



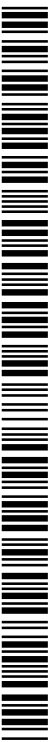
- (51) **International Patent Classification:**  
*A61B 5/00* (2006.01)     *A61M 1/00* (2006.01)  
*A61B 5/145* (2006.01)
- (21) **International Application Number:**  
PCT/IB2015/001971
- (22) **International Filing Date:**  
25 September 2015 (25.09.2015)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
14306496.2 26 September 2014 (26.09.2014) EP  
15306462.1 18 September 2015 (18.09.2015) EP
- (71) **Applicant:** SOFRADIM PRODUCTION [FR/FR]; 116  
avenue du Formans, F-01600 Trevoux (FR).
- (72) **Inventor:** BAYON, Yves; 116 avenue du Formans, F-  
01600 Trevoux (FR).
- (81) **Designated States** (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,  
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,

DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,  
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,  
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,  
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,  
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,  
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

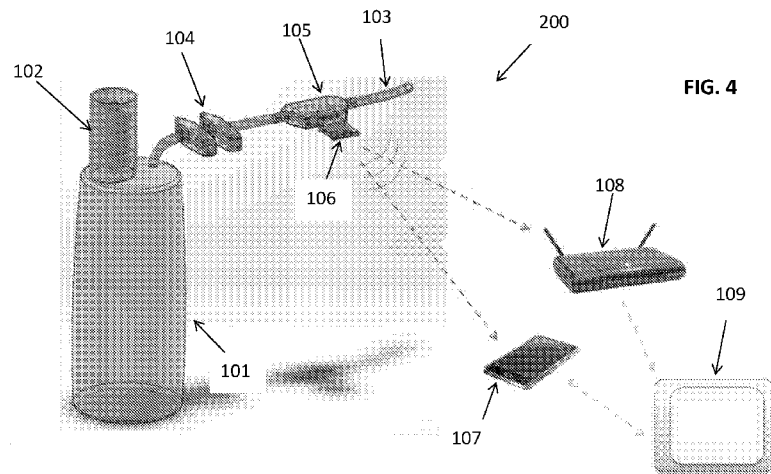
**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments (Rule 48.2(h))



WO 2016/046634 A1

(54) **Title:** SYSTEM AND METHOD FOR EARLY DETECTION OF POST-SURGERY INFECTION



(57) **Abstract:** In-vivo systems and methods for the detection of early signs of post-surgery infection are described. The in-vivo systems include a drain system with a tube configured to drain fluids from a surgery site, at least one sensor unit for sensing the presence of at least one infection biomarker, a processor for processing a signal generated by the at least one sensor unit, a transmitter for transmitting the signal, and a notification system for receiving the signal, analyzing the signal by comparing it to a threshold, determining presence of infection, and generating an indication on the presence of infection.

## **SYSTEM AND METHOD FOR EARLY DETECTION OF POST-SURGERY INFECTION**

### **FIELD OF THE INVENTION**

[001] This application relates to the field of systems and methods of detection. In particular, the present invention relates to systems and methods for detection of early signs of post-surgery infection.

### **BACKGROUND**

[002] In some cases, a patient that undergoes surgery may require a drain left in the surgery site for about 1-2 days (or sometimes for even longer periods of time, e.g., 1-2 weeks). Typically, such drains are monitored by the medical staff every few hours, in order to determine the state of the surgery site, e.g., whether the surgery site is healing properly with no interruptions or whether an infection may have developed. When monitoring of such drains takes place only every few hours, an infection may already be at a progressive stage before it is noticed and properly treated. Furthermore, the signs that physicians usually examine in order to detect presence of infection are signs that appear when an infection is in progressive state, and which may not be detectable by typical monitoring at an early stage of the infection. There is, therefore, a need for improved systems and methods for early and continuous detection of post-surgery infection.

### **SUMMARY OF THE INVENTION**

[003] Embodiments of the present invention provide in-vivo systems and methods for early and continuous detection of infection. These systems may include external tubes with capabilities of monitoring in-vivo fluids flowing there through. Examples for such systems may include urinary catheters, peritoneal dialysis systems, hemo/renal dialysis systems, shunts, catheters, or drain systems located in close proximity to a surgical site, for monitoring post-surgery infection. Such systems enable detection of early signs of infection, when an infection is in its initial stage only, well before it becomes progressive and severe, and thus appropriate treatment may be provided well before the patient's or surgery site's condition is critical. These systems may also incorporate real-time continuous automatic self-monitoring without human

intervention, and may generate an indication of the presence and even the various stages of infection, if any, e.g., mild, progressive or severe. Either the care provider or the patient may be notified by the indication as to presence (and possibly the stage) of infection. In some embodiments, systems of the invention include sensors for sensing presence of various infection biomarkers, i.e., biomarkers that indicate presence of infection. Such infection biomarkers may, in some cases, be direct biomarkers, which may increase when an infection occurs. Direct infection biomarkers may be bacteria species. For example, direct infection biomarkers may be bacteria commonly associated with clinical/nosocomial infections including *Staphylococcus*, *Escherichia*, *Pseudomonas*, *Streptococcus*, *Enterococcus* and *Enterobacter* species, bacteria associated with gastro-intestinal leaks such as commensal bacteria commonly found in the gastro-intestinal bacteria flora and/or alternatively pathogen bacteria potentially colonizing the gastro-intestinal tract. In addition, direct infection biomarkers may also include non specific bacteria species, which produce and release, for example, sulfur related gases, hydrogen, and ammonia. Direct biomarkers of specific bacteria may further include bacteria which release or “exhale” volatile organic compounds, by endogenous metabolism of these bacteria. That is, following an addition of defined chemicals or biochemicals to the bacteria’s environment, the chemicals/biochemicals are metabolized or transformed into volatile organic compounds by these bacteria species.

[004] In some embodiments, direct infection biomarkers may include specific genetic material signatures, e.g., bacteria species or subspecies specific DNA primers, which may be used for at least the semi-quantification (in Colony Forming Units (CFU) per milliliter, i.e., [CFU/ml]) of bacteria of interest by polymerase chain reaction (PCR).

[005] However, in other cases, infection biomarkers may be indirect biomarkers that are an indirect byproduct of presence of infection, e.g., pH, lactic acid, exudate flow, fluid viscosity, local/systemic oxygen saturation, and local/systemic temperature. Further examples of indirect biomarkers may be immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF- $\alpha$ , pancreas enzymes such as amylase, inflammatory parameters such as Lipopolysaccharide Binding Protein (LBP), and metabolic parameters such as glucose.

[006] Changes (e.g., increase or decrease) in the level or concentration of indirect biomarkers may indicate on the presence of infection.

[007] In some embodiments, the systems include more than one sensor for sensing more than one type of infection biomarker, either direct or indirect. In some embodiments, there may be a combination of sensors, some for sensing indirect infection biomarkers and some for sensing direct infection biomarkers.

[008] According to some embodiments, a system for detecting early signs of post-surgery infection in a patient may include a drain system comprising a tube configured to drain fluids from a surgery site, at least one sensor unit for sensing the presence of at least one infection biomarker, a processor for processing a signal generated by the at least one sensor unit, a transmitter for transmitting the processed signal, and a notification system for receiving the processed signal, analyzing the processed signal by comparing it to a threshold (either a predetermined threshold or an adaptive and changing threshold that may be based on changing parameters of the sensed biomarkers and/or on the rate of change of such parameters), determining presence of infection, and generating an indication on the presence of infection.

[009] In some embodiments, the drain system may further comprise a container into which the fluids passing through the tube are drained.

[0010] In some embodiments, the at least one infection biomarker is selected from a group of indirect infection biomarkers consisting of: pH, lactic acid, and flow rate of exudate, or a combination thereof. Further examples of indirect biomarkers, which an infection biomarker may be selected from may be immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF- $\alpha$ , pancreas enzymes such as amylase, inflammatory parameters such as Lipopolysaccharide Binding Protein (LBP), and metabolic parameters such as glucose. In other embodiments, the at least one infection biomarker is a direct infection biomarker, which is a bacteria specie selected from the group consisting of: *Escherichia coli*, *Pseudomonas* spp., *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., *Enterococcus* spp., *Klebsellia* spp., *Proteus* spp., *Serratia* spp., *Morganella* spp. and other Enterobacteriaceae, or a combination thereof. In other embodiments, other

bacteria specie may be selected. In some embodiments, the direct infection biomarker may include specific genetic material signatures, e.g., bacteria species or subspecies specific DNA primers, which may be used for at least the semi-quantification (in Colony Forming Units (CFU) per milliliter, i.e., [CFU/ml]) of bacteria of interest by polymerase chain reaction (PCR).

[0011] According to some embodiments, the system may comprise a first sensor for sensing an indirect infection biomarker selected from the group consisting of: pH, lactic acid, and flow rate of exudate, or a combination thereof, and a second sensor for sensing a direct infection biomarker selected from the group consisting of: *Escherichia coli*, *Pseudomonas* spp., *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., *Enterococcus* spp., *Klebsellia* spp., *Proteus* spp., *Serratia* spp., *Morganella* spp. and other Enterobacteriaceae, or a combination thereof. In such embodiments, the notification system comprises an analyzer for analyzing signals detected by the first and second sensors, and determining the presence of infection.

[0012] According to some embodiments, the notification system comprises an analyzer for analyzing the processed signal and determining the presence of infection. In some embodiments, the analyzer further determines the stage of infection.

[0013] In some embodiments, when said infection biomarker is pH; a first indication may be generated if the level of pH is equal to or below 7.1, and a second indication may be generated if the level of pH is equal to or below 6.8. When said infection biomarker is lactic acid; a first indication may be generated during the first hour post-surgery if the concentration of lactic acid is equal to or above a threshold of 3mM, a second indication may be generated if the concentration of lactic acid is above the threshold for 6 hours after the first indication, and a third indication may be generated if the concentration of lactic acid is above the threshold for 24 hours after the first indication.

[0014] In some embodiments, when said infection biomarkers are immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF $\alpha$  ; a first indication may be generated if the level of at least one of these mediators is above 100 % of a baseline/threshold value. In some embodiments, the baseline value may be obtained during the surgery or from the very first fractions of the collected exudates. A second indication may be generated if the level of at least

one of these mediators is above 200% of the baseline value, or if the level of at least two of these mediators is above 100% of the baseline value, or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours .

[0015] In some embodiments, when said infection biomarker is LBP; a first indication may be generated if the level of LBP is above 100% of a baseline value. In some embodiments, the baseline value may be obtained during the surgery or from the very first fractions of the collected exudates. A second indication may be generated if the level of LBP is above 200% of the baseline value, or if the level of LBP is observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours .When said biomarker is glucose; a first indication may be generated if the level of glucose is below at least 20 % of a normal value (indicatively 8 [mmol/l]), and with a decreasing trend during at least a day, while a second indication may be generated if the level of glucose is below 30% of the baseline/normal value with a decreasing trend during at least 2 days. When said biomarker is amylase; a first indication may be generated if the level of amylase is above 100 U/l, before the first 24 hours post-surgery, while a second indication may be generated if such level of amylase of above 100 U/l is observed over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0016] In some embodiments, when the infection biomarker is a flow rate of exudate; a first indication may be generated 6 hours post-surgery if the flow rate is above 5[ml/hr], a second indication may be generated 6 hours post-surgery if the flow rate is above 10[ml/hr], and a third indication may be generated 6 hours post-surgery if the flow rate is above 20[ml/hr]. When the infection biomarker is a non-hemolytic bacteria specie; a first indication may be generated if Colony Forming Units (CFU) is above  $10^2$  [CFU/ml], a second indication may be generated if CFU is above  $10^3$  [CFU/ml], and a third indication may be generated if CFU is above  $10^4$  [CFU/ml]. When the infection biomarker is a hemolytic bacteria specie (e.g., S aureus, hemolytic Streptococci, hemolytic E. coli subspecies); a first indication may be generated if Colony Forming Units (CFU) is above  $10^1$  [CFU/ml], a second indication may be generated if CFU is above  $10^2$  [CFU/ml], and a third indication may be generated if CFU is above  $10^3$  [CFU/ml].

[0017] In some embodiments, the threshold may be predetermined based on, for example experiments, whereas in other embodiments, the threshold may be adjustable and may be changed by the notification system according to changes in the trend of the parameters of the at least one infection biomarker that are sensed by the at least one sensor.

[0018] According to some embodiments, the transmitter wirelessly transmits the processed signals to the notification system. In some embodiments, an indication may be displayed on a display unit, e.g., a screen.

[0019] In some embodiments, the sensor may sense the presence of infection biomarkers continuously. In other embodiments, the sensor may sense the presence of infection biomarkers periodically, e.g., every few minutes or even within periods of time shorter than 1 minute. Typically, the periods during which the sensors may sense presence of the infection biomarkers may be designed to correspond to the type of biomarker.

[0020] In some embodiments, typically when the infection biomarker is an indirect biomarker, the sensor may be located along the tube. Yet, in other embodiments, typically when the infection biomarker is a direct biomarker, the sensor may be located within the container. In yet other embodiments, when infection biomarkers are indirect biomarkers such as immune-modulating mediators (e.g., IL-1, IL-6, IL-10 and TNF $\alpha$ ) or LBP, or when infection biomarkers are direct biomarkers such as bacteria DNA, which are specifically detected and identified by PCR DNA primers; these biomarkers cannot be sensed continuously along the tube. Therefore, in such cases, the tube may be equipped with a system that enables collection of samples, preferably semi-automatically, more preferably automatically, for detection and measurements of the markers of interest by point of care (POC) analyzers.

[0021] According to some embodiments, a method for determining early signs of post-surgery infection in a patient may comprise the steps of: sensing presence of at least one infection biomarker by using a sensor incorporated in a drain system, processing signals generated by the sensor, transmitting the processed signals to a notification system, receiving the processed signals by the notification system, analyzing the processed signals by comparing the signals to a threshold, and determining the presence of infection.

[0022] According to some embodiments, when infection biomarkers cannot be sensed continuously along the tube, a method for determining early signs of post-surgery infection in a patient may comprise the steps of: measuring presence of at least one infection biomarker by using a point of care (POC) analyzer for examining samples collected in a drain system, processing signals generated by the POC analyzer, transmitting the processed signals to a notification system, receiving the processed signals by the notification system, analyzing the processed signals by comparing the signals to a threshold, and determining the presence of infection.

[0023] In some embodiments, the method may further comprise the step of generating an indication on presence of infection, based on signals generated either by one or more sensors incorporated in the drain system, or by POC analyzers, or by any combination of the above sensors or analyzers. In some embodiments, the step of sensing presence of infection biomarkers may be carried out continuously, while in other embodiments, the step of sensing presence of infection biomarkers may be carried out periodically.

#### **BRIEF DESCRIPTION OF THE INVENTION**

[0024] The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawings in which:

[0025] **FIG. 1** is a schematic illustration of a drain system for detection of post-surgery infection, in accordance with an embodiment of the invention;

[0026] **FIG. 2** is a schematic illustration of a sensor system for sensing indirect infection biomarkers, in accordance with an embodiment of the invention;

[0027] **FIG. 3** is a schematic illustration of a sensor system for sensing direct infection biomarkers, in accordance with an embodiment of the present invention;

[0028] **FIG. 4** is a schematic illustration of a drain system including a notification system, in accordance with an embodiment of the invention;

[0029] **FIG. 5** is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with an embodiment of the invention;



[0030] **FIG. 6** is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with another embodiment of the invention; and

[0031] **FIG. 7** is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with yet another embodiment of the invention.

[0032] It will be appreciated that, for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn accurately or to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity, or several physical components may be included in one functional block or element. Further, where considered appropriate, reference numerals may be repeated among the figures to indicate corresponding or analogous elements.

#### **DETAILED DESCRIPTION OF THE INVENTION**

[0033] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as to not obscure the present invention.

[0034] Reference is now made to **FIG. 1**, which is a schematic illustration of a drain system for detection of post-surgery infection, in accordance with an embodiment of the invention. Drain system **100** may comprise a drain tube **103**, which is configured to drain in-vivo fluids that are accumulating in close proximity to the surgery site. Tube **103** may connect between the surgery site and a container or canister **101**. The in-vivo fluids that pass through tube **103** may gather in container **101**, such that drained fluids are collected within container **101**. Drain systems of such type, which comprise a tube and container into which fluids drain, are known as closed drain systems. In other embodiments, drain system **100** may be an open drain system, while not comprising a container, and thus fluids are drained onto a dressing or something of the sort. However, closed drain systems provide airtight circuits that prevent various

contaminations from entering the surgery site, in a more efficient manner compared to open drain systems, thus system **100** may preferably be a closed drain system.

[0035] In some embodiments, drain system **100** may comprise a suction element **102**, which may cause low or high pressure in order to actively suck fluids from the surgery site through tube **103** and into container **101**. However, in other embodiments, drain system **100** need not comprise an active suction element **102**, and drainage from the surgery site may operate passively.

[0036] In some embodiments, drain system **100** may further comprise various types of sensors for sensing presence of either direct infection biomarkers, e.g., by sensor system **104**, or indirect infection biomarkers, e.g., by sensor system **105**. Direct infection biomarkers may be various types of bacteria or bacteria byproducts that may be present within in-vivo fluids flowing from the surgery site, at very early stages of an infection that may begin at the surgery site following surgery. When infection occurs at the surgery site, the concentration of such direct infection biomarkers may increase, thus monitoring presence and concentration of direct infection biomarkers, may indicate on presence of infection, and even on the stage of infection, whether, for example, mild, progressive or severe. Direct infection biomarkers may, for example, be bacteria commonly associated with clinical/nosocomial infections including Staphylococcus, Escherichia, Pseudomonas, Streptococcus, Enterococcus, Serratia, Klebsellia, Morganella, Proteus and other Enterobacter species, bacteria associated with gastro-intestinal leaks such as commensal bacteria commonly found in the gastro-intestinal bacteria flora and/or alternatively pathogen bacteria potentially colonizing the gastro-intestinal tract. In addition, direct infection biomarkers may also include nonspecific bacteria species, which produce and release, for example, sulfur related gases, hydrogen, and ammonia. Direct biomarkers of specific bacteria may further include bacteria which release or “exhale” volatile organic compounds, by the metabolism of these bacteria. That is, following an addition of defined chemicals or biochemicals to the bacteria’s environment, the chemicals/biochemicals are metabolized (either by endogenous metabolism or by exogenous metabolism of these bacteria) or transformed into volatile organic compounds by these bacteria species. In some embodiments, direct infection biomarkers may include specific genetic material signatures, e.g.,

bacteria species or subspecies specific DNA primers, which may be used for at least the semi-quantification (in Colony Forming Units (CFU) per milliliter, i.e., [CFU/ml]) of bacteria of interest by polymerase chain reaction (PCR).

[0037] Indirect infection biomarkers may be biomarkers that are an indirect byproduct of presence of infection, e.g., pH, lactic acid, exudate flow, fluid viscosity, local/systemic oxygen saturation, and local/systemic temperature. For example, when an infection occurs in the surgery site, pH may decrease relatively to standard pH of in-vivo fluids. Thus, monitoring the level of pH may indicate on presence of infection. Furthermore, the level of pH, and/or the time it took the pH level to decrease to its new lower level may even indicate on the stage of infection, e.g., mild, progressive or severe. If the infection biomarker is chosen to be lactic acid, then in presence of infection, the concentration of lactic acid is expected to increase rapidly, thus a sensor should be able to detect lactic acid presence and concentration. Further examples of indirect biomarkers may be immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF- $\alpha$ , pancreas enzymes such as amylase, inflammatory parameters such as Lipopolysaccharide Binding Protein (LBP), and metabolic parameters such as glucose.

[0038] In some embodiments, system **100** may comprise more than one sensor for sensing more than one type of infection biomarker. In some embodiments, there may be a combination of sensors, some for sensing indirect infection biomarkers and some for sensing direct infection biomarkers. For example, system **100** may only comprise sensor system **104** for sensing direct infection biomarkers. System **100**, and thereby sensor system **104** may comprise more than one sensor unit for sensing more than one type of direct infection biomarkers. In other embodiments, system **100** may only comprise sensor system **105** for sensing indirect infection biomarkers. System **100**, and thereby sensor system **105** may comprise more than one type of sensor unit for sensing more than one type of indirect infection biomarkers. Yet, in other embodiments, system **100** may comprise a combination of sensor system **104** for sensing indirect infection biomarkers and sensor system **105** for sensing indirect infection biomarkers. System **100** may comprise more than one type of sensor units for sensing more than one type of direct infection biomarkers (e.g., sensor units that are incorporated in sensor system **104**), as well as more than one type of sensor units for sensing more than one type of indirect infection

biomarkers (e.g., sensor units that are incorporated in sensor system **105**). Typically, the more types of biomarkers that system **100** is configured to detect, the more accurate system **100** may be with detecting presence of infection at the surgery site, and furthermore with detecting the stage of infection. Any combination of sensors and any number of sensors may be incorporated as part of system **100**. For example, sensor system **104** may comprise a sensor for detecting Staphylococcus, and sensor system **105** may comprise one sensor unit for detecting pH levels and another sensor unit for detecting concentration of lactic acid. Other embodiments may comprise other combinations.

[0039] In some embodiments, each of sensor systems **104** and/or **105** may be connected to an electronic board **106**. Electronic board **106** may comprise a transmitter and antenna (not shown) that may transfer detections of the biomarkers by sensor systems **104** and/or **105** to an external receiver (as illustrated in system **200**, **FIG. 4**). Electronic board **106** may comprise a power supply, e.g., at least one battery for supplying power to all of the electronic components within. Electronic board **106** may further comprise a processor (not shown), for processing signals generated by at least one sensor systems **104** and/or **105** prior to the signals being transmitted to an external receiver. The processor within electronic board **106** may perform complete processing of the signals generated by the sensors, such that the transmitted signals may be displayed to a user or may be used to generate a notification to the user with respect to presence of infection, and in some cases with respect to the stage of infection. In other embodiments, the processor may only perform initial processing on the signals generated by the sensors, and then the processed signals may be transmitted to an external receiver for further processing.

[0040] Reference is now made to **FIG. 2**, which is a schematic illustration of a sensor for sensing indirect infection biomarkers, in accordance with an embodiment of the invention. According to some embodiments, sensor system **105** may be used for the detection of indirect infection biomarkers, e.g., pH, lactic acid, exudate flow, fluid viscosity, local/systemic oxygen saturation, and local/systemic temperature. Further examples of indirect biomarkers may be immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF- $\alpha$ , pancreas enzymes such as amylase, inflammatory parameters such as Lipopolysaccharide Binding Protein (LBP), and

metabolic parameters such as glucose. If sensor system **105** detects at least one of the above mentioned indirect infection biomarkers, it may indicate on presence and in some cases on the stage of infection.

[0041] Typically, a sensor for sensing indirect infection biomarker is located along tube **103**, such to continuously detect changes occurring in level, or concentration, and so on, of the indirect biomarkers. In some embodiments, sensor system **105** may be located within drain tube **103** that is inserted into the patient thus having the advantage of sensor system **105** being closer to the surgical or wound site in order to monitor the presence of infection more closely. In other embodiments, sensor system **105** may be located along tube **103**, thus having the advantage of monitoring only the contents of the flow of exudate leaving the surgical site, which may be more accurate compared to monitoring presence of infection in close proximity to the surgical site, since along tube **103** there is typically less noise from materials present in the surgical site following surgery, which may not be relevant to presence of bacteria. Sensor system **105** for sensing indirect infection biomarkers is typically not located within container **101**, since if located within the container, sensor system **105** would not be able to detect continuous real-time changes of the level or concentration of the indirect biomarkers while these changes occur but rather sensor system **105** would only be able to detect accumulation of the indirect biomarkers, and this is less appropriate for the type of indirect infection biomarkers.

[0042] In some embodiments, sensor system **105** may comprise more than one sensor units for sensing presence, level or concentration of more than one type of indirect infection biomarker. For example, sensor system **105** may comprise sensor **123** for sensing pH (in some embodiments, sensor **123** may comprise more than one sensor for sensing pH, e.g., two or three sensors for sensing pH, in order to provide a more accurate detection), temperature sensor **121** used for pH adjustment and/or for sensing an additional indirect infection marker, i.e., temperature, and sensor **124** for sensing lactic acid. Other types of sensors and other combination of sensors may be incorporated as part of sensor system **105**.

[0043] In some embodiments, sensor system **105** may be hollow in order to enable passage of drained fluids that pass through tube **103** to also pass through sensor system **105**, thus

enabling contact between the drained fluids and the at least one sensor implemented as part of sensor system **105**. Each of the various sensors incorporated as part of sensor system **105** requires fluids to be in contact with the respective sensing elements, thus fluids drained through tube **103** are required to pass through sensor system **105** and to be in contact with the various sensing elements.

[0044] Temperature sensor **121** may sense the local increase of temperature by sensing the temperature of fluids drained from the surgery site through tube **103**. When an infection begins, it may cause an increase in temperature, thus sensing changes in temperature may indicate on presence of infection.

[0045] pH sensor **123** may sense the level of pH of fluids drained from the surgery site through tube **103**. pH sensor **123** may comprise more than one sensors for sensing pH in order to compare between detections of the plurality of pH sensors and thus enable a better and more precise determination of pH level. Typically, pH sensor **123** is combined with a temperature sensor for pH adjustment, since pH may be affected by temperature changes. When infection is present, the pH of the area of infection typically decreases as a consequence of the inflammation reaction and innate immunity activation by bacteria, which leads to the release of content by macrophage and neutrophil phagosomes. The intraphagosomal pH in macrophages progressively decreases to a pH level of 4-5, after 15 to 60 minutes from the beginning of inflammation. This acidification is important for bacterial killing. Neutrophil phagosomes are less acidic, and some studies even report a transient alkalinization. Neutrophils and macrophages comprise the “front line” in trying to eliminate bacterial infection, operating at a very early stage. Therefore, by detecting a decrease in pH levels, an indication of the presence of infection may be made.

[0046] In some embodiments, pH sensor **123** may, for example, be an ion-sensitive field-effect transistor (ISFET) pH-sensor by *Sentron Europe BV*, The Netherlands, or pH microsensors or non-invasive pH sensors by *PreSens - Precision Sensing GmbH*, Germany, though other pH sensors may be incorporated in sensor system **105**.

[0047] Lactic acid sensor **124** may sense the concentration of lactic acid in fluids that are drained from the surgery site by tube **103**. Lactic acid is generated by different routes as a

resultant of the metabolic consequences of endotoxins of Gram negative bacteria (e.g., *Pseudomonas* species, or Enterobacteriaceae). Endotoxins may cause vascular collapse and reduce tissue perfusion and oxygenation at the locally infected tissues, leading to increased lactate production. Lactic acid may also increase after the alteration in distribution and/or expression of lactic dehydrogenase isozymes, due to bacteria infection. Although lactic acid may also be generated in increased amounts due to other conditions such as acute illnesses (e.g., pyelonephritis, acute arteriosclerotic heart disease, acute pancreatitis, pneumonia, acute gastrointestinal bleeding, acute alcoholism, peritonitis, acute hepatitis, acute fatty metamorphosis of liver), an increase in concentration of lactic acid in local tissue fluids such as exudates or cerebrospinal fluids is most often the consequence of bacteria infection. In presence of infection, lactic acid concentrations typically increase, thus if lactic acid sensor **124** senses an increase in lactic acid concentration, positive indication of the presence of infection may be made.

[0048] Other sensing units may be incorporated within sensor system **105**. Some examples for additional sensing units may be of sensors for sensing viscosity, exudate levels or flow rate or exudate. The higher the viscosity and exudate levels or flow rate coming out from local tissue, i.e., tissue at the surgery site, the higher the chances are for presence of an infection. Wound exudate is generally defined as 'what is coming out of the wound', 'wound fluid', 'wound drainage' and 'an excess of normal fluid'. It is currently known that wound exudate is produced in response to a complicated interaction between wound aetiology, wound healing physiology, wound environment and compounding pathological processes. Exudate is derived from fluid that has leaked out of blood vessels and it closely resembles blood plasma. Fluid leaks from capillaries into body tissues at a rate that is determined by the permeability of the capillaries and the pressures (hydrostatic and osmotic) across the capillary walls. In a wound, the initial injury initiates inflammation, an early stage of the healing process. Mediators involved in inflammation, e.g., histamine released by mast cells, increase capillary permeability so that white blood cells can escape and the blood vessels leak more fluid. The excess fluid enters the wound where it forms the basis of the exudate. In a healing wound, exudate production generally reduces over time. However, in a wound that is not healing as expected,

exudate production may continue and may be excessive due to ongoing inflammatory or other processes such as bacteria infection, which may fuel an exacerbated inflammation. Beyond the volume increase of exudate, the viscosity increase may also be indicative of bacteria infection and may be examined by a variety of sensors, comprising, for example, pressure sensors.

[0049] In some embodiments, sensor system **105** may comprise a pH sensor and a lactic acid sensor, or a pH sensor and a flow rate of exudate sensor, or a lactic acid sensor and a flow rate of exudate sensor or a pH sensor, a lactic acid sensor and a flow rate of exudate sensor. Other embodiments may comprise other combinations of pH, lactic acid and flow rate sensors along with other possible sensors, e.g., sensors for measuring temperature, sensors for measuring viscosity, sensors measuring oxygen saturation, and so on.

[0050] The temperature level detected by sensor **121** may (either prior to being transmitted to an external receiver, or after the detected signals are transmitted to an external receiver) be compared to a threshold. Such analysis of the detected signals of comparing the temperature level to a threshold enables not only a determination as to the presence of infection but also to a determination as to the stage of infection, whether mild, progressive or severe, and thus patient treatment may be modified and fitted accordingly. In some embodiments, sensor 121 may detect the rate of change of temperature, and said rate of change may be compared to a threshold, in order to determine the presence of infection.

[0051] According to some embodiments, each type of detected signals is compared to a different, respective threshold. In some embodiments, the threshold may either be a predetermined threshold or it may be an adjustable threshold, e.g., a threshold that may change according to the changing levels of biomarkers or may change according to the increase or decrease in the trend of sensed levels of biomarkers. An adjustable threshold may, for example, change depending on the time that had passed from surgery. That is, a certain threshold that may be adequate within a short time period post-surgery may no longer be relevant after a longer time period post-surgery. For example, if the sensor is for sensing pH, the threshold for determining presence of infection soon after surgery may be a pH of 7.1. If the sensor, e.g., sensor **123**, senses a pH level lower than 7.1, a positive indication may be made as to presence of infection. However, several hours to days post-surgery, the threshold



indicating presence of infection may be even lower than 7.1, and should be around 6.8. That is, if several hours or several days after surgery, the detected level of pH is 7.1, a definite indication as to presence of infection may not be made. However, if the sensed pH level is below 6.8, a positive indication as to presence of infection may be made. Other threshold levels of pH may be used.

[0052] In some embodiments, sensor system **105** may comprise a reference electrode or reference sensor **122** in order to serve as a reference to the various types of sensors, and thus a processor may compare the sensing signals of the various sensors to those of the reference signals, thereby determining whether or not the signals sensed by the sensors indeed indicate presence of infection. In some embodiments, following comparison between the signals sensed by the sensors to those sensed by the reference, an indication may be made as to the stage of infection, in addition to the presence of infection.

[0053] According to some embodiments, sensor system **105** may further comprise a memory unit **125** for recording the signals sensed by the sensing units in sensor system **105**. Memory unit **125** may be an EEPROM (Electrically Erasable Programmable Read-Only Memory) or any other unit of the sort. In some embodiments, memory unit **125** may comprise a processor for processing the signals generated by sensor system **105**. However, in other embodiments, memory unit **125** need not comprise a processor, and processing may be done in the external receiver (shown in **FIG. 4**).

[0054] In some embodiments, sensor system **105** may further comprise electrical contacts **115**, which may be open to accept an electronic board, e.g., electronic board **106** (**FIG. 1**). As described with respect to **FIG. 1**, electronic board **106** may comprise a transmitter and antenna (not shown) that may transfer detections of presence of the biomarkers generated by sensor systems **105** to an external receiver (illustrated in system **200**, **FIG. 4**). Electronic board **106** may comprise a power supply, e.g., at least one battery for supplying power to all of the electronic components within. Electronic board **106** may further comprise a processor for processing signals generated by sensor system **105** prior to the signals being transmitted to an external receiver. The processor within electronic board **106** may perform complete processing of the signals generated by the sensor system or the sensor units, such that the transmitted

signals may be displayed to a user or may be used to generate a notification to the user with respect to presence of infection, and in some cases with respect to the stage of infection. In other embodiments, the processor may only perform initial processing on the signals generated by the sensors, and then the processed signals may be transmitted to an external receiver for further processing.

[0055] Reference is now made to **FIG. 3**, which is a schematic illustration of a sensor system for sensing direct infection biomarkers, in accordance with an embodiment of the present invention. According to some embodiments, sensor system **104** may be used for the detection of direct infection biomarkers, which include various types of bacteria, e.g., *Escherichia coli*, *Pseudomonas* spp including *Pseudomonas aeruginosa* and *Pseudomonas putida*, *Staphylococcus* spp including *Staphylococcus aureus*, *Streptococcus*, *Enterococcus*, *Serratia*, *Klebsellia*, *Morganella*, *Proteus* and *Enterobacteriaceae*.

[0056] In some embodiments, sensor system **104** may comprise sensor units, which may detect presence of volatile organic compounds. Such volatile organic compounds may serve as a signature of specific bacteria species or a group of bacteria species, e.g., sulfur compounds. That is, determining presence of various volatile organic compounds by at least one sensor, and analysing the signals generated by the sensor, may provide qualitative data, i.e., identification of presence of bacteria. In some embodiments, such analysis may further provide quantitative data, i.e., bacteria contamination or infection severity stage or level.

[0057] The gradual increase in bacteria concentration corresponds to the different stages of bacteria invasion into the surgery site. For example, the stage of colonization of bacteria may be generally expressed by values less than  $10^2$  Colony Forming Units per millileter [CFU/ml], the stage of contamination may be generally expressed by values between  $10^2$  and  $10^6$  [CFU/ml], and the stage of infection may be generally expressed by values above  $10^6$  [CFU/ml]. Detecting  $10^2$  [CFU/ml] by sensor system **104** may assist in diagnosing early infection stage prior to clinical observational signs of infection.

[0058] When the infection biomarker is a hemolytic bacteria specie (e.g., *S aureus*, hemolytic *Streptococci*, hemolytic *E. coli* subspecies, the stage of contamination may be generally expressed by values between  $10^1$  and  $10^4$  [CFU/ml], and the stage of infection may be generally

expressed by values above  $10^4$  [CFU/ml]. Detecting  $10^1$  [CFU/ml] by sensor system **104** may assist in diagnosing early infection stage prior to clinical observational signs of infection.

[0059] In some embodiments, sensor system **104** may comprise a heating resistor for controlling the temperature of the chamber of sensor system **104** to be, for example, 30°C or 37°C, for increasing the sensitivity level or the detection level of sensor system **104**. Other temperature levels may be kept within the chamber of sensor system **104**, while providing an optimal temperature for increasing the sensitivity level or the detection level of sensor system **104**.

[0060] In some embodiments, sensor system **104** may comprise at least one opening **134** through which tube **103**, which drains the fluids from the surgery site may pass, such that drained in-vivo fluids may be in contact with the sensing units within sensor system **104** and thus be examined for presence of bacteria that may indicate on presence of infection. In some embodiments, sensor system **104** may comprise at least one illumination source **131**, e.g., an LED, for illuminating the in-vivo fluids that pass through tube **103**. Sensor system **104** may further comprise a photodetector **132** for detecting illumination that passed from illumination source **131** and through the in-vivo fluids that pass through sensor system **104**.

[0061] Sensor system **104** may further comprise a sol-gel material **133** or any other kind of materials that may capture bacteria within it, assuming bacteria is flowing within the in-vivo fluids drained from the surgery site. Sol-gel material **133** may refer to a material that is made of a gel-like network containing a liquid phase and a solid phase, typically comprising metal oxides, e.g., oxides of silicon and titanium. If bacteria is present within the fluids drained from the surgery site, while passing through tube **103** and through sensor system **104**, such bacteria may be caught within material **133** and thus be illuminated by illumination source **131** and examined by photodetector **132**. Sol-gel **133** may be located in between illumination source **131** and photodetector **132**, such that light from illumination source **131** may illuminate sol-gel **133**, may pass through sol-gel **133**, and may reach photodetector **132**. Changes in characteristics of light detected by photodetector **132** compared to the light irradiated from illumination source **131** may indicate on presence of bacteria, and even on concentration of bacteria present within sol-gel **133**. Typically, sol-gel **133** may be located on the same axis along which illumination

source **131** and photodetector **132** are located. In some embodiments, sol-gel **133** may be located at other locations, while ensuring that light from illumination source **131** may pass through sol-gel **133** and be detected by photodetector **132**.

[0062] According to some embodiments, sensor system **104** may be designed to detect at least one type of bacteria. That is, sol-gel material **133** may be designed to capture at least one type of bacteria. However, according to other embodiments, sol-gel material **133** may be designed to capture more than one type of bacteria, and thus illumination source **131** may comprise more than one illumination source for illuminating and causing a reaction with the more than one type of bacteria. Furthermore, photodetector **132** may also be designed to detect light signals of more than one type of illumination source, such to enable detection of more than one type of bacteria. Since different bacteria may be activated or may change some characteristics of light of a certain wavelength, in order to detect more than one type of bacteria, illumination source **131** should comprise more than one type of illumination source, each illuminating at a different wavelength. Thus, photodetector **132** should be designed to detect those different wavelengths, following a possible reaction between light from each of the illumination sources and its corresponding bacteria.

[0063] According to some embodiments, sensor system **104** may be located within drain tube **103** where tube **103** is inserted into the surgical site, i.e., in close proximity to the surgical site, thus having the advantage of being closer to the surgical or wound site in order to monitor presence of infection more closely. In other embodiments, sensor system **104** may be located along tube **103**, thus having the advantage of monitoring only the contents of the flow of exudate leaving the surgical site. However, in yet other embodiments, sensor system **104** may be located in container **101**, thus having the advantage of sensing the overall concentration or level of the direct infection biomarkers, i.e., of the bacteria, and in some cases the overall rate of change of concentration or level of bacteria, which may be more accurate than any single discrete reading of exudate at a given instance. For direct infection biomarkers, i.e., for bacteria, monitoring accumulation of bacteria and thus monitoring concentration of bacteria compared to monitoring single discreet readings of presence of bacteria in exudate is more accurate and may help avoid “false” alarms in detection of the presence of infection.

[0064] Reference is now made to **FIG. 4**, which is a schematic illustration of a drain system including a notification system, in accordance with an embodiment of the invention. System **200** may comprise a drain system comprising a drain tube **103** for draining exudate from the surgery site and into a container **101**, where the exudate is accumulated. Container **101** may comprise a suction element **102**, which may cause low or high pressure in order to actively suck fluids or exudate from the surgery site through tube **103** and into container **101**. However, in other embodiments, drain system **100** need not comprise an active suction element **102**, and drainage from the surgery site may operate passively. Also, in other embodiments, drain tube **103** need not drain fluids into a container but rather may be part of an open system, thereby draining fluids onto a dressing or something of the sort.

[0065] System **200** may further comprise at least one sensor system **104** for detecting direct infection biomarkers, and at least one sensor system **105** for detecting indirect infection biomarkers. Each of sensor systems **104** and **105** may comprise more than one sensor unit for detecting more than one type of an infection biomarker. In some embodiments, each of sensor systems **104** and/or **105** may be connected to an electronic board **106**. Electronic board **106** may comprise a transmitter and antenna (not shown) that may transfer detections of the infection biomarkers done by sensor systems **104** and/or **105** to an external receiver. Typically, the transmission of data collected by both or either of sensor systems **104** or **105** may be wireless transmission, e.g., based on radio frequency, Bluetooth, Wireless Local Area Network (WLAN) or Wi-Fi, or any other kind of wireless transmission. According to some embodiments, the external receiver may either be a mobile device, e.g., mobile phone **107**, which may receive the signals related to sensing presence of infection biomarkers generated by at least one sensor unit, through Bluetooth. According to other embodiments, the external receiver may be some kind of modem **108** for receiving the signals generated by at least one sensor unit through WLAN or Wi-Fi. Other types of receivers, typically wireless receivers may be used as part of system **200**. In other embodiments, the external receiver may not be a wireless receiver but rather be a wired receiver; i.e., one that electronic board **106** may be connected to through wires and transmission of data may be done through physical wires. In some embodiments, the external receiver may comprise a processor for processing a signal generated by at least one

sensor unit, which may be encapsulated by either of sensor systems **104** or **105**. In other embodiments, the external receiver need not comprise a processor.

[0066] According to some embodiments, sensor systems **104** and/or **105** may communicate with remote devices **107** and **108** as described in US Patent No. 8750396, which is commonly owned by the assignee of the present application and is incorporated herein by reference in its entirety. In some embodiments, sensor systems **104** and/or **105** may transmit patient information to remote devices as described in US Patent Application No. 13/942225, which is commonly owned by the assignee of the present application and is incorporated herein by reference in its entirety.

[0067] In some embodiments, system **200** may further comprise a notification system **109**. Notification system **109** may receive the detected data or signals from the external receiver for processing and for generating an indication as to the presence of an infection at the surgery site. Notification system **109** may comprise a processor for processing the signals generated by the sensor systems or sensor units. If external receiver **107** or **108**, or even electronic board **106** comprises a processor, then notification system **109** need not necessarily comprise a processor. Notification system **109** may further comprise an analyzer for analyzing the processed signals by comparing the processed signals to a threshold. Each of the biomarkers, whether a direct infection biomarker or an indirect infection biomarker may have its own specific threshold to which the detected and processed signals are compared. After the analyzer compares the processed signals to a threshold, an indication may be generated as to the presence of infection at the surgical site. The indication as to presence of infection by system **109** may be made by generating some kind of alert noticed by the operator of system **200**, e.g., a physician or a nurse or any other healthcare provider, or may be noticed by the patient who underwent the surgical operation. Various types of notifications may be generated by notification system **109**, for example, a sound of some sort may be generated, a light source may be turned on or may change its color once presence of infection is determined, a literal indication may appear on a display unit, e.g., a screen of notification system **109**, and so on.

[0068] According to some embodiments, notification system **109**, and more specifically, the analyzer that is incorporated within notification system **109** may determine the presence of

infection, as well as determine the stage of infection. Determining the stage of infection may correspond to determining whether the infection is at a first stage, a second stage or a third stage, and so on. Typically, the first stage of infection corresponds to a mild stage, e.g., the infection is at a very early stage and may not be detectable by typical monitoring; the second stage of infection may correspond to a progressive stage, e.g., the infection is progressing and is no longer in its initial mild stage; and the third stage may correspond to a severe stage of infection, e.g., the infection is at a critical stage and requires immediate treatment. Other definitions to the different stages of infection may be used.

[0069] In some embodiments, the thresholds to which the signals may be compared, may be predetermined prior to the beginning of the sensing or detecting procedure by the specific sensors. Yet, in other embodiments, the thresholds may be adaptive to changes in the sensed levels or concentration of the various infection biomarkers. Adaptive thresholds may mean that the analyzer may change the threshold's value based on changes in the sensed signals, or based on the analysis of the trend of the sensed signals. For example, if the biomarker is pH, and pH levels are initially low, soon after surgery, then an appropriate threshold may be lower than what a predetermined threshold would have been, and vice versa. An increase or decrease in the trend of sensed signals may be used to adjust the threshold according to which an indication of presence of infection as well as of the stage of infection may be generated. In some embodiments, the threshold may be based on the rate of change of the level or concentration of any infection biomarker. For example, if a rapid increase in the level or concentration of an infection biomarker is detected, the threshold value should be higher than what a predetermined threshold would have been without detecting the rate of change in the level or concentration of the infection biomarker. In the above example of a rapid increase in levels of the infection biomarker, one can assume there may be a leak from the in-vivo area that is being monitored, e.g., from the surgery site or from the GI tract, etc., which causes such an increased rate of change. Thus, the threshold requires adjustment such to avoid "false" alarms in the detection of infection.

[0070] For example, if the infection biomarker is pH, a first indication, which may correspond to a mild stage of infection, may be generated if the level of pH is equal to or below 7.1. That is,

notification system **109** may generate a first indication as to presence of infection and as to the stage of infection, which is an initial and mild stage of infection if the level of pH sensed by the pH sensor (which may be part of sensor system **105**) is equal to or below 7.1. In other embodiments, a different threshold may be used to which the sensed pH signals may be compared. A second indication, which may correspond to a progressive or severe stage of infection, may be generated if the level of pH is equal to or below 6.8. That is, notification system **109** may generate a second indication per presence of infection as well as the stage of infection being progressive or severe, if the signals detected by the pH sensor are equal to or below 6.8. Other thresholds for such a second indication, indicating a more progressed stage or level of infection may be used.

[0071] Furthermore, if the infection biomarker is pH, the threshold according to which indications on the presence (and level) of infection may be made, may be based on the rate of change of the level of pH, which is typically a decrease in case of an infection. For example, a first indication, which may correspond to a mild stage of infection, may be generated if the mean decrease rate is above 0.1[pH unit/hour] for longer than 1 hour. A second indication, which may correspond to a progressive stage of infection, may be generated if the mean decrease rate is above 0.1[pH unit/hour] for more than 3 hours. A third indication, which may correspond to a severe stage of infection, may be generated if the mean decrease rate is above 0.1[pH unit/hour] for more than 6 hours. In another example, if the mean decrease rate is above 0.2[pH unit/hour] for more than 1 hour, a second indication, which may correspond to a progressive stage of infection, may be generated. In other embodiments, other mean decrease rates and/or other time lines may be chosen.

[0072] In other examples, the threshold according to which indications on the presence (and level) of infection may be made, may be based on the total time that a pH level stays substantially unchangeable with respect to a threshold/baseline level. For example, a first indication, which may correspond to a mild stage of infection, may be generated if the total time of pH level being below the baseline, e.g., below 7.1, is longer than 1 hour. A second indication, which may correspond to a progressive stage of infection, may be generated if the total time of pH level being below the baseline of e.g., 7.1, is longer than 3 hours. A third



indication, which may correspond to a severe stage of infection, may be generated if the total time of pH level being below the baseline, e.g., below 7.1, is longer than 6 hours. In other embodiments, other time lines and/or other thresholds or baselines may be chosen.

[0073] In case the biomarker is lactic acid, a first indication, which may correspond to a mild stage of infection, may, for example, be generated by notification system **109** during the first hour post-surgery (or so), if the concentration of lactic acid is equal to or above a threshold of 3[mM]. Such an indication may indicate presence of infection, and yet further indicate on the stage of infection being mild, thus detecting early signs of post-surgery. In other embodiments, the threshold to which the concentration of lactic acid that is sensed, e.g., by sensor system **105**, may be compared to, may be different than 3[mM]. In other embodiments, the analyzer within notification system **109** may compare the sensed concentration of lactic acid to a different threshold. Typically, the appropriate threshold may be predetermined according to experiments examining the changes in lactic acid concentration that are typical to early stages of infection. In some embodiments, the threshold need not be predetermined but may rather be an adaptive threshold, which may change according to initial level of concentration of lactic acid soon after surgery, or according to the slope of change of lactic acid concentration during a few periodic sensing events by, e.g., sensor system **105**.

[0074] A second indication, which may correspond to a progressive stage of infection, may, for example, be generated by notification system **109** if the concentration of lactic acid is above the threshold for 6 hours after the first indication. That is, if the sensed concentration level of lactic acid is still above the threshold of 3[mM] for 6 hours after the first indication, the analyzer that is included in notification system **109**, which compares the sensed concentration level to the threshold, may generate a notification that not only is there presence of infection but also that the infection is in progressive stage. A third indication, which may correspond to a severe stage of infection, may, for example, be generated if the concentration of lactic acid is above the threshold for 24 hours after the first indication. The analyzer within notification system **109** may compare the sensed concentration of lactic acid to the threshold of 3[mM] and if the sensed concentration is above the threshold for 24 hours after the first indication, then the analyzer may generate an indication and notification of presence of an infection as well as on

the stage of infection being severe. Once the care provider is notified on the stage of the infection in the surgery site, let alone the presence of infection, the care provider may use the most appropriate means (e.g., medicaments) in treating such an infection. Other timelines and other thresholds may be used for generating any of the indications mentioned above.

[0075] Furthermore, if the infection biomarker is lactic acid, the threshold according to which indications on the presence (and level) of infection may be made, may be based on the rate of change of the level of lactic acid, which is typically an increase in case of an infection. For example, a first indication, which may correspond to a mild stage of infection, may be generated if the mean increase rate is above 0.1 [mM/hr] for more than 1 hour post-surgery. A second indication, which may correspond to a progressive stage of infection, may be generated if the mean increase rate is above 0.1 [mM/hr] for more than 3 hours post-surgery. A third indication, which may correspond to a severe stage of infection, may be generated if the mean increase rate is above 0.1 [mM/hr] for more than 6 hours post-surgery. In another example, if the mean increase rate is above 0.2[mM/hr] for more than 1 hour post-surgery, a second indication, which may correspond to a progressive stage of infection, may be generated. In other embodiments, other mean increase rates and/or other time lines may be chosen.

[0076] In other examples, the threshold according to which indications on the presence (and level) of infection may be made, may be based on the total time that lactic acid level stays substantially unchangeable with respect to a threshold/baseline level. For example, a first indication, which may correspond to a mild stage of infection, may be generated if the total time that concentration of lactic acid stays above the baseline, e.g., above 3[mM], is longer than 1 hour. A second indication, which may correspond to a progressive stage of infection, may be generated if the total time that concentration of lactic acid stays above the baseline, e.g., above 3[mM], is longer than 3 hours. A third indication, which may correspond to a severe stage of infection, may be generated if the total time that concentration of lactic acid stays above the baseline, e.g., above 3[mM], is longer than 6 hours. In other embodiments, other time lines and/or other thresholds or baselines may be chosen.

[0077] In case the infection biomarker is a flow rate of exudate coming out of the surgery site, a first indication, which may correspond to a mild stage of infection, may, for example, be

generated by notification system **109**, 6 hours post-surgery if the flow rate is above 5 milliliter per hour [ml/hr]. The analyzer within notification system **109** may compare the flow rate sensed by sensor system **105**, to the threshold of 5[ml/hr] 6 hours post-surgery. If the sensed flow rate exceeds the threshold of 5[ml/hr], then the analyzer and thus notification system **109** may generate an indication or alert not only of the presence of infection but also of the stage of infection being mild. The value of the threshold may be different than 5[ml/hr], while being indicative of a mild stage of infection, thus detecting early signs of post-surgery. The threshold value may be predetermined based on experiments examining behavior and characteristics of an infection in a surgical site. In other embodiments, the threshold may not be predetermined but rather may change in accordance with changes in the sensed flow rate. For example, if the initial flow rate is already close to the threshold value, notification system **109** may adjust the threshold value to be different than the initially chosen threshold. Furthermore, the threshold may change while corresponding to the changes in sensed values of flow rate.

[0078] A second indication, which may correspond to a progressive stage of infection, may, for example, be generated 6 hours post-surgery if the flow rate is above 10[ml/hr]. If the sensed flow rate exceeds the new threshold of 10[ml/hr] following 6 hours from surgery, then the analyzer or notification system **109** may generate an indication not only of the presence of infection but also of the stage of infection being progressive. Other threshold values and other timings may be selected. In some embodiments, the threshold value may be adaptive or changeable such to correspond to changes in the sensed parameters.

[0079] A third indication, which may correspond to a severe stage of infection, may, for example, be generated 6 hours post-surgery if the flow rate is above 20[ml/hr]. notification system **109** may generate an indication to the presence of infection as well as to the stage of infection being severe, if following 6 hours from surgery, the flow rate sensed by sensor system **105** exceeds 20[ml/hr]. Other threshold values and other timings may be selected. In some embodiments, the threshold value may be adaptive or changeable such to correspond to changes of the sensed parameters.

[0080] In case the infection biomarkers are immune-modulating mediators, such as IL-1, IL-6, IL-10 and TNF $\alpha$ ; a first indication may be generated if the level of at least one of these

mediators is above 100% of a baseline/threshold value. In some embodiments, the baseline value may be obtained during the surgery or from the very first fractions of the collected exudates. A second indication may be generated if the level of at least one of these mediators is above 200% of the baseline value, or if the level of at least two of these mediators is above 100% of the baseline value, or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours .

[0081] In case the infection biomarker is LBP; a first indication may be generated if the level of LBP is above 100% of a baseline value. In some embodiments, the baseline value may be obtained during the surgery or from the very first fractions of the collected exudates. A second indication may be generated if the level of LBP is above 200% of the baseline value, or if the level of LBP is observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours .When said biomarker is glucose; a first indication may be generated if the level of glucose is below at least 20 % of a normal value (indicatively 8 [mmol/l]), and with a decreasing trend during at least a day, while a second indication may be generated if the level of glucose is below 30% of the baseline/normal value with a decreasing trend during at least 2 days. When said biomarker is amylase; a first indication may be generated if the level of amylase is above 100 U/l, before the first 24 hours post-surgery, while a second indication may be generated if such level of amylase of above 100 U/l is observed over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0082] In case the biomarker is a direct infection biomarker, i.e., bacteria specie, the biomarker may be selected from the group consisting of: Escherischia coli, Pseudomonas spp., Pseudomonas aeruginosa, Pseudomonas putida, Staphylococcus spp., Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus spp., Enterococcus spp., Klebsellia spp., Proteus spp., Serratia spp., Morganella spp. and other Enterobacteriaceae, or a combination thereof. When the infection biomarker is a non-hemolytic bacteria specie, a first indication, which may correspond to a mild stage of infection, may, for example, be generated by notification system **109** if Colony Forming Units (CFU) is above  $10^2$  [CFU/ml]. That is, if the number of colony units formed following surgery exceeds  $10^2$  per milliliter, then notification system **109** may generate an indication of presence of infection and of the stage of infection being mild. A second

indication, which may correspond to a progressive stage of infection, may, for example, be generated by notification system **109** if CFU is above  $10^3$  [CFU/ml]. A third indication, which may correspond to a severe stage of infection, may, for example, be generated by notification system **109** if CFU is above  $10^4$  [CFU/ml]. Other threshold values and other timings may be selected. In some embodiments, the threshold value may be adaptive or changeable such to correspond to changes of the sensed parameters.

[0083] When the infection biomarker is a hemolytic bacteria specie (e.g., S aureus, hemolytic Streptococci, and hemolytic E. coli subspecies), a first indication which may correspond to a mild stage of infection, may be generated if Colony Forming Units (CFU) is above  $10^1$  [CFU/ml], a second indication, which may correspond to a progressive stage of infection, may be generated if CFU is above  $10^2$  [CFU/ml], and a third indication, which may correspond to a severe stage of infection, may be generated if CFU is above  $10^3$  [CFU/ml].

[0084] In some embodiments, the readings or sensing of presence of any direct infection biomarker, should take place at least every increase of 1 Log of CFU. An increase of 0.3 Log of CFU is substantially equivalent to one doubling time of bacteria, thus readings of presence of bacteria should typically be done every two doubling times. Some examples for doubling times for various bacteria may be as follows:

- for Klebsellia spp, Proteus spp, Serratia, Morganella, and E coli type bacteria, doubling time may be every 20 to 45 minutes;

- for Pseudomonas type bacteria, doubling time may be every 30 to 40 minutes;

- for Sthaphylococcus type bacteria, doubling time may be every 20 to 30 minutes; and

- for Streptococcus type bacteria, doubling time may be every 20 to 30 minutes.

Accordingly, for Pseudomonas type bacteria, sensing of presence of these bacteria should be done at least every one hour.

[0085] In some embodiments, in case the doubling time of a certain bacteria is quicker than the doubling time mentioned above with respect to the various types of bacteria, then an indication that may correspond to a more progressive stage of infection may be generated, compared to the indication that would have been generated if the doubling time was similar to those mentioned above. For example, if the biomarker is S. aureus, which is Staphylococci and a

hemolytic type bacteria, a detection of  $10^2$  [CFU/ml] may generate a second alert level, as mentioned above. However, if the doubling time of *S. aureus* is less than 20 minutes, which is the typical doubling time for Streptococcus type bacteria, this may cause an indication that may correspond to a higher stage of infection, e.g., a severe stage of infection.

[0086] In some embodiments, the infection biomarker may be temperature. However, more important than measuring the discrete level of temperature, is measuring the rate of change of temperature, since the rate of change of temperature is a good indication on the presence of infection. The higher the rate of change in temperature is, the more progressed the infection is. For example, a first indication, which may correspond to a mild stage of infection, may, for example, be generated by notification system **109** if a rate of change in temperature is  $0.5[^\circ\text{C}/\text{hr}]$ , and a second indication, which may correspond to a progressive or severe stage of infection, may be generated if a rate of change in temperature is  $1^\circ\text{C}/\text{hr}$ .

[0087] In some embodiments, there may be additional biomarkers for early infection diagnosis, for example, **Group A** may comprise the following biomarkers: RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) Osteopontin, or Macrophage migration inhibitory factors (MIP) – e.g., MIP-1, MIP-1a, MIP-1b, MIP-2 and, IL-21. A first indication may be generated if the level of at least one of the mediators/biomarkers mentioned in Group A is greater than two times the baseline value. The baseline/initial value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively, according to the mean or median values observed in healthy patients. A second indication may be generated if the level of at least one of these mediators is greater than three and a half times the baseline value or if at least one of these mediators is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3 and 4), which generated a first indication level or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0088] Additional biomarkers may comprise other inflammatory markers IL- $1\beta$ , and IL-8. A first indication on presence of infection may be generated if the level of at least one of these biomarkers is greater than three times the baseline/initial value (the initial value may be

obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication on presence of infection may be generated if the level of at least one of these biomarkers is greater than five times the baseline value or if at least one of these biomarkers is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0089] Other examples of biomarkers from Group A may comprise additional inflammatory markers, Monocyte chemotactic proteins, e.g., MCP-1, and MCP-2. A first indication on presence of infection may be generated if the level of at least one of these biomarkers is greater than two times a baseline value (the initial/baseline value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication may be generated if the level of at least one of these mediators/biomarkers is greater than five times the baseline value or if at least one of these mediators is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0090] Further examples of biomarkers from Group A may comprise additional inflammatory markers IL-17, IL-18, and IL-27. A first indication on presence of infection may be generated if the level of at least one of these biomarkers is below 80% of a baseline value (the baseline/initial value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication may be generated if the level of at least one of these biomarkers is below 66% of the baseline value or if at least one of these biomarkers is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which

generated a first indication level or if such levels are observed with increasing or decreasing trends over at least two consecutive measurements within intervals in the range of 4 to 24 hours, according to the trend of biomarkers for infection diagnosis.

[0091] In some embodiments, there may be additional biomarkers for early infection diagnosis, for example, **Group B** may comprise biomarkers with procoagulant or anticoagulant activities. The biomarkers of Group B should preferably be monitored during the first post-operative day (i.e., the first day following surgery), when the exudates typically contain substantial amounts of blood. Examples of such biomarkers may be Antithrombin III, Protein C, and Protein S. A first indication on presence of infection may be generated if the level of at least one of these biomarkers is below 80% of a baseline value (the baseline value may be obtained during the surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication may be generated if the level of at least one of these mediators/biomarkers is below 66% of the baseline value or if at least one of these sub-group biomarkers from Group B is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level or if such levels are observed with increasing or decreasing trends over at least two consecutive measurements within intervals in the range of 4 to 24 hours, according to the trend of biomarkers for infection diagnosis.

[0092] Other examples of biomarkers from Group B may comprise F1.2, and Thrombomodulin. A first indication on presence of infection may be generated if the level of at least one of these mediators is greater than one and a half times a baseline value (the baseline value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication on presence of infection may be generated if the level of at least one of these mediators is greater than two and a half times the baseline value or if at least one of these sub-group of biomarkers from Group B is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level or if such levels are observed



with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0093] Another example for a coagulation biomarker from Group B is D-Dimer. A first indication on presence of infection may be generated if the level of at least one of these mediators is greater than five times a baseline value (the initial/baseline value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication may be generated if the level of at least one of these mediators is greater than ten times the baseline value or if at least one of these sub-group of biomarkers from Group B is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level or if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hrs.

[0094] Yet a further example of biomarkers of Group B may comprise Platelet Factor 4, Plasminogen activator inhibitor, TAT, and cross-linked fibrin. A first indication on presence of infection may be generated if the level of at least one of these biomarkers is greater than two times the baseline value (the baseline/initial value may be obtained during surgery or from the very first fractions of the collected exudates, or alternatively according to the mean or median values observed in healthy patients). A second indication may be generated if the level of at least one of these mediators is greater than three and a half times the baseline value or if at least one of these sub-group of biomarkers from Group B is combined with at least one biomarker selected from all of the above mentioned biomarkers (with respect to the biomarkers disclosed in the description of FIGs. 1, 2, 3, and 4), which generated a first indication level if such levels are observed with an increasing trend over at least two consecutive measurements within intervals in the range of 4 to 24 hours.

[0095] In some embodiments, there may be additional miscellaneous biomarkers for early infection diagnosis, for example, **Group C** may comprise cell receptor type markers, such as: CC chemokine receptor (CCR), CCR 3, C5L2, CRTh2, Soluble Fas receptor (soluble), Fc-gamma RIII, soluble FLT-1, GP130, soluble IL-2 receptor, soluble phospholipase A2 including Group II (PLA2-

II), soluble RAGE, soluble ST2 (IL-1 receptor), Toll-like receptor (TLR) 2, TLR 4, Transient receptor potential vanilloid, (TRPV)1, soluble TREM-1, soluble TNF-receptor, soluble Urokinase type plasminogen activator receptor (uPAR), ADAMTS-13, Angiopoietin – e.g. Angiopoietin-1 , Angiopoietin-2 –, Endothelial leukocyte adhesion molecule (ELAM)-1, Endothelial progenitor cells (cEPC), Endocan, Endothelin-1, soluble Intracellular adhesion molecule (ICAM)-1, Laminin, Neopterin, Platelet-derived growth factor (PDGF)-BB, E-Selectin, Soluble L-Selectin, P-Selectin, Vascular cell adhesion molecule (VCAM)-1, Vascular endothelial growth factor (VEGF), von Willebrand factor and antigen, Adrenomedullin, Proadrenomedullin, Anandamide, Angiotensin converting enzyme (ACE), 2-arachidonoylglycerol, Copeptin, C-type natriuretic peptide (CNP), Cycling nucleotides, Elastin, cGRP, 47 kD HK, Neuropeptide Y, Nitric oxide (NO), nitrate, nitrite, Substance P, Tetrahydrobiopterin, Vasoactive intestinal peptide (VIP), Serum amyloid A (SAA), Ceruloplasmin, C-reactive protein (CRP), Ferritin, Alpha1-acid glycoprotein, Hepcidin, Procalcitonin, Pentraxin 3, Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP), Carbonyl phosphate synthase (CPS)-, Endothelin-1, pro-endothelin-1, Filterable cardiodepressant substance (FCS), Gc-globulin, Glial fibrillary acidic protein (GFAP), alpha glutathione S-transferase (GST), Hepatocyte growth factor (HGF), MEGX test, Myocardial angiotensin II, NSE, Pancreatitis-associated protein-I, Pre B cell colony-enhancing factor (PBEF), Protein S-100b, Surfactant protein – e.g. Surfactant protein A, Surfactant protein B, Surfactant protein C, Surfactant protein D, Troponin, Alpha2 macroglobulin, Albumin, Anti-endotoxin core antibodies (EndoCab), Apolipoprotein CI, Bcl-2, Beta-thromboglobulin, Caspase-1, Ceramide, Cholesterol, Complement factors – e.g. C3, C4, C5a –, Terminal complement complex, Dendritic cell, Dipeptidylpeptidase, Diiodotyrosine (DIT), Eicosanoid, Elastase, Elastase, a1-antitrypsin complex, Erythropoietin, F2, Fatty acid amide hydrolase, Free DNA, G-CSF, GM-CSF, Gelsolin, Ghrelin, Growth arrest specific protein (Gas), Heat shock proteins (HSP) – e.g. HSP 70, HSP 72, HSP 73, HSP 90, HSP 32 –, HDL cholesterol, soluble HLA-G5 protein, H2S, Hyaluronan, Hydrolytic IgG antibodies, Inter-alpha inhibitor proteins (Ialpalp), Intracellular nitric oxide in leukocyte, IP-10, Lactoferrin, Leptin, Serum lysozyme, Matrix-metalloproteinases (MMP) – e.g. MMP-2, MMP-9, MMP-1, MMP-8, MMP-13, MMP-7, MMP-3, MMP-10 –, Neurotensin, Nociceptin, Orphanin FQ, NF-kB, Nucleosomes, Peptidoglycan, Amino-acids, Fibronectin, Plasmin alpha2-

antiplasmin complex, Renin, Resistin, Selenium, Selenoprotein P, Bicarbonate, Sphingomyelinase, Sulfite, Transforming growth factor (TGF) – e.g. TGF- $\beta$ , Tissue Inhibitor of Metalloproteinases (TIMP) – e.g. TIMP-1, TIMP-2, TIMP-3, Uric acid, Annexin V binding, Xanthine oxidase, soluble CD11b, Heparin Binding Protein (HPB), soluble receptor of advanced glycation end-products (RAGE), IL-10, IL-13, GM-CSF, IP-10, IFN $\gamma$ , IL-1 $\alpha$ , GP130, IL-2 receptor, Fas, TNF-Receptor 1, and TNF-Receptor 2.

[0096] In some embodiments, Biomarkers from **Group A** are less accurate in being indicative of presence of infection compared to the biomarkers listed with respect to FIGs. 1, 2, 3, and 4. However, the biomarkers listed as part of **Group A** may still provide information on the presence of infection, with or without the biomarkers listed in FIGs. 1, to 4. Biomarkers from **Group B** are a bit less preferable than those in **Group A**, and biomarkers from **Group C** are less preferable than those in **Group B**. However, biomarkers from any of groups A, B or C may be used either alone, in any combination with other biomarkers from groups A, B or C, in combination with biomarkers listed with respect to FIGs. 1-4 or without such combination, in order to provide information on the presence of infection.

In some embodiments, all the disclosed biomarkers (those listed in **FIGs. 1-4, Group A, Group B, and Group C**) may be combined with cell analysis for early infection diagnosis, since changes in cell formulation may be indicative of infection events. Preferably, analysis of cells, which are involved in the inflammatory reaction and/or infection, e.g., neutrophils, mast cells, basophils, eosinophils, mononuclear cells (i.e., monocytes, macrophages), and lymphocytes, and more preferably analysis of neutrophils, macrophages and lymphocytes, may be combined with detection of at least one of the biomarkers listed above. In some embodiments, the analysis of macrophages may be carried out at the level of subtypes, for example, classically activated macrophages, or M1 and macrophages, and alternatively activated or M2, alternatively, LPS/IFN $\gamma$  activated macrophages and IL-4 activated macrophages. In some embodiments, the analysis of lymphocytes may be carried out at the level of subtypes, for example, innate immune cells, including Natural Killer cells, TH1 CD4 $^+$  cells and CD8 $^+$  cytotoxic T lymphocytes. These analyses may comprise the use of immuno-assays, for a combination of cell surface markers, for example, clusters of differentiation (CD) – e.g., MHC class I, CD4, CD8 [T

Lymphocyte], CD14, CD33, CD86, CD206, CD56 [Natural Killer], CD66b [Granulocytes, Neutrophils], and CD64. The analyses may comprise identification of cell types derived from the analysis of specific single cell surface markers or a combination of cell surface markers; more preferably cell subtypes, as mentioned above. A first indication on presence of infection may be generated if there is a persisting increase trend of at least 50% above baseline values, for any one of the above mentioned cells, in intervals within the range of 4 to 24 hours. In some embodiments, the examination and determination of the increasing trend should preferably be done during the first few days post-surgery.

[0097] In some embodiments, as described above, the stages of infection defined as mild, progressive, and severe, may correspond to a first indication of infection, a second indication of infection, and a third indication of infection, respectively.

[0098] In some embodiments, other stages besides mild, progressive or severe may be defined by the user or operator of system **200**, according to which a notification of presence and stage or level of infection may be generated.

[0099] In some embodiments, system **200** may comprise more than one type of biomarkers, either more than one type of indirect biomarker, or more than one type of direct biomarkers, or a combination of at least one direct biomarker and at least one indirect biomarker. When system **200** comprises more than one type of biomarker, a combined threshold that takes into consideration the plurality of types of biomarkers may be one according to which a notification as to presence of infection as well as the stage of infection may be generated by notification system **109**. For example, system **200** may comprise one sensor unit for detecting the level of pH and another sensor for detecting concentration of lactic acid, such that the biomarkers that system **200** is required to detect are pH and lactic acid. If the analyzer within notification system **109** records pH below or equal to 7.1, and lactic acid concentration increase of 0.1[mM/hr] for more than 1 hour, then notification system **109** may generate an indication or alert referring not to a first stage of infection being mild, but rather to a second indication, which may correspond to a progressive stage of infection. That is, if each of the biomarkers were detected alone, notification system **109** would have generated a first indication of presence of infection, and one which may correspond to a mild stage of infection. Whereas,

when more than one type of biomarker is detected by system **200** and each of the biomarkers exceeds their corresponding threshold, it may be concluded that the stage of infection is in fact more progressed, thus notification system **109** may generate a second indication, which may correspond to a progressive stage of infection. It seems that when system **200** comprises sensors for sensing more than one type of biomarkers, system **200** may be more accurate, not only as per presence of infection, but also as per the stage of infection.

[00100] According to some embodiments, each of the sensor units or sensor systems within system **200** may sense presence of its corresponding infection biomarkers continuously, e.g., the sensors may be activated without stopping. In other embodiments, each of the sensors may sense the presence of their corresponding infection biomarkers periodically, e.g., every few minutes. For example, metabolism modifications are quite rapid. Thus, pH that drops due to degranulation of polymorphonuclear cells and macrophages may be observed in less than 1 minute. Changes in lactic acid concentration may take more time, e.g., approximately less than 5 minutes. Flow rate of exudates may be even more gradual, e.g., may change in less than 15 minutes. Thus, if a sensor is to sense presence of pH, the sensor should sense the levels of pH, if not continuously, then at least within periods of time that are shorter than 1 minute. If the sensor is to sense concentration of lactic acid, the sensor should sense the concentration, if not continuously, then at least within periods of time shorter than 5 minutes. And if sensor is to sense flow rate of exudates, the sensor should sense the flow rate if not continuously then at least within periods of time shorter than 15 minutes.

[00101] If system **200** is to sense presence of direct infection biomarkers, i.e., bacteria specie, then the sensor should sense the formation of bacteria colonies continuously, and if not continuously then periodically within time periods shorter than 10 minutes.

[00102] In some embodiments, The correlation between a combination of any listed markers and post-operative infection may be analyzed by multivariate analysis, by using bespoke statistical and mathematical models (i.e., using such models per each particular person/patient), for example, Chain Model, Bayesian Models, logistic regression, canonical correlation analysis, principal component analysis, or any other model of the sort. Using statistical and mathematical models, as described above, may provide access to average and

standard deviations thus providing estimates and margins of error, and provide access to correlations thus providing quantifying relationships between pairs of variables. The correlation coefficients may measure the strength of the linear association between numerical variables. In some embodiments, prediction ellipses in scatter plots as a visual test for bivariate normality can also give an indication of the strength of the correlation.

[00103] In some embodiments, the use of bespoke statistical and mathematical models may help predict the likelihood of early post-operative infection with associated probability of post-operative infection certainty. The level of alert may then be generated by the level of probability of confirmed early diagnosis of post-operative infection.

[00104] In some embodiments, early diagnosis of complications may further be refined by associating the combination of infection biomarkers with patient's data, for example, from the Electronic Medical Record (EMR), the Electronic Health Record (EHR). This may ultimately lead to the implementation of clinical algorithms for analyzing the correlation between post-operative infection and the combination of markers completed with various attributes of a particular patient's medical data, by using big data analytics such as data collection (data mining), data analysis, statistical analysis, predictive modelling and predictive model deployment. Depending on the complexity of the data and the availability of the data sets, machine learning algorithms may also be explored in order to improve the correlation analysis.

[00105] In some embodiments, the use of bespoke data analytics may help predict the likelihood of early post-operative infection with associated probability of post-operative infection certainty from the combination of infection biomarkers and patient medical data, for each particular patient. The level of alert may then be generated by the level of probability of confirmed early diagnosis of post-operative infection. For example, a first level of alert may be generated if probability of post-operative infection is equal or higher than 50%; a second level of alert may be generated if probability of post-operative infection is equal or higher than 75%; and a third level of alert may be generated if probability of post-operative infection alert is equal or higher than 90%.

[00106] Reference is now made to **FIG. 5**, which is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with an embodiment of the invention. According to some embodiments, a method for determining early signs of an infection in the surgical site may comprise the step of sensing presence of at least one infection biomarker by using a sensor incorporated in a drain system (**500**). The drain system may either be a closed loop drain system that comprises a container into which the exudates are drained, or an open loop drain system, in which the fluids are drained onto a dressing of some kind. The method may further comprise the steps of processing signals generated by the sensor (**510**), transmitting the processed signals to a notification system (**520**), and receiving the processed signals by the notification system (**530**). In some embodiments, transmission of the processed signals may be done wirelessly. In some embodiments, the notification system may be similar to notification system **109** (**FIG. 4**). In some embodiments, the system may further comprise the step of analyzing the processed signals by comparing the signals to a threshold (**540**). The threshold may either be a predetermined threshold or an adjustable threshold that may be constantly changed based on the trend of sensed parameters related to the infection biomarkers. According to some embodiments, the method may further comprise the step of determining the presence of infection (**550**). In some embodiments, the method may further comprise a step of determining the stage of infection and not only determining presence of an infection, e.g., whether the stage of the infection is mild, progressive or severe, though other stages may be defined by the user or operator of the system, e.g., system **200**.

[00107] In some embodiments, the step of sensing presence of infection biomarkers is carried out continuously. In other embodiments, the step of sensing presence of infection biomarkers is carried out periodically. In some embodiments, periodical sensing may be adjusted per type of biomarker. For example, if the biomarker is pH, then sensing may be done in periods of less than 1 minute, and if the biomarker is bacteria specie, the sensing may be done every 10 minutes or less.

[00108] Reference is now made to **FIG. 6**, which is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with another

embodiment of the invention. According to some embodiments, a method for determining presence of an infection at a surgical site, following surgery of a patient, may comprise the following steps: sensing presence of at least one infection biomarker by using a sensor incorporated in a drain system (600), processing signals generated by the sensor (610), transmitting the processed signals to a notification system (620), and receiving the processed signals by the notification system (630). According to some embodiments, the method may further comprise the steps of selecting a threshold based on changing levels of biomarkers along time (640). The method may further comprise the step of analyzing the processed signals by comparing the signals to the threshold (650). In some embodiments, the threshold may be a predetermined threshold or may be an adjustable threshold that may be changed by the notification system according to the increase or decrease of the trend of the sensed parameters related to an infection biomarker or to a plurality of infection biomarkers, over time.

[00109] According to some embodiments, the method may further comprise the steps of determining the presence of infection (660), and generating an indication on presence of infection (670). In some embodiments, the method may comprise the step of generating an indication of the stage of infection, e.g., mild, progressive or severe, though other stages may be chosen, thus defining the corresponding level of the threshold.

[00110] In some embodiments, the step of sensing presence of infection biomarkers is carried out continuously. In other embodiments, the step of sensing presence of infection biomarkers is carried out periodically. In some embodiments, periodical sensing may be adjusted per type of biomarker. For example, if the biomarker is pH, then sensing may be done in periods of less than 1 minute, and if the biomarker is bacteria specie, the sensing may be done every 10 minutes or less.

[00111] Reference is now made to **FIG. 7**, which is a flow chart depicting a method for determining early signs of post-surgery infection in a patient, in accordance with yet another embodiment of the invention. According to some embodiments, when infection biomarkers cannot be sensed continuously along the tube, a method for determining early signs of post-surgery infection in a patient may comprise the steps of: measuring presence of at least one infection biomarker by using a point of care (POC) analyzer for examining samples collected in a



drain system (700), processing signals generated by the POC analyzer (710), transmitting the processed signals to a notification system (720), and receiving the processed signals by the notification system (730). According to some embodiments, the method may further comprise the steps of selecting a threshold value (740) and analyzing the processed signals by comparing the signals to the threshold value (750). In some embodiments, the threshold may be a predetermined threshold or may be an adjustable threshold that may be changed by the notification system according to the increase or decrease of the trend of the sensed parameters related to an infection biomarker or to a plurality of infection biomarkers, over time.

[00112] According to some embodiments, the method may further comprise the step of determining the presence of infection (760). In some embodiments, the method may further comprise the step of generating an indication on presence of infection (770). In some embodiments, the method may comprise the step of generating an indication of the stage of infection, e.g., mild, progressive or severe, though other stages may be chosen, thus defining the corresponding level of the threshold.

[00113] In some embodiments, the POC analyzer may be incorporated in the drain system, while in other embodiments the POC analyzer may be located externally to the drain system while samples that are collected in a semi-continuously manner by the drain system may enter the POC analyzer, e.g., the POC analyzer may be fed with the samples collected by the drain system either manually, semi-automatically or fully-automatically.

[00114] It will be appreciated that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention is defined only by the claims which follow.

## CLAIMS

1. A system for detecting early signs of post-surgery infection in a patient, said system comprising:
  - a drain system comprising a tube configured to drain fluids from a surgery site;
  - at least one sensor unit for sensing the presence of at least one infection biomarker;
  - a processor for processing a signal generated by said at least one sensor unit;
  - a transmitter for transmitting the signal; and
  - a notification system for receiving the signal, analyzing the signal by comparing it to a threshold, determining presence of infection, and generating an indication on the presence of infection.
2. The system according to claim 1, wherein said drain system further comprises a container into which the fluids passing through the tube are drained.
3. The system according to claim 1 or claim 2, wherein said at least one infection biomarker is selected from the group consisting of: pH, lactic acid, flow rate of exudate, immune-modulating mediators, pancreas enzymes, inflammatory parameters, and metabolic parameters, or a combination thereof.
4. The system according to claim 3, wherein said at least one infection biomarker is a bacteria species selected from the group consisting of: *Escherichia coli*, *Pseudomonas* spp., *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., *Enterococcus* spp., *Klebsellia* spp., *Proteus* spp., *Serratia* spp., *Morganella* spp. and other Enterobacteriaceae, or a combination thereof.
5. The system according to any one of claims 1 to 4, wherein said system comprises a first sensor for sensing an infection biomarker selected from the group consisting of: pH, lactic acid, flow rate of exudate, immune-modulating mediators, pancreas enzymes, inflammatory parameters, and metabolic parameters, or a combination thereof, and a second sensor for sensing an infection biomarker selected from the group consisting of: *Escherichia coli*, *Pseudomonas* spp., *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., *Enterococcus* spp., *Klebsellia* spp., *Proteus* spp., *Serratia* spp., *Morganella* spp. and other Enterobacteriaceae, or a combination thereof.
6. The system according to claim 5, wherein said notification system comprises an analyzer for analyzing signals detected by said first and second sensors and determining the presence of infection.

7. The system according to any one of claims 1 to 6, wherein said notification system comprises an analyzer for analyzing the processed signal and determining the presence of infection.
8. The system according to claim 7, wherein said analyzer further determines the stage of infection.
9. The system according to claim 8, wherein when said infection biomarker is pH; a first indication is generated if the level of pH is equal to or below 7.1, and a second indication is generated if the level of pH is equal to or below 6.8.
10. The system according to claim 8, wherein when said infection biomarker is lactic acid; a first indication is generated if the mean increase rate of concentration of lactic acid is above a threshold of 0.1 [mM/hr] for longer than 1 hour post-surgery, a second indication is generated if the mean increase rate is above the threshold for longer than 3 hours post-surgery, and a third indication is generated if the mean increase rate is above the threshold for longer than 6 hours post-surgery.
11. The system according to claim 8, wherein when said infection biomarker is a flow rate of exudate; a first indication is generated 6 hours post-surgery if the flow rate is above 5[ml/hr], a second indication is generated 6 hours post-surgery if the flow rate is above 10[ml/hr], and a third indication is generated 6 hours post-surgery if the flow rate is above 20[ml/hr].
12. The system according to claim 8, wherein when said infection biomarker is a bacteria species; a first indication is generated if Colony Forming Units (CFU) is above  $10^2$  [CFU/ml], a second indication is generated if CFU is above  $10^3$  [CFU/ml], and a third indication is generated if CFU is above  $10^4$  [CFU/ml].
13. The system according to any one of claims 1 to 12, wherein said transmitter wirelessly transmits the processed signals to the notification system.
14. The system according to any one of claims 1 to 13, wherein said indication is displayed on a display unit.
15. The system according to any one of claims 1 to 14, wherein said sensor is located along the tube.
16. The system according to any one of claims 2-15, wherein said sensor is located within the container.
17. The system according to any one of claims 1 to 16, wherein said sensor senses the presence of infection biomarkers continuously.

18. The system according to any one of claims 1 to 16, wherein said sensor senses the presence of infection biomarkers periodically.
19. A method for determining early signs of post-surgery infection in a patient, said method comprising:
  - sensing presence of at least one infection biomarker by using a sensor incorporated in a drain system;
  - processing signals generated by the sensor;
  - transmitting the signals to a notification system;
  - receiving the signals by the notification system;
  - analyzing the signals by comparing the signals to a threshold; and
  - determining the presence of infection.
20. The method according to claim 19, wherein said method further comprises the step of generating an indication on presence of infection.
21. The method according to claim 19 or 20, wherein said step of sensing presence of infection biomarkers is carried out continuously.
22. The method according to claim 19 or 20, wherein said step of sensing presence of infection biomarkers is carried out periodically.
23. The method according to any one of claims 19 to 22, further comprising the step of selecting the threshold, which the signals are compared to, based on the changing levels of biomarkers over time, prior to the step of analyzing the signals.

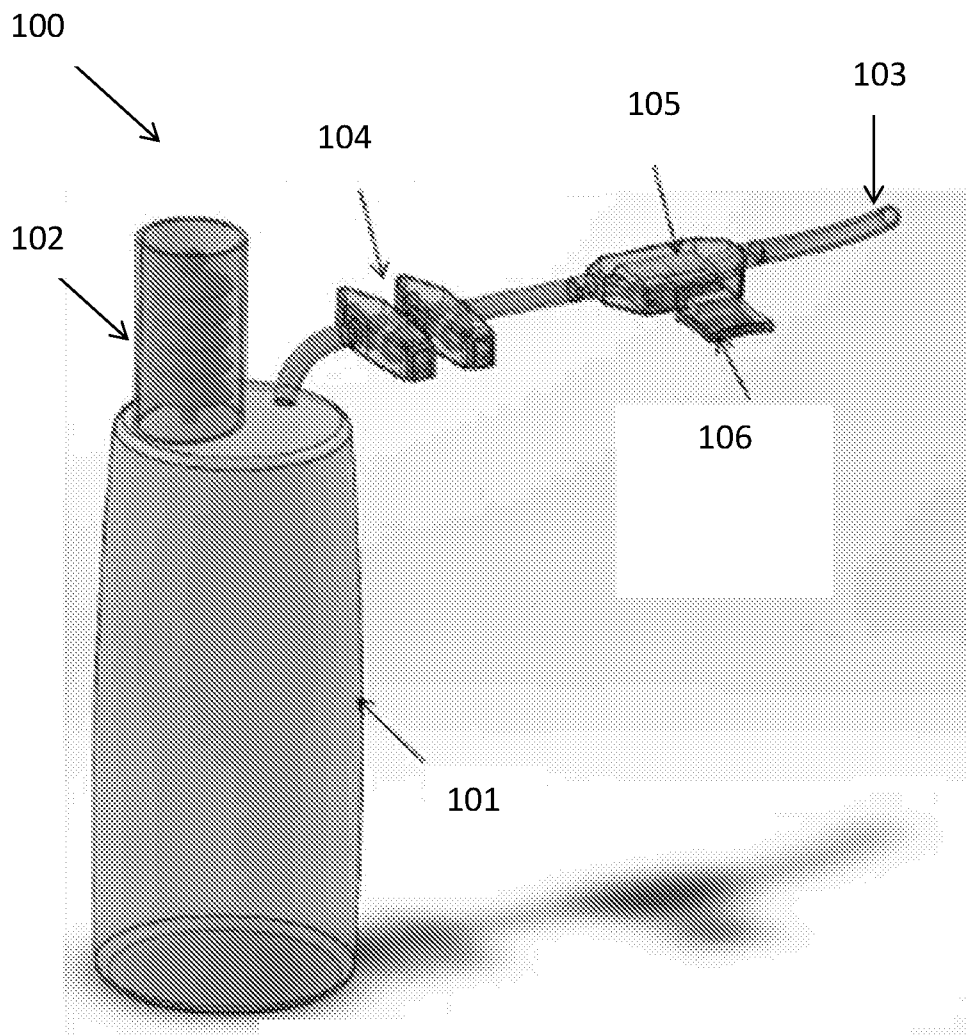


FIG. 1

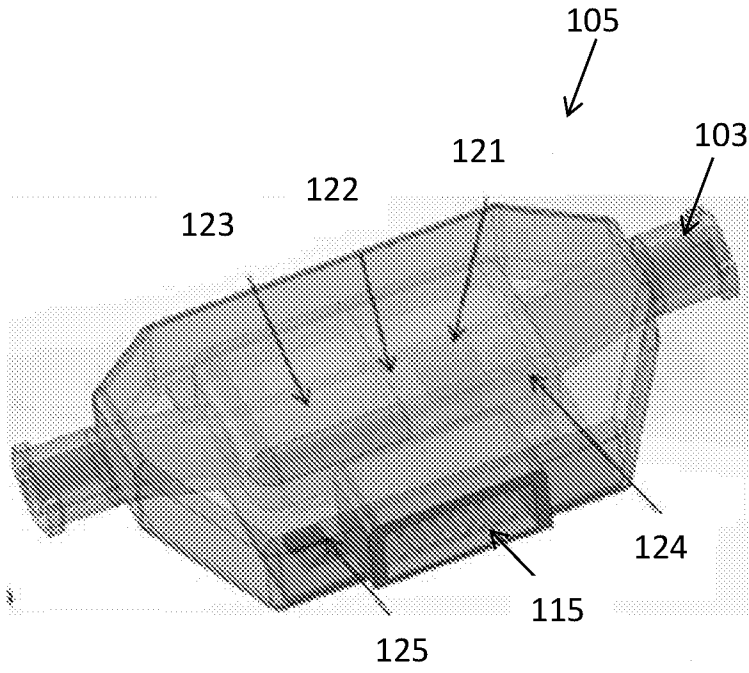


FIG. 2

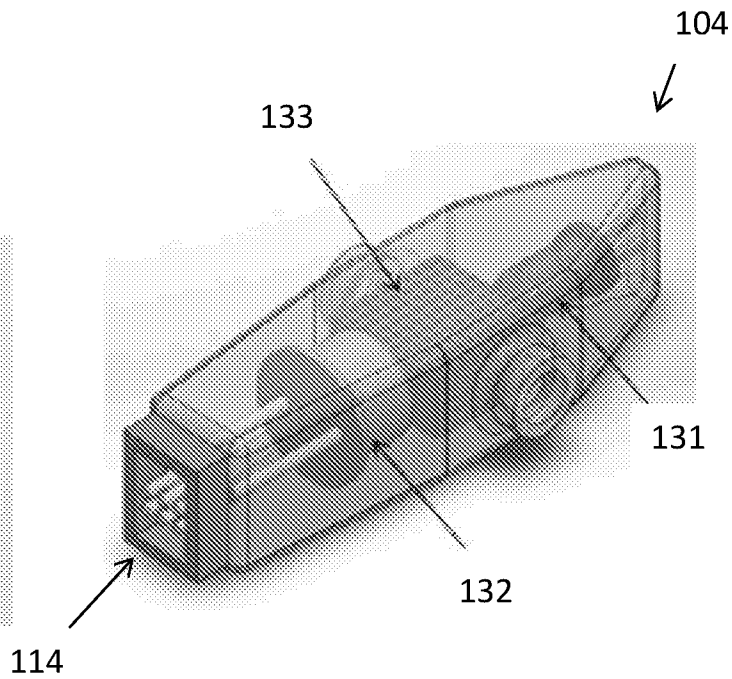


FIG. 3

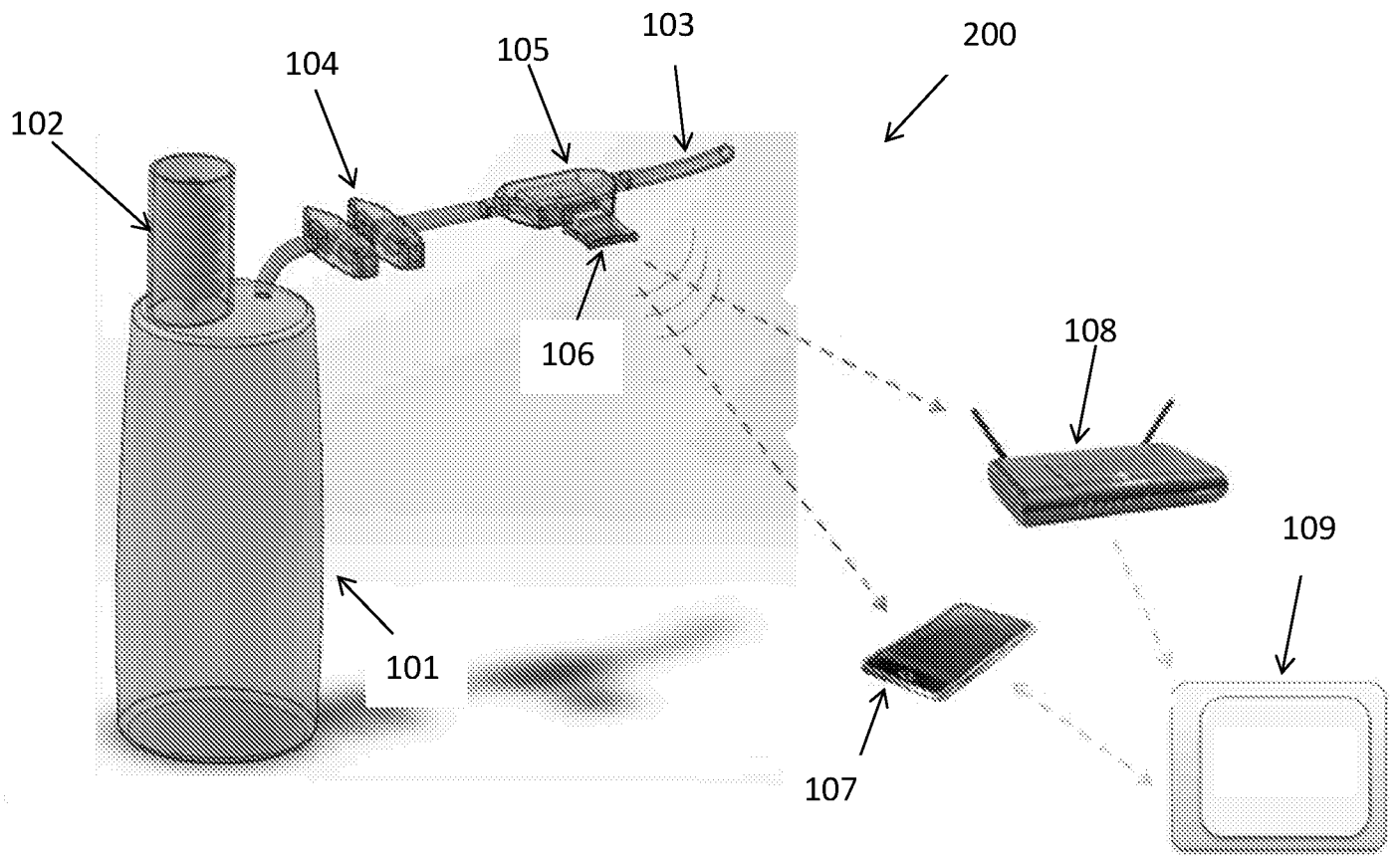


FIG. 4

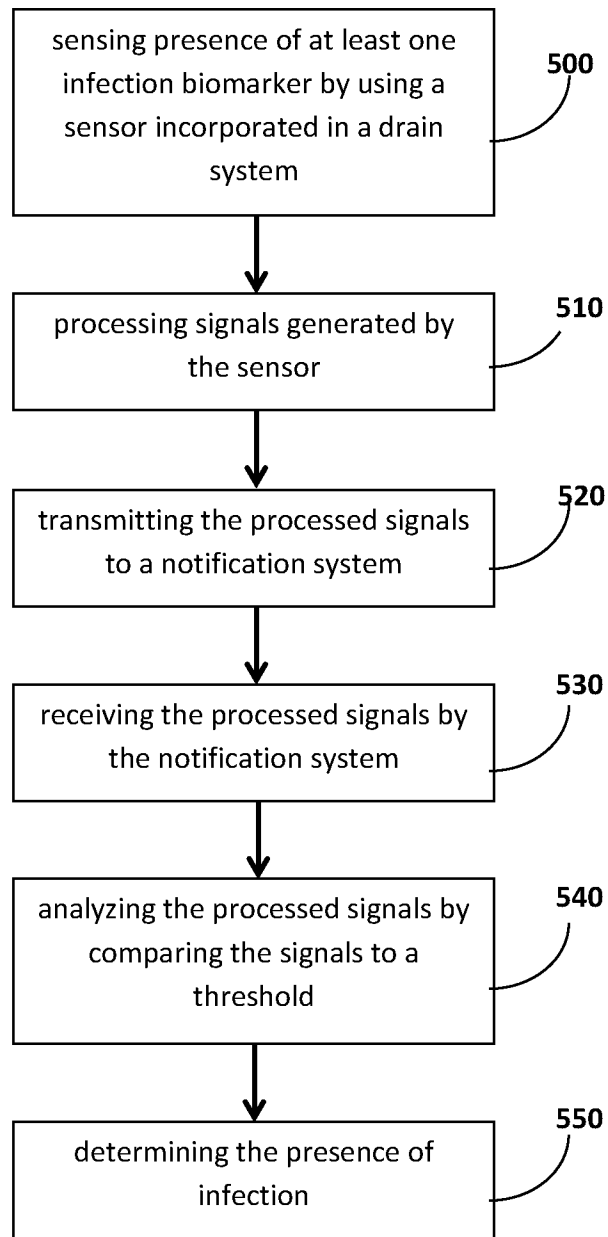


FIG. 5



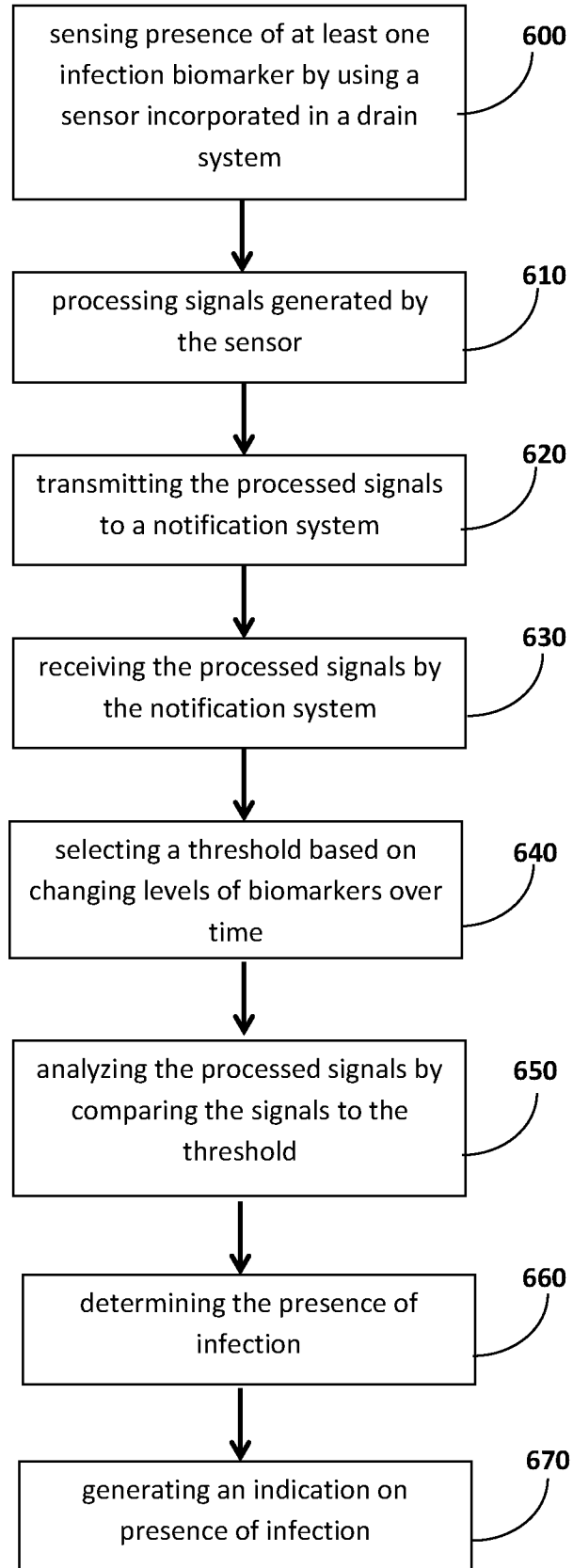


FIG. 6

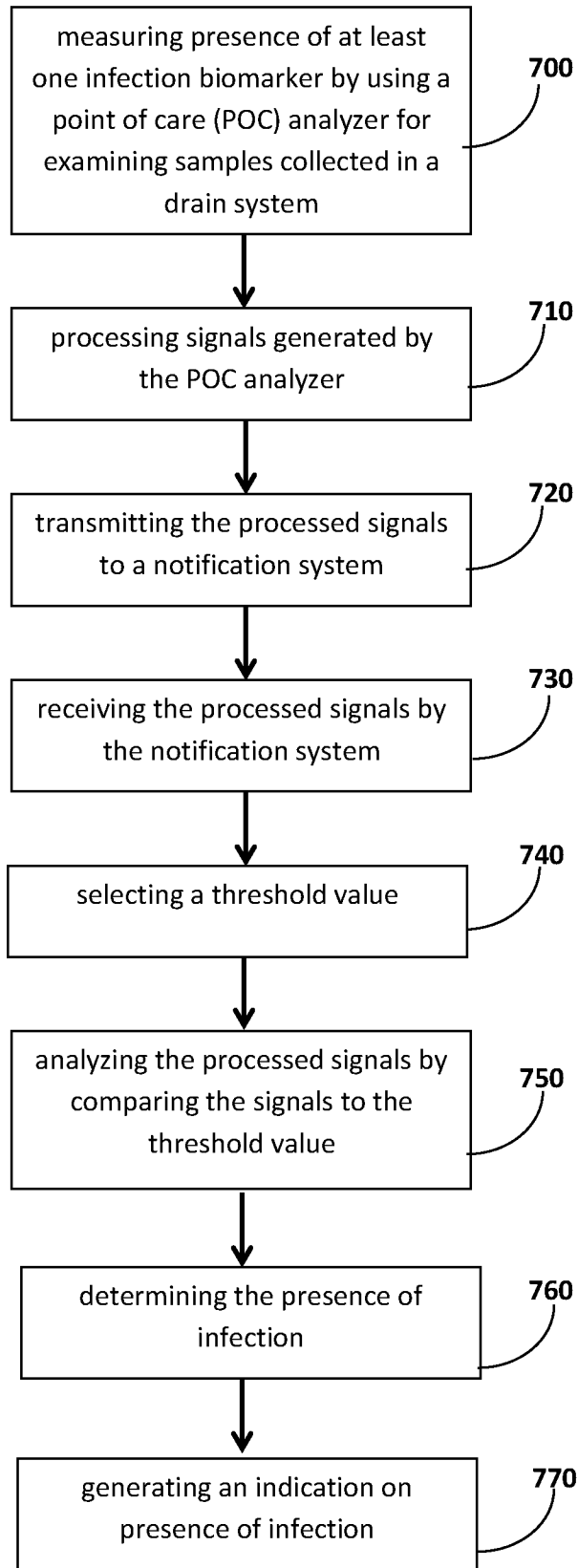


FIG. 7

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/IB2015/001971

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61B5/00  
 ADD. A61B5/145            A61M1/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 A61B A61M

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/043650 A2 (THERANOVA LLC [US]) 20 March 2014 (2014-03-20) abstract; figures 1,2 paragraphs [0014], [0061] - [0066], [0102] - [0103] the whole document -----	1-18
X	US 2009/155770 A1 (BROWN TAMEKA [US] ET AL) 18 June 2009 (2009-06-18) abstract; figures 1,8 paragraphs [0001], [0023] - [0024], [0029], [0030], [0045] - [0048] paragraphs [0051], [0053], [0056], [0058], [0060] the whole document ----- -/--	1-18

Further documents are listed in the continuation of Box C.                       See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search  25 January 2016	Date of mailing of the international search report  08/02/2016
--	--

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Furlan, Stéphane
--	--

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2015/001971

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/262322 A1 (GERBER MARTIN T [US] ET AL) 23 October 2008 (2008-10-23) abstract; figures 1,5A,7,8A-8C paragraphs [0002], [0030] - [0039], [0042], [0044], [0050] the whole document -----	1,3-18
A	US 2008/064980 A1 (LEE KENT [US] ET AL) 13 March 2008 (2008-03-13) paragraphs [0005], [0047] - [0052] -----	1-18
A	CHALUPA P ET AL: "Evaluation of potential biomarkers for the discrimination of bacterial and viral infections", INFECTION ; A JOURNAL OF INFECTIOUS DISEASE, URBAN & VOGEL, MU, vol. 39, no. 5, 1 July 2011 (2011-07-01), pages 411-417, XP019966308, ISSN: 1439-0973, DOI: 10.1007/S15010-011-0126-4 the whole document -----	1-18
A	US 2008/269582 A1 (MANSOUR HEBAH NOSHY [US] ET AL) 30 October 2008 (2008-10-30) abstract paragraphs [0002], [0014] - [0016], [0030] - [0031], [0036]; claims 19,20 the whole document -----	1-18

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2015/001971

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 19-23  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claims 19-23 define a diagnostic method practised on the human or animal body in the meaning of Rule 39.1(iv) PCT. Therefore, according to Article 17(2)(a)(i) PCT no written opinion regarding novelty, inventive step or industrial applicability is given for these claims.
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/IB2015/001971
---

Patent document cited in search report	Publication date	Publication date	Patent family member(s)	Publication date
WO 2014043650	A2	20-03-2014	NONE	
US 2009155770	A1	18-06-2009	US 2009155770 A1	18-06-2009
			WO 2009074890 A2	18-06-2009
US 2008262322	A1	23-10-2008	US 2008262322 A1	23-10-2008
			US 2008262332 A1	23-10-2008
			US 2008262380 A1	23-10-2008
			WO 2008130406 A1	30-10-2008
			WO 2008130407 A1	30-10-2008
US 2008064980	A1	13-03-2008	NONE	
US 2008269582	A1	30-10-2008	NONE	