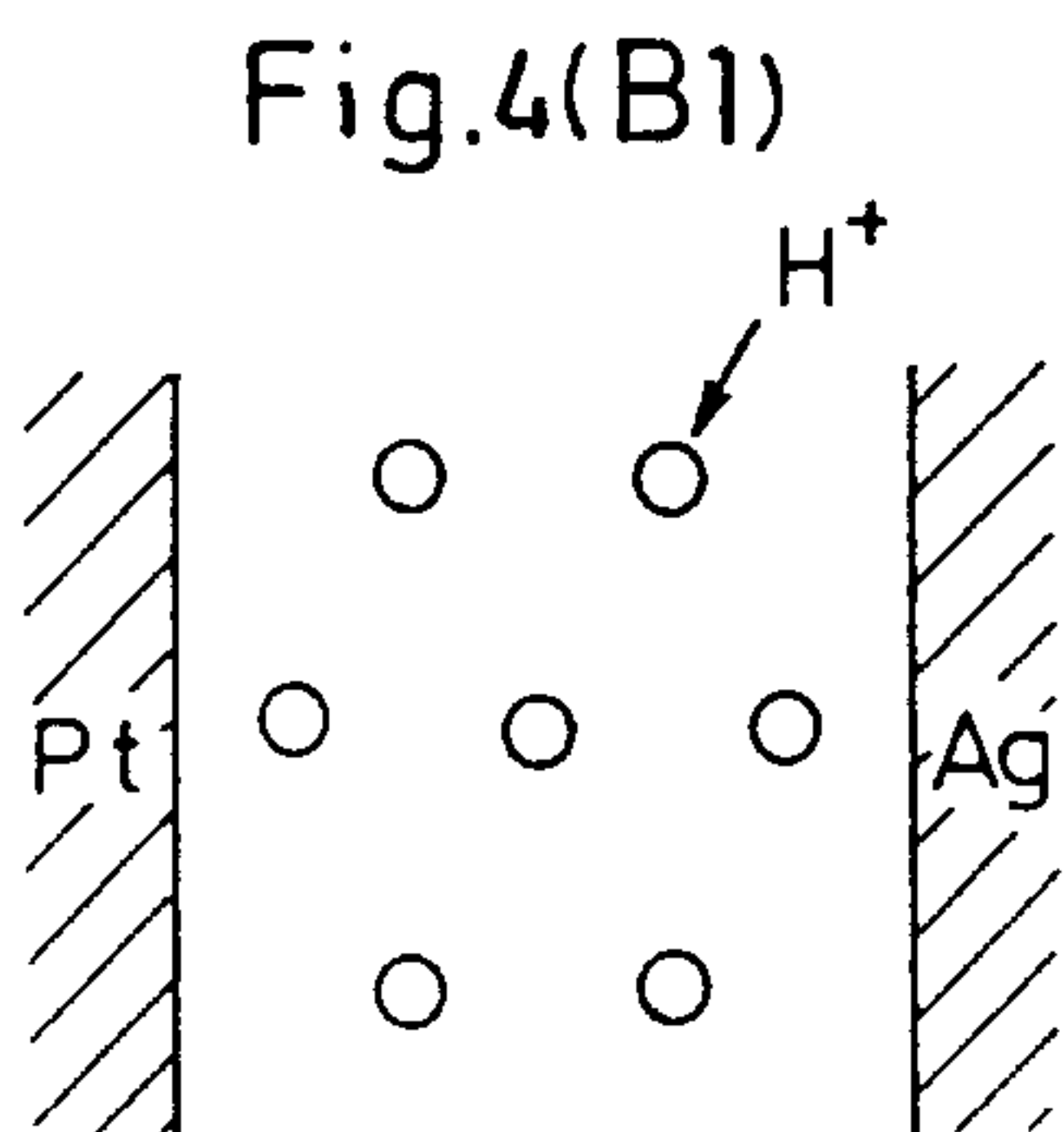
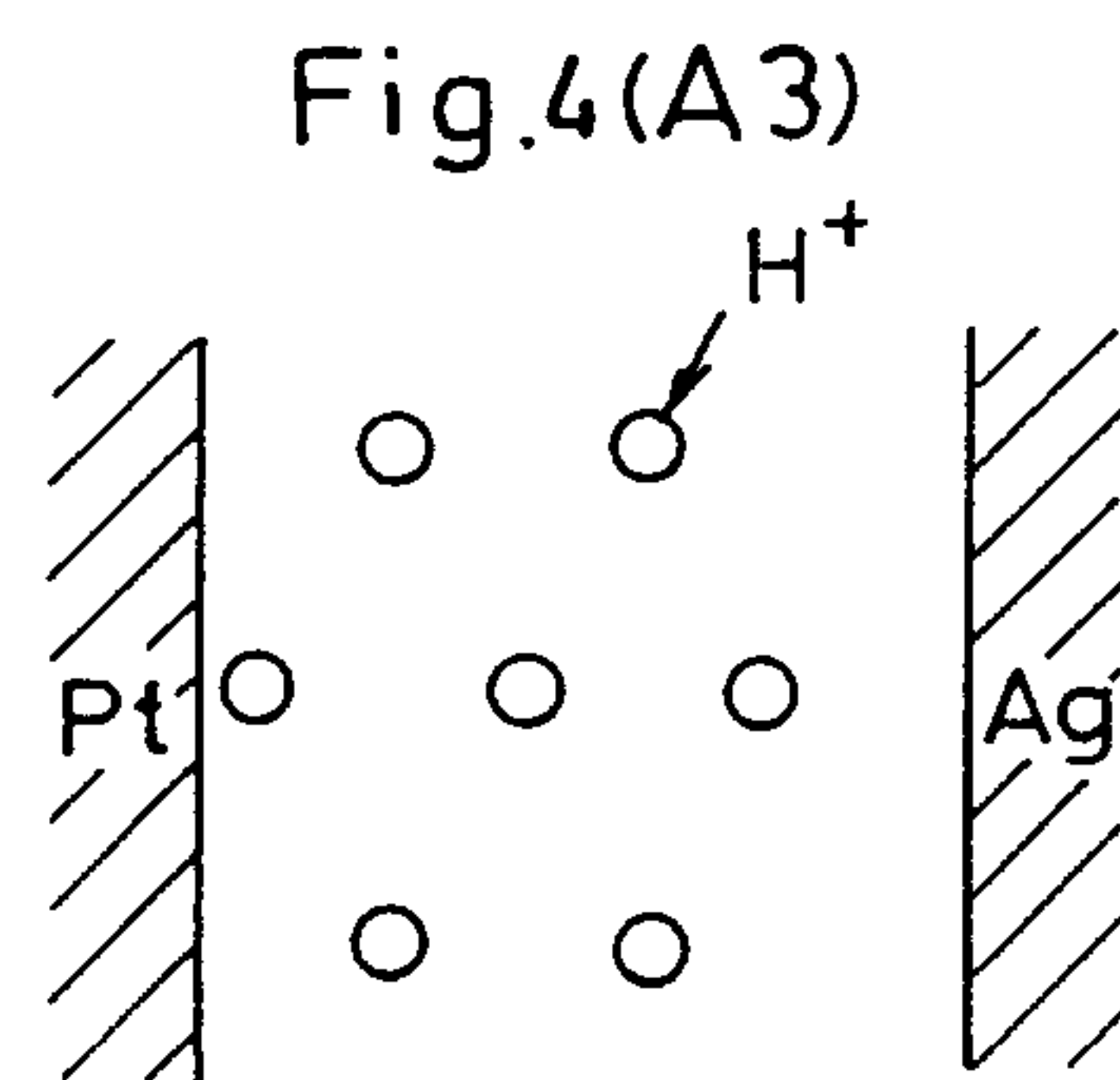
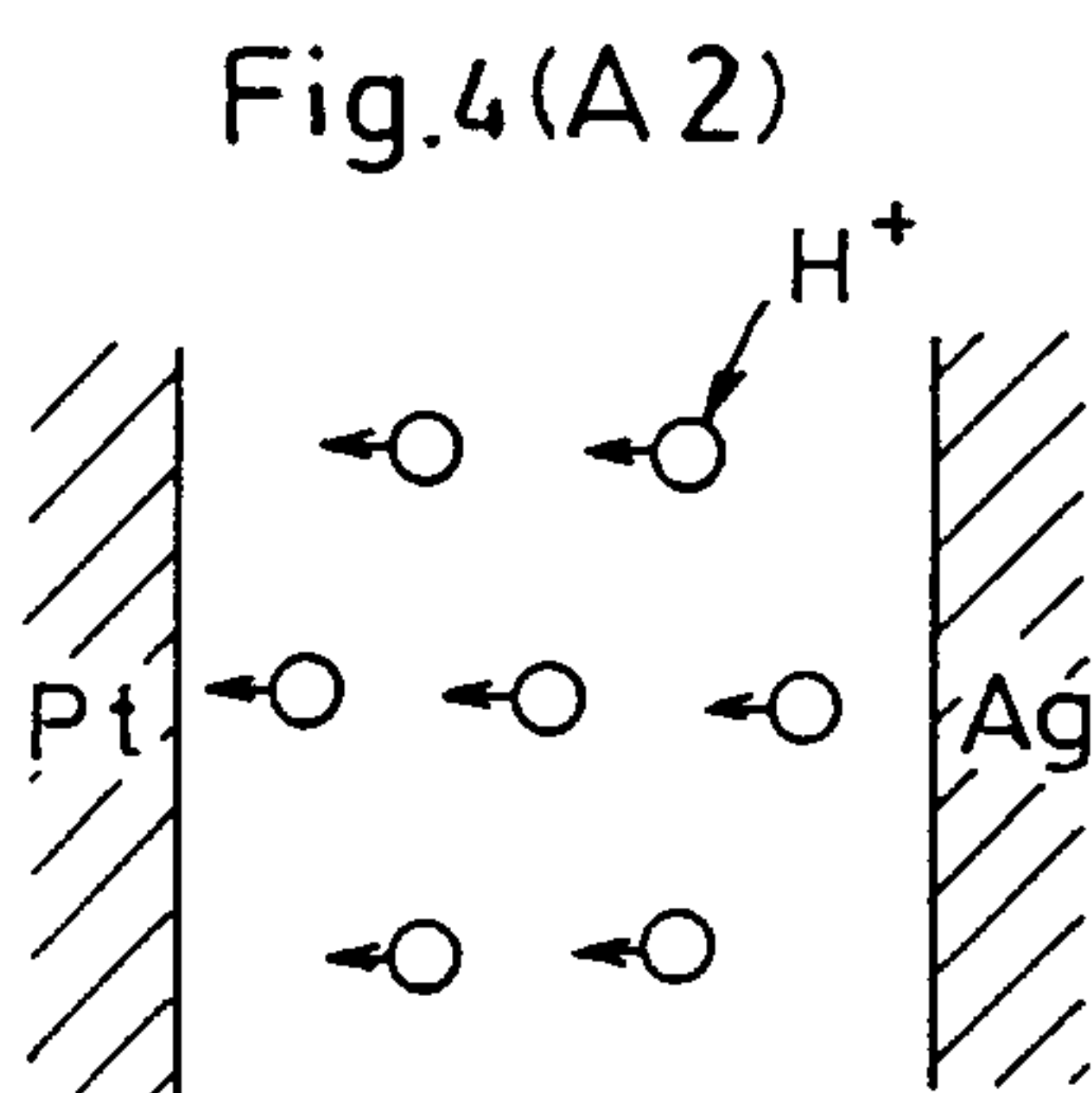
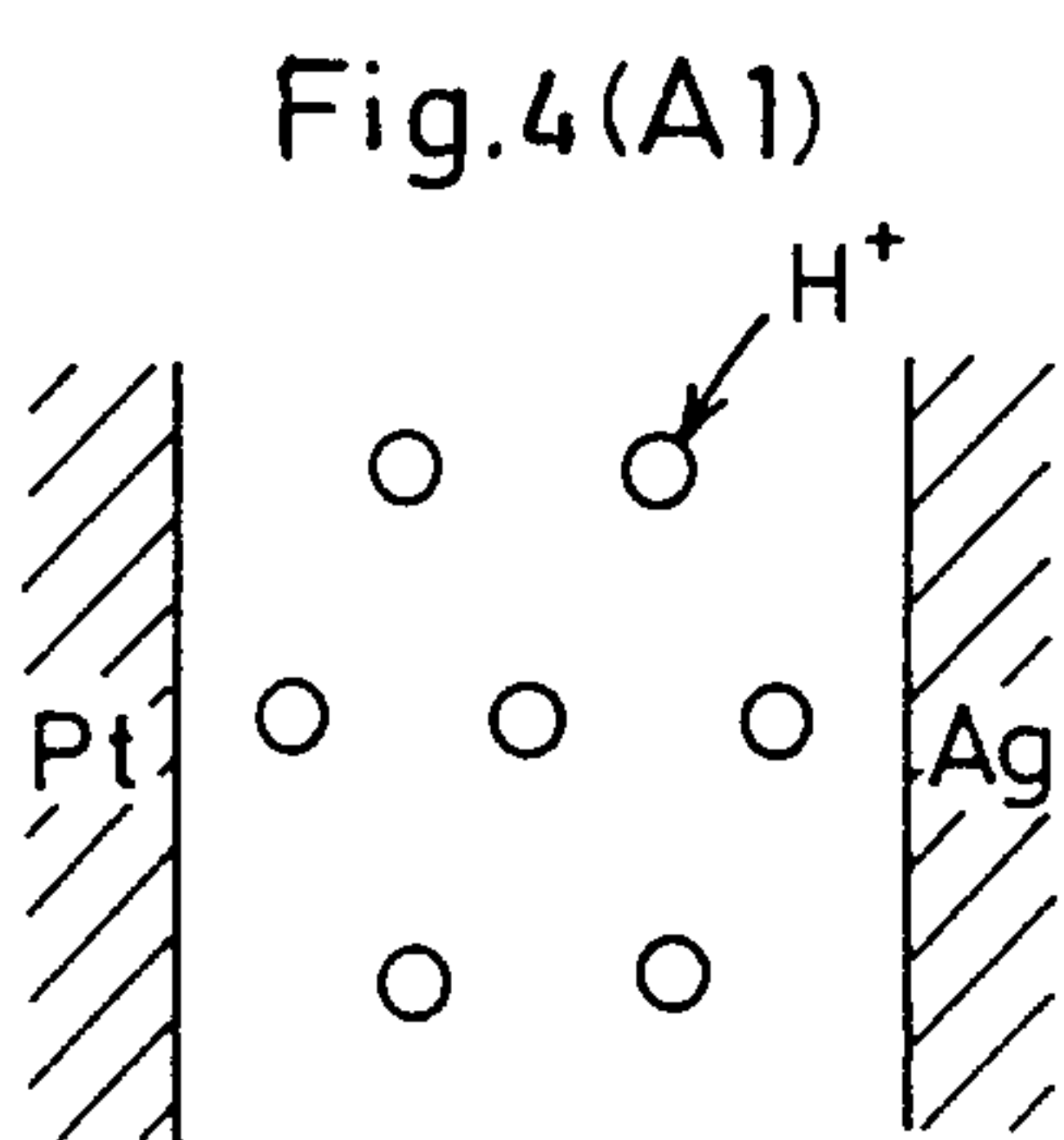
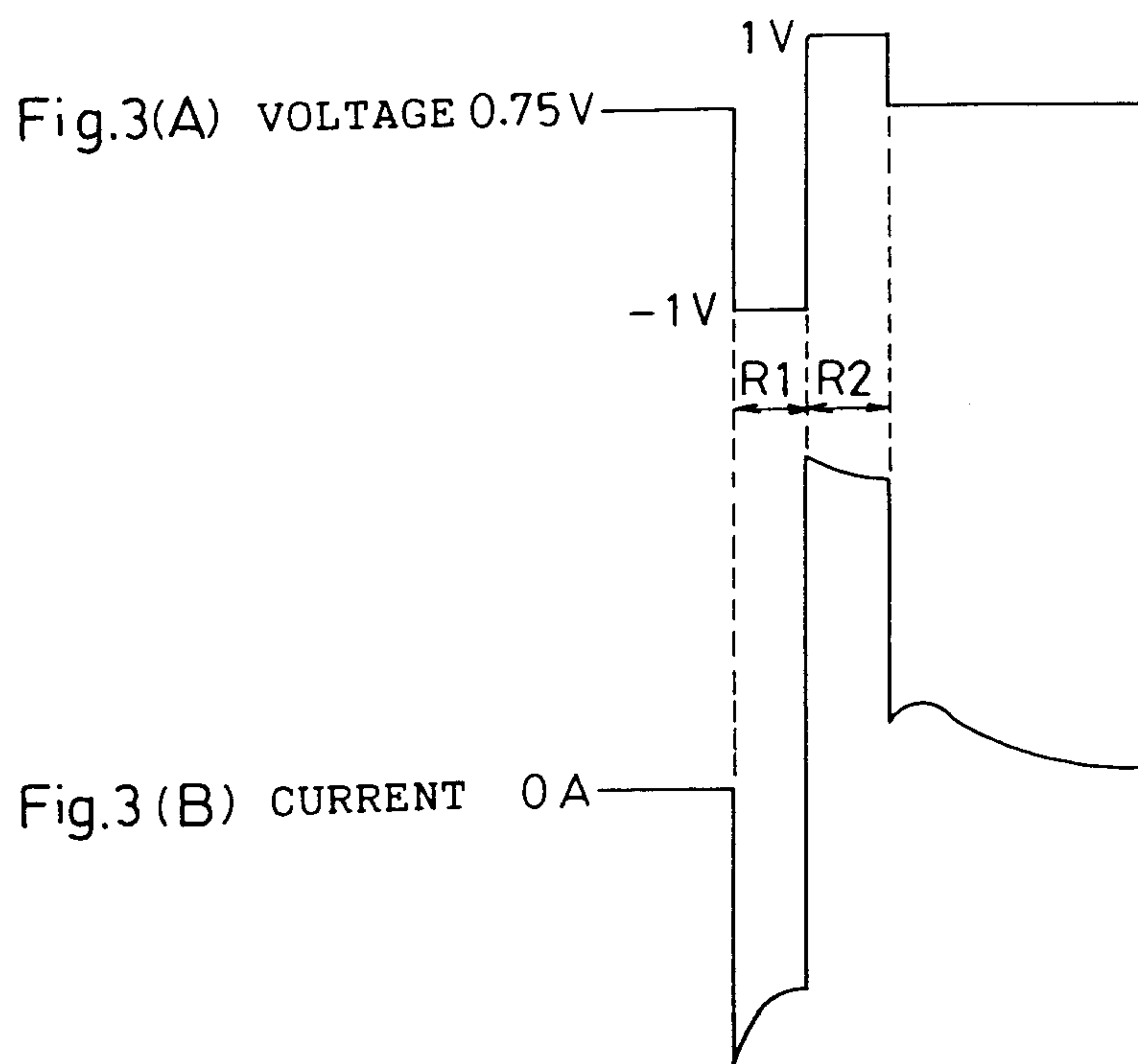




Fig. 5

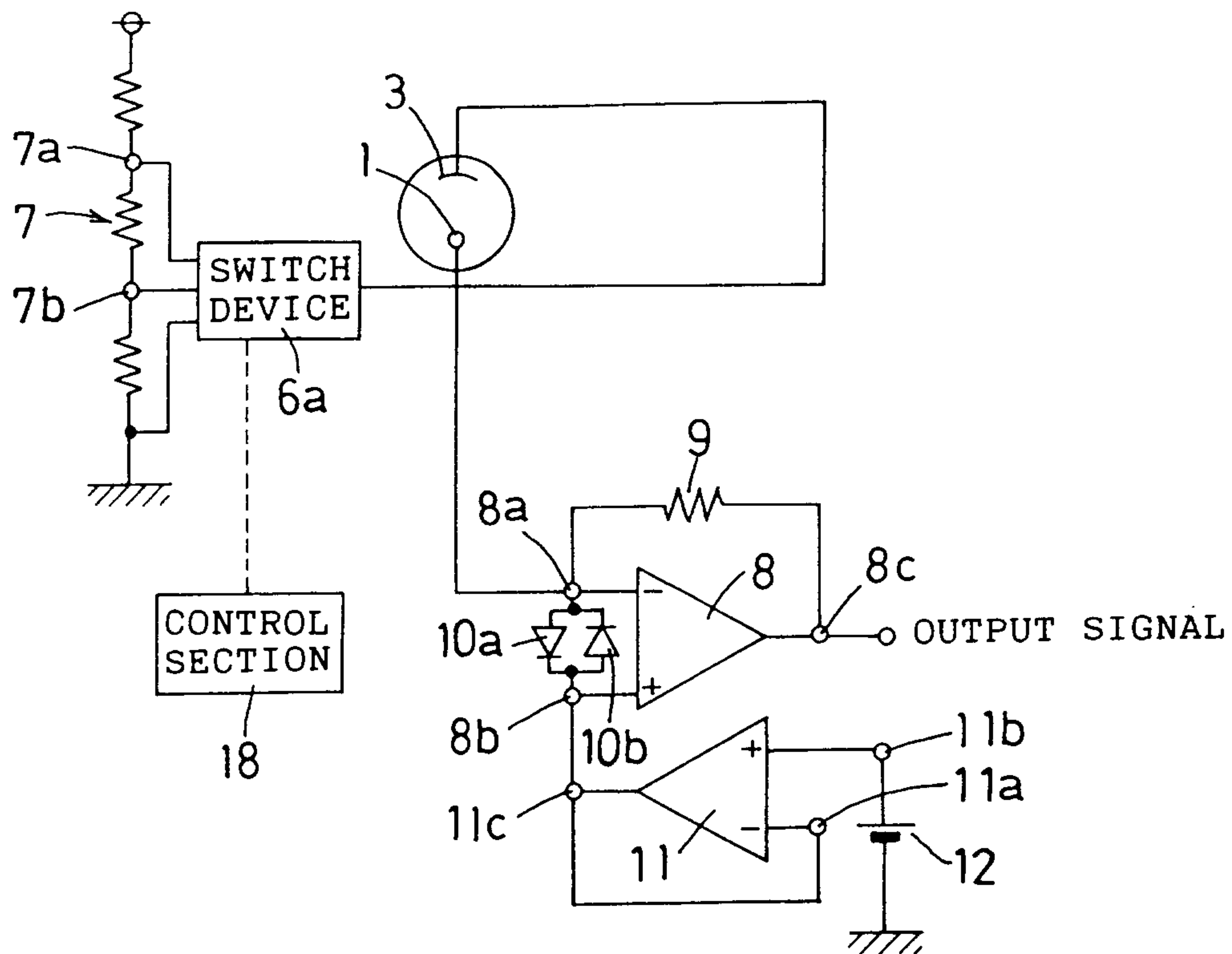
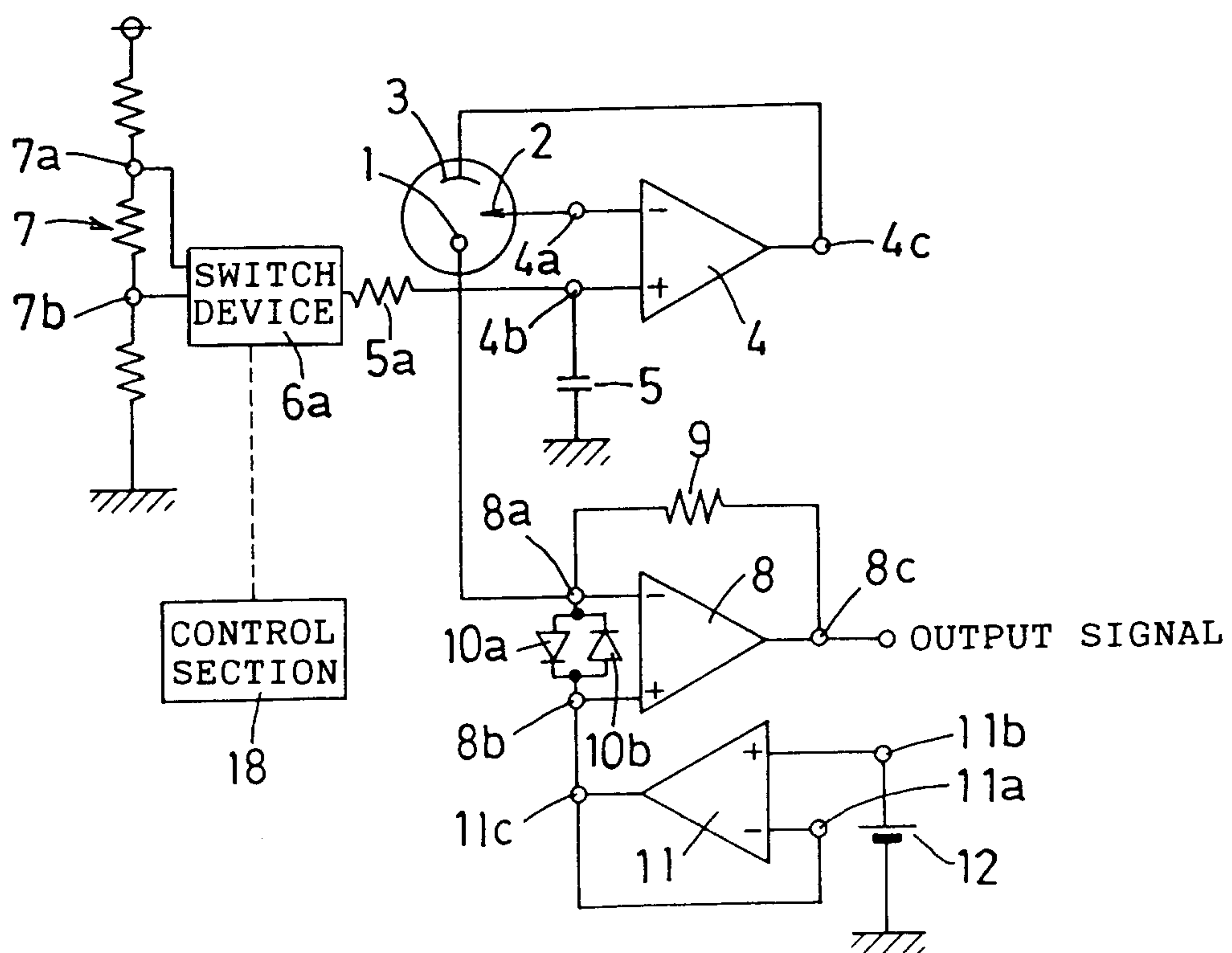


Fig. 6



by ROGERS, Bereskin & Parr

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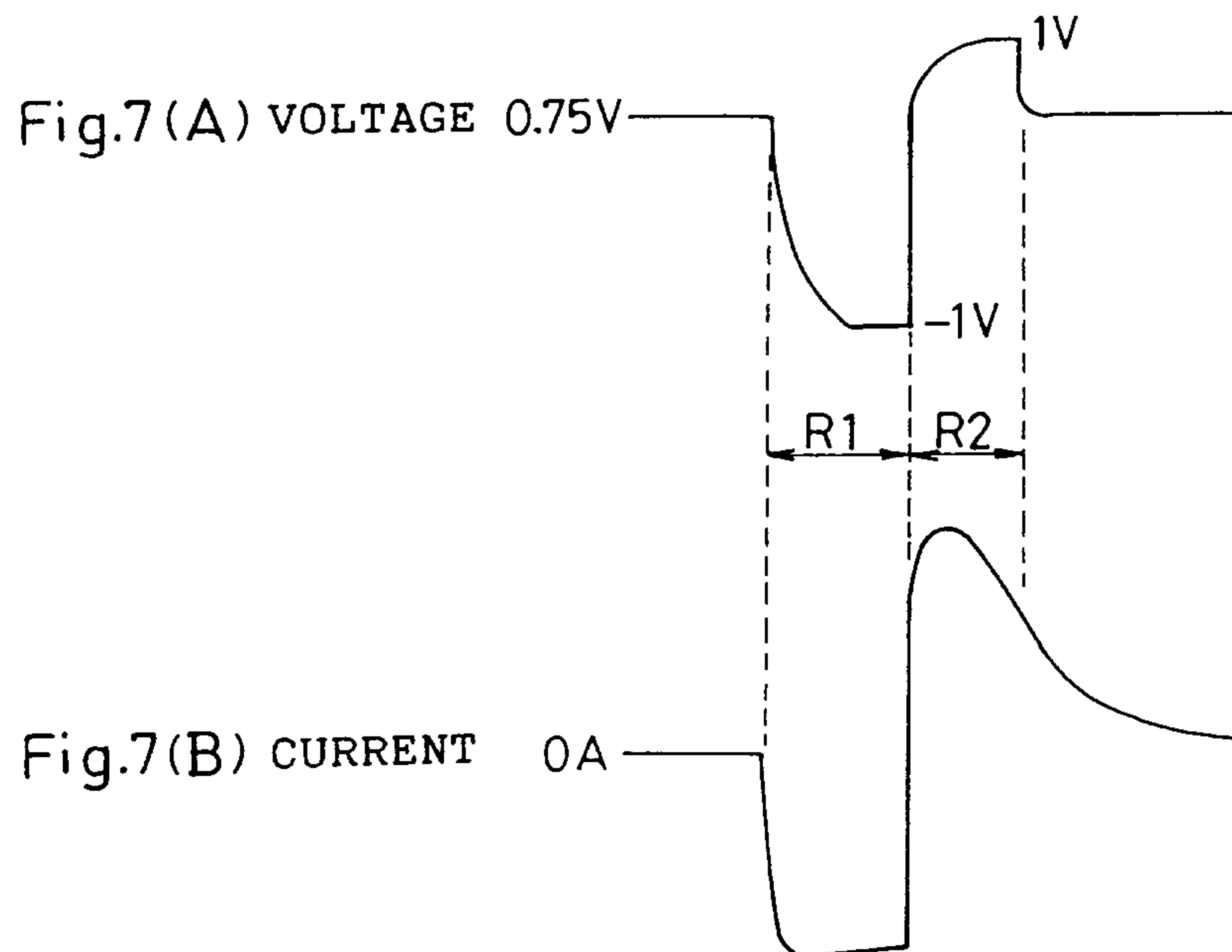
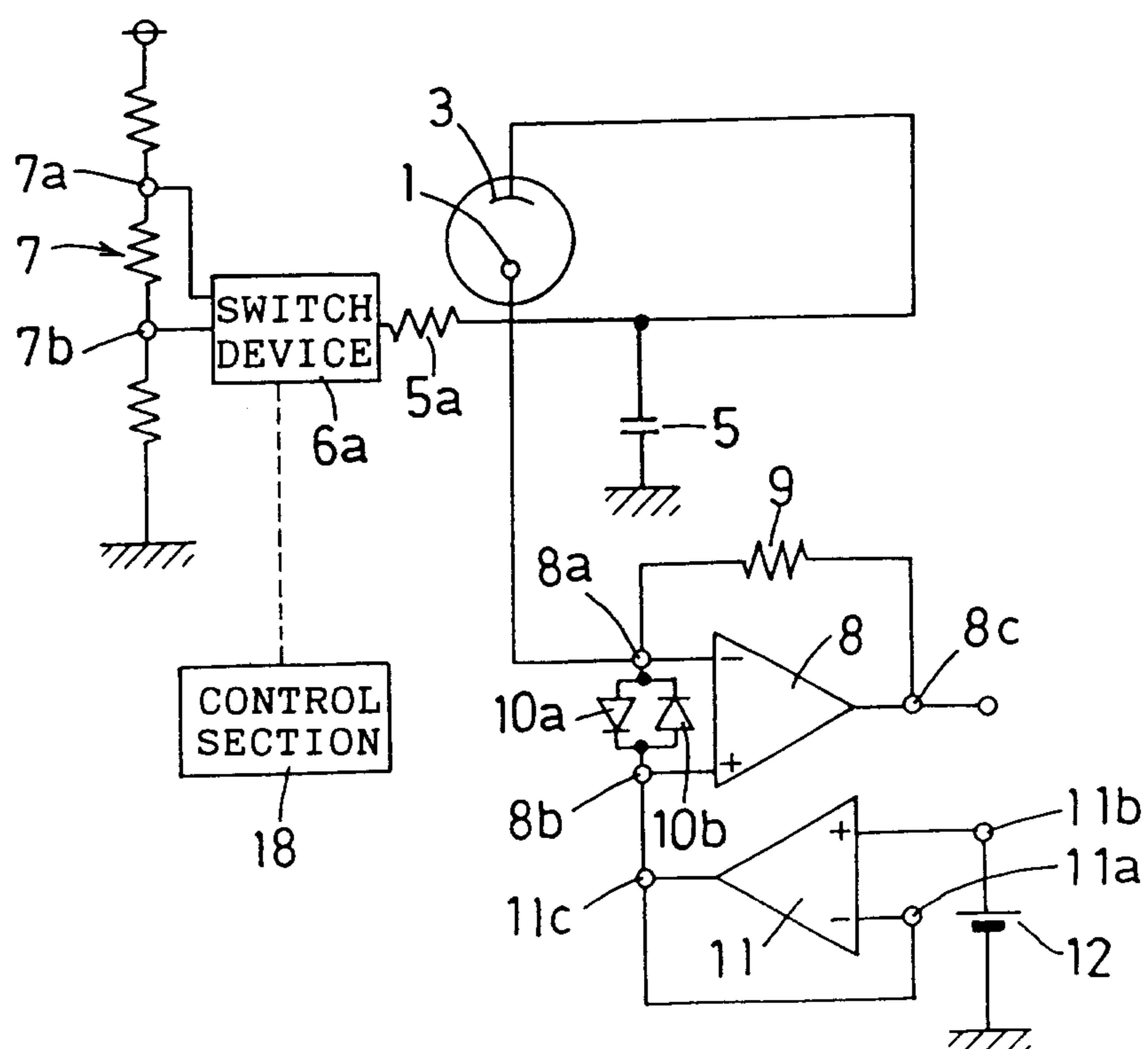


Fig. 8



by ROGERS, Bereskin & Parr