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DESCRIPTION

Field of the invention

[0001] The present invention relates to a novel sensor device for tracking position and process parameters in a container (e.g. a bioreactor).

Background of the invention

[0002] The acquisition of process parameters in large-scale vessels, such as large tanks, reactors, fermenters and bioreactors, is of great interest for the investigation and optimization of industrial processes. This is especially the case for bioreactors, where several process parameters, such as the temperature profile, distribution of pH, oxygen levels, growth rate of the biomass, gas-liquid fraction in the substrates as well as flow characteristics, such as velocity profiles, dead zone locations are of interest to operators.

[0003] Measurements of few basic physical parameters, such as temperature and local velocities, allows to draw conclusions regarding the efficiency of the mixing and heating regimes, but the acquisition of spatial parameter distributions in larger vessels is quite difficult. Moreover, the measurement and monitoring of significant parameters in reactor vessels is hampered by limited access to the process itself, because sensor mounting or cable connections are not feasible or desired. Thus, due to the large dimensions of many industrial vessels, the acquired data may not be fully representative of the whole volume.

[0004] The last years remote sensing and autonomous sensor concepts have gained increasing attention. For example, the article by Thiele et al 2010 describes a neutrally buoyant self-powered sensor particle for the measurement of process parameters including temperature, absolute pressure (i.e. immersion depth) and acceleration data.

In the Thiele article is determined the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the container based the sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container.

In the Thiele article is also determined one horizontal position of the sensor device in the liquid medium of the container based the sampled accelerometer data, wherein a characteristic acceleration profile is derived from the sensor device contacting the impeller/agitator. Further, the article by Reinecke et al., describes a particle sensor where the position determination is based on an electrical resistance tomography system (ERT) that was applied onto the bioreactor. Such a system is based on conductivity measurements and only allows for observation of the particle from the outside. Thus, in the article by Reinecke et al the detection of the particle is not based on acceleration, but were calculated from the temporal difference between the drops of the fluctuating conductivity signals from the ERT measurements.

Summary of the invention

[0005] The problem to be solved by the present invention is to provide an improved sensor device for tracking process parameters (e.g. pH, temperature, etc.) in a container (e.g. bioreactors).

[0006] The solution is based on the finding by the present inventors that in a container (e.g. a bioreactor) comprising a liquid medium, a wall and an agitator (e.g. an impeller) it is possible to significantly improve in particular the precision in the determination of the horizontal position of the sensor device within the container based on the finding that it is possible to differentiate the acceleration profile derived from when the sensor device contacts the wall of the container from the acceleration profile derived from when the sensor device contacts the agitator.

Based on this finding, it is then possible to make a software algorithm capable of identifying this acceleration difference and thereby determining when the device contacts the agitator or contacts the wall of the container and thereby obtaining the position of the sensor device nearby the agitator or nearby the wall.

[0007] Accordingly, with respect to horizontal position the sensor device as described herein is capable of determining two different horizontal positions of the sensor device in the liquid medium of the container - i.e. when it contacts the wall and when it contacts the agitator. As discussed above, the sensor of the Thiele et al article only determines one horizontal position of the sensor device in the liquid medium of the container.

[0008] As discussed herein, the fact that the sensor device as described herein is capable of determining two different horizontal positions (i.e. when it contacts the wall and when it contacts the agitator) is a significant advantage in general.

For instance, in relation to a preferred embodiment herein where the sensor device also comprises a gyroscope sampling data about angular velocity one may get a significant improved determination in the precision of the position, orientation, and velocity (direction and speed of movement) of the moving sensor device within the liquid media, since one has two well defined previously determined positions (i.e. when contacting the wall or agitator) to use in a process of calculating the sensor device current position by using a previously determined position and the previously determined position is when the device contacts the agitator and when the device contacts the wall of the container.

[0009] In working example herein is shown an example of a sensor device of the present invention a process of calculating its position during different time periods of a fermentations reaction in a bioreactor container and measuring relevant fermentation reactions parameters such as temperature and pH levels.

[0010] Accordingly, a first aspect of the present invention relates to a sensor device comprising a house (10), wherein the house (10) comprises:

1. (a) a position determination unit (1) comprising an accelerometer and a pressure sensor,
2. (b) a microcontroller unit (3) comprising a software algorithm configured for determining position of the sensor device,
3. (c) a power management unit (5),
4. (d) a process parameter sensor (2), and
5. (e) a communication unit (4) adapted for communicating with a user interface; and

wherein the software algorithm in (b) can determine the position of the sensor device in a container comprising a liquid medium, a wall and an agitator wherein the algorithm is an algorithm comprising the following steps:

(i) sampling data about pressure and acceleration from the position determination unit (1) of item (a); and

(iia) determining the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the container based on the in step (i) sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container; and

(iib): determining horizontal position of the sensor device in the liquid medium of the container based on the in step (i) sampled accelerometer data, wherein a first acceleration profile is derived from the sensor device contacting the agitator and a second acceleration profile is derived from the sensor device contacting the wall of the container and wherein the first and second acceleration profiles are different and the algorithm is capable of identifying this difference and thereby determining when the device contacts the agitator or contacts the wall of the container.

[0011] An example of a sensor device is shown in figure 1 - the non-limiting numbering in the first aspect refers to this figure 1.

[0012] The term "agitator" is well known in the art and is understood by the skilled person in the present context to relate to a rotating component that move liquid medium by rotation. As known in the art - an example of a suitable agitator is an impeller.

[0013] The actual mathematics (e.g. integration based mathematics) and specific software language used for making a software algorithm of the first aspect may be seen as based on standard well known mathematics and software language - i.e. based on the teaching herein and the common general knowledge of the skilled person, it is routine work for the skilled person to make a software algorithm of the first aspect of the present invention.

[0014] A second aspect of the invention relates to use of the sensor device of first aspect and relevant embodiments thereof for measuring position and process parameters in a container

comprising a liquid medium, a wall and an agitator.

[0015] A third aspect of the invention relates to a method for determining the position of the sensor device of the first aspect and any relevant embodiments thereof in a container comprising a liquid medium, a wall and an agitator comprising the steps of:

(i) sampling data about pressure and acceleration from the position determination unit (1) of item (a); and

(iia) determining the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the container based on the in step (i) sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container; and

(iib): determining horizontal position of the sensor device in the liquid medium of the container based on the in step (i) sampled accelerometer data, wherein a first acceleration profile is derived from the sensor device contacting the agitator and a second acceleration profile is derived from the sensor device contacting the wall of the container and wherein the first and second acceleration profiles are different and the algorithm is capable of identifying this difference and thereby determining when the device contacts the agitator or contacts the wall of the container.

[0016] Embodiments of the present invention are described below, by way of examples only.

Drawing description

[0017]

Figure 1: An example of a sensor device of the present invention. In Figure 1a is shown an example of a sensor device in a two-part form - this sensor was used in Example 2 herein. In Figure 1b is shown a block diagram of the sensor device's electronics.

Figure 2: An example of a sensor device sampling process parameters in a bioreactor.

Figure 3: An example of a measured impact profile - see working Example 2 herein for further details.

Figure 4: Comparison of theoretically determined impact and experimentally determined impact - see working Example 2 herein for further details. □: Theoretically determined wall impact. ○: Theoretically determined impeller impact. ■: Experimentally determined wall impact. ●: Experimentally determined impeller impact. Impacts outside the gray lines are a result of momentary pressure increases caused by impacts.

Detailed description of the invention**Sensor device:**

[0018] The overall design of the sensor device is based on a house (10), wherein the house (10) comprises:

1. (a) a position determination unit (1) comprising an accelerometer and a pressure sensor,
2. (b) a microcontroller unit (3) comprising a software algorithm configured for determining position of the sensor device,
3. (c) a power management unit (5),
4. (d) a process parameter sensor (2), and
5. (e) a communication unit (4) adapted for communicating with a user interface;

[0019] An example of a sensor device is shown in figure 1.

[0020] Preferably, the weight of the sensor device is from 1 mg to 1 kg, such as from 1 g to 500 g or such as from 2 g to 250 g.

If the sensor device is shaped as a sphere - the size of the sensor device is a size with a diameter from 0,1 mm to 200 cm, such as a diameter from 1 mm to 100 cm or such as a diameter from 1 cm to 20 cm.

House (10)

[0021] The sensor device comprises a preferably rigid and stable, non-deformable house part that may be constructed from a bio compatible product including metal, wood, bamboo and plastic such as organic thermoplastic polymer plastic including polyether ether ketone (PEEK) and polyaryl ether ketone (PAEK). The house (10) may have one or more openings to the exterior thereby allowing the process parameter sensors (2) to obtain process data from the outside environment. In one embodiment, the sensor device is made of a bio compatible product including metal, wood, bamboo and plastic such as organic thermoplastic polymer plastic including polyether ether ketone (PEEK) and polyaryl ether ketone (PAEK).

[0022] The house (10) may be constructed as a two-part shell that can be opened and closed for adapting the type of process parameter sensors (2), the communication unit (4), power management unit (5) or other relevant components of the sensor device. It may however, also be constructed as a one piece closed body intended for single use usage. Thus, in one

embodiment, the house (10) is on 2-part form. In another embodiment, the house (10) is molded as one.

[0023] The house (10) is normally constructed to be water and air tight for protecting the inside electronics from water and gasses. In one embodiment, the sensor device is water tight. In another embodiment, the sensor device is air tight.

[0024] The house (10) may be adapted to be neutrally buoyant, positively buoyant or negatively buoyant depending on the use of the sensor device. It may also be constructed to be a self-buoyant meaning that it is able to adjust its buoyancy to the depth of interest. In one embodiment, the sensor device is neutrally buoyant, positively buoyant or negatively buoyant. In a preferred embodiment, the sensor device is self-buoyant.

[0025] The house (10) holds the all the necessary elements required for the sensor device to operate and collect the relevant process parameters. Such elements include but are not limited to

a position determination unit (1), a microcontroller unit (3), a power management unit (5), a process parameter sensor (2), a communication unit (4). In one embodiment, the house (10) further comprises a data storage unit.

Position determination unit (1)

[0026] The position determination unit (1) comprises an accelerometer and a pressure sensor.

[0027] Examples of herein suitable pressure sensors are well known in the art and the skilled person knows how to select a suitable pressure sensor.

[0028] The pressure sensor may be of the type selected from the group consisting of a strain gauge pressure sensor, capacitance pressure transducer, piezoelectric pressure transducer, piezoresistive strain gauge sensor, piezoelectric sensor and piezo resistive bridge sensor. The pressure sensors may be housed in a shell allowing its application to aggressive media. The shell may be constructed from materials including stainless steel, plastic. In one embodiment, the pressure sensor is selected from the group consisting of a strain gauge pressure sensor, a capacitance pressure transducer, a piezoelectric pressure transducer, a piezoresistive strain gauge sensor, a piezoelectric sensor and a piezo resistive bridge sensor. In another embodiment, the pressure sensor detects depth.

[0029] Examples of herein suitable accelerometers are well known in the art and the skilled person knows how to select a suitable accelerometer.

[0030] Modern commercial accelerometers are often small micro electro-mechanical systems (MEMS) that include an acceleration sensor and an angular velocity sensor (i.e. a gyroscope).

[0031] In a preferred embodiment, the position determination unit (1) of item (a) further comprises a gyroscope and the software algorithm comprises further following step:

(iii) sampling data about angular velocity from the gyroscope in the position determination unit (1) of item (a).

[0032] Preferably, gyroscope is an inertial gyroscope, such as a MEMS gyroscope.

[0033] In order to further refine the positioning of the sensor device - the position determination unit (1) may further comprise e.g. a microphone, a magnetometer or a capacitive sensor.

[0034] The position determination unit (1) may further comprise a tilt sensor, an inclinometer or other devices including piezoelectric, piezoresistive, capacitive sensor, or micro electromechanical systems components.

[0035] Sensors with digital output are convenient when the data must be transmitted without further noise degradation.

All MEMS gyroscopes take advantage of the Coriolis effect. The motion sensor may sense motion along one axis of motion or multiple axes of motion, such as the three orthogonal axes X, Y, and Z. The output can be analog, digital or ratiometric to the supply voltage, or any of various types of pulse modulation. The rate at which the motion sensor communicates and/or stores motion data may vary from approximately 1 hertz (Hz) to approximately 1 kHz. However, any rate may be employed. In one embodiment, the accelerometer is selected from an inertial sensor, such as a MEMS inertial sensor.

Microcontroller unit (3)

[0036] Examples of herein suitable microcontroller unit (3) are well known in the art and the skilled person knows how to select a suitable microcontroller unit (3).

[0037] Preferably, the microcontroller unit (MCU) acts as a small computer on a single integrated circuit or on a few single integrated circuits. The microcontroller unit (3) may comprise a general purpose programmable processor or controller for executing application programming or instructions related to the device. Furthermore, it can perform operations for configuring and transmitting information as described herein. The microcontroller unit (3) may have one or more central processing units (CPUs) or microprocessors along with RAM for data and calculation, a ROM for boot, memory for program storage and programmable input/output peripherals. As examples, the memory/storage may comprise a computer-readable device, RAM, ROM, DRAM, SDRAM, and/or other storage device(s) and media. The CPU controls the program execution and numerous peripherals for communication with onboard sensors. The software algorithm is part of the program and preferably resides in the memory. The timers are used for timing external event, generating event on periodic basis and for generation of pulse-width modulation (PWM) signals. By way of example, the MCU may comprise a specially

configured Application Specific Integrated Circuit (ASIC) or other integrated circuit, a digital signal processor, a controller, a hardwired electronic or logic circuit, a programmable logic device or gate array, a special purpose computer, or the like. In one embodiment, the microcontroller unit (MCU) comprises a microprocessor as means for data processing.

Power management unit (5)

[0038] Examples of herein suitable power management units (5) are well known in the art and the skilled person knows how to select a suitable power management unit (5).

[0039] The sensor device can be reliant on different power consumption depending on the overall state of the system. The different units of sensor device can be powered down individually in order to save power. The power management unit (5) may be any type of unit capable of storing power over a period of time, such as a rechargeable battery (e.g., Nickel Cadmium or "NiCd", Nickel Metal Hydride or "NiMH", Lithium Ion or "Li Ion", Sealed Lead Acid or "SLA"), a capacitor, a potential-energy-based power storage unit, a chemical-energy-based power storage unit, a kinetic-energy-based power storage unit, or some combination thereof. Reference to the "battery" of the sensor device herein should be understood to refer to any of these types of power storage units. The power management unit (5) may also include embedded sensors and/or processors. For example, some rechargeable batteries (e.g., most modern lithium-ion rechargeable batteries) include sensors and processors that, working together, limit or otherwise control discharging and recharging of the rechargeable battery in ways that help preserve or increase the battery's lifespan, or that help prevent potentially dangerous conditions from forming while the rechargeable battery is discharging or recharging. In one embodiment, the sensor device comprises a power management unit (5). In another embodiment power management unit (5) comprises a battery such as a rechargeable battery.

Process parameter sensor (2)

[0040] Examples of herein suitable process parameter sensors (2) are well known in the art and the skilled person knows how to select a suitable process parameter sensor (2) in relation to process parameters of interest (e.g. pH, temperature, level of Oxygen etc.).

[0041] The skilled person knows which sensors that may be suitably for monitoring different process parameters in e.g. large vessels during for example fermentation processes or e.g. water purification.

[0042] In a preferred embodiment, the process parameter sensor (2) is a sensor that can measure at least one parameter from the group of parameters consisting of: temperature, salts, oxygen, carbon dioxide, a gas, pH, amount of media components such as sugars (e.g. glucose), amino acid and metabolites (e.g. lactate, acetate, ethanol).

[0043] Preferably, the process parameter sensor (2) is a sensor that can measure at least one parameter from the group of parameters consisting of: temperature, oxygen and pH.

[0044] Preferably, the parameter sensor (2) can measure at least two parameter - such as e.g. temperature and pH.

[0045] Other important process parameters could be cell size, cell numbers and cell aggregation. Examples of different sensor that may be used for measuring such process parameters include light sensor, fluorescence sensors, conductivity sensors, optical sensors, temperature sensors, pressure sensors, pH sensors, turbidity sensors, oxygen sensors, carbon dioxide sensors, linear sensor arrays, phased sensor arrays, as well as any other appropriate type and/or arrangement of sensors. Moreover, sensors could also be in the form of cameras and light scatter apparatus. In one embodiment, the process parameter sensor (2) comprises one or more sensors selected from the group consisting of a pH sensor, an oxygen sensor, a refractive index sensor, a cell density sensor, and a temperature sensor.

Communication unit (4)

[0046] Examples of herein suitable communication units (4) are well known in the art and the skilled person knows how to select a suitable communication unit (4).

[0047] The communication unit (4) is adapted for communicating with a user interface - as understood by the skilled person this is necessary for that the measured process parameters can be received to a user interface (e.g. a computer or screen placed outside the container comprising a liquid medium (e.g. a bioreactor with fermentation liquid medium).

[0048] The communication unit (4) may include a transmitter and receiver which can transmit and receive signals respectively, to and from other wireless devices. It also contains one more antennas for use in wireless communications such as multi-input multi-output (MIMO) communications, Bluetooth®, etc. The antennas can include, but are not limited to directional antennas, omnidirectional antennas, monopoles, patch antennas, loop antennas, microstrip antennas, dipoles, and any other antenna(s) suitable for communication transmission/reception.

[0049] The communication unit (4) may also optionally contain a security module. This security module can contain information regarding but not limited to, security parameters required to connect the device to an access point or other device or other available network(s), and can include WEP or WPA security access keys, network keys, etc. The WEP security access key is a security password used by Wi-Fi networks. Knowledge of this code will enable a wireless device to exchange information with the access point. The information exchange can occur through encoded messages with the WEP access code often being chosen by the network administrator. WPA is an added security standard that is also used in conjunction with network

connectivity with stronger encryption than WEP. In one embodiment the communication is wireless. In another embodiment, the position determination unit (1), the microcontroller unit (3), the power management unit (5), the process parameter sensor (2), and the communication unit (4) are assembled on one printed circuit board (PCB).

Software algorithm as such

[0050] The actual mathematics (e.g. integration based mathematics) and specific software language used for making a software algorithm of the first aspect may be seen as based on standard well known mathematics and software language - i.e. based on the teaching herein and the common general knowledge of the skilled person, it is routine work for the skilled person to make a software algorithm of the first aspect of the present invention.

[0051] In working example herein is provided a discussion of examples of suitable preferred relevant actual mathematics (e.g. integration based mathematics) and specific software language used for making a software algorithm as described herein.

Software algorithm - step (i) sampling data from the position determination unit (1)

[0052] This may be done according to the art - the skilled person knows how to sample data about a parameter of interest - such as e.g. pressure and/or acceleration obtained from the used sensors of the position determination unit (1).

Software algorithm - step (iia) determining the immersion depth and vertical position

[0053] As discussed above - step (iia) of the first aspect relates to determining the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the container based on the in step (i) sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container.

[0054] This may be done according to the art - e.g. as discussed in above discussed article by Thiele et al 2010.

Software algorithm - step (iib) determining the horizontal position

[0055] As discussed above - step (iib) of the first aspect relates to determining horizontal position of the sensor device in the liquid medium of the container based on the in step (i) sampled accelerometer data, wherein a first acceleration profile is derived from the sensor

device contacting the agitator and a second acceleration profile is derived from the sensor device contacting the wall of the container and wherein the first and seconds acceleration profiles are different and the algorithm is capable of identifying this difference and thereby determining when the device contacts the agitator or contacts the wall of the container.

[0056] As discussed above, this is a novel essential step of the present invention.

In essence, the present inventors identified that the difference in the first (agitator) acceleration profile and the second (wall) acceleration profile is big enough in order to be measured properly (e.g. in bioreactor) and thereby be used to differentiate between contact/impact of the sensor device and the wall or the agitator by use a of suitable software algorithm.

Software algorithm - sensor device with gyroscope

[0057] In a preferred embodiment, the sensor device of first aspect is a sensor device, wherein the position determination unit (1) of item (a) further comprises a gyroscope and the software algorithm comprises further following step:

(iii) sampling data about angular velocity from the gyroscope in the position determination unit (1) of item (a); and

(iv): determining position of the sensor device via the microcontroller unit (3) of item (b) of the first aspect, wherein the in step (i) of the first aspect sampled accelerometer data and the in step (iii) sampled gyroscope data continuously calculate the position, orientation, and velocity (direction and speed of movement) of the moving sensor device within the liquid media of the container by a process of calculating the sensor device current position by using a previously determined position and the previously determined position is when the device contacts the agitator and when the device contacts the wall of the container as determined in step (iib) of the first aspect.

[0058] As understood by the skilled person, the sampled data of step (iv) are used to continuously calculate the position, orientation, and velocity (direction and speed of movement) of the moving sensor device.

[0059] As known the art - in e.g. navigation, dead reckoning or dead-reckoning (also ded for deduced reckoning or DR) is the process of calculating one's current position by using a previously determined position - i.e. navigation dead reckoning known methods may be seen as suitable herein relevant methods for step (iv) above.

Use of the sensor device for measuring process parameters in a container:

[0060] As discussed above, a second aspect of the invention relates to use of the sensor device of first aspect and relevant embodiments thereof for measuring position and process parameters in a container comprising a liquid medium, a wall and an agitator.

[0061] As known in the art - an example of a suitable agitator is an impeller. Accordingly, in an embodiment of the present invention the agitator is an impeller.

[0062] Preferably, the container (e.g. a bioreactor) is a container comprising at least 100 L of liquid medium, such as at least 1000 L of liquid medium.

[0063] The liquid medium of the container may preferably comprise a polypeptide of interest, e.g. a protein of interest such as e.g. an enzyme of interest.

[0064] Preferably, the container is a bioreactor.

When the container is a bioreactor it is preferred that the liquid medium is a fermentation liquid medium, where it may be preferred that the bioreactor is used for growth of microorganism such as e.g. bacterial, fungal, yeasts or mammalian cell.

[0065] Preferably, the growth of microorganism is for recombinant production of a polypeptide of interest, e.g. a protein of interest such as e.g. an enzyme of interest.

[0066] In the preferred embodiment, the container is cylindrical.

An advantage of use of a cylindrical container is that the composition (e.g. amount of O₂ and pH level) is similar at one immersion depth (vertical position) and the same distance from e.g. the wall (horizontal position) of the container.

[0067] As used herein the term "bioreactor" refers to any device or system that supports a biologically active environment. In one case but not limited to, a bioreactor is a container or vessel in which is carried out a chemical process which involves organisms or biochemically active substances derived from such organisms. This process can either be aerobic or anaerobic. Bioreactors are commonly cylindrical, ranging in size from some litres to cubic meters, and are often made of stainless steel but could also be made of other materials such as disposable materials.

[0068] A bioreactor may also refer to a device or system meant to grow cells or tissues in the context of cell culture. On the basis of mode of operation, a bioreactor may be classified as batch, fed-batch or continuous (e.g. continuous stirred-tank reactor model). An example of a bioreactor is the chemostat. The bioreactor may be equipped with one or more inlets for supplying new fresh or concentrated medium to the cells, and with one or more outlets for harvesting product or emptying the bioreactor. Additionally, the bioreactor may be equipped with at least one outlet constructed in such a way that a separation device can be attached to the bioreactor. Typically the bioreactor's environmental conditions like gas (i.e., air, oxygen, nitrogen, carbon dioxide) flow rates, temperature, pH and dissolved oxygen levels, and agitation speed/circulation rate can be closely monitored and controlled.

A method for determining the position of the sensor device:

[0069] As discussed above, a third aspect of the invention relates to a method for determining the position of the sensor device of the first aspect and any relevant embodiments thereof in a container comprising a liquid medium, a wall and an agitator comprising the steps of:

(i) sampling data about pressure and acceleration from the position determination unit (1) of item (a); and

(iia) determining the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the container based on the in step (i) sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container; and

(iib): determining horizontal position of the sensor device in the liquid medium of the container based on the in step (i) sampled accelerometer data, wherein a first acceleration profile is derived from the sensor device contacting the agitator and a second acceleration profile is derived from the sensor device contacting the wall of the container and wherein the first and second acceleration profiles are different and the algorithm is capable of identifying this difference and thereby determining when the device contacts the agitator or contacts the wall of the container.

[0070] Preferred embodiments of the individual steps are described above.

EXAMPLES**EXAMPLE 1: Software algorithm**

[0071] The actual mathematics (e.g. integration based mathematics) and specific software language used for making a software algorithm of the first aspect may be seen as based on standard well known mathematics and software language - i.e. based on the teaching herein and the common general knowledge of the skilled person, it is routine work for the skilled person to make a software algorithm of the first aspect of the present invention.

[0072] Below is provided a discussion of examples of suitable preferred relevant actual mathematics (e.g. integration based mathematics) and specific software language used for making a software algorithm as described herein.

[0073] The developed positioning Algorithm has roots in literature from pedestrian inertial

navigation. Raw output data from the position determination unit (1) (acceleration and angular velocity in 3 axis) over a time interval is used to obtain the position of the particle. The acceleration [m/s/s] measured by the accelerometer is integrated twice to obtain the distance travelled [m] during a period, while the gyroscope which measures angular velocity [rad/sec], needs to be integrated once to obtain the rotation [rad]. Before integrating the raw data, the following operations have to be performed.

1. 1. Gravity compensation is required (subtraction of gravitational acceleration from accelerometer output). Before the subtraction is done, the coordinates of the IMU (body coordinates) must be facing in the same direction as the "world frame" or "navigation frame". This requires rotation operations which can be carried out by the use of quaternions. Quaternions are a convenient way of representing rotations and can easily be converted to rotation matrices or Euler's angles [1]. This first step is represented below:

$$a_n = R_n f_n - g$$

Where a_n is the acceleration in world frame, R_n is a rotation matrix, f_n is the measured acceleration (specific force) and g is the gravitational acceleration vector, $g = [0\ 0\ 9.81]^T$. n refers to the current state.

2. 2. The acceleration in world frame, a_n , can now be integrated over the sample period twice to obtain the position.
3. 3. MEMS sensors are very sensitive and errors from double integration accumulate rapidly. These errors can be restrained by using independent inputs describing the same variables. An example of this is the zero velocity update (ZUPT) [2]. ZUPT exploits moments with none or little motion to correct the calculated velocity.

[0074] Furthermore, there are several ways to obtain better estimates of the position. In this algorithm, the Kalman filter [3] based on the states and models by [4], is used to obtain the best estimates that includes noise and bias of the measurements.

The filter uses the basic mechanical equations of motions,

$$p_n = p_{n-1} + v_{n-1}T_s + \frac{1}{2}a_nT_s^2, \quad (1)$$

$$v_n = v_{n-1} + a_nT_s, \quad (2)$$

Where p is the position, v , the velocity, a , the acceleration and T_s is the sample period. The angles are updated by:

$$q_n = \Omega(\omega_n T_s) q_{n-1},$$

where q_n and q_{n-1} are quaternions describing the rotation at the current state and previous state, respectively. ω_n is a vector containing the input angles obtained by gyroscope measurements, and Ω is a quaternion update matrix.

The state vector used in the model are:

$$x_n = [p_{x,n} \ p_{y,n} \ p_{z,n} \ v_{x,n} \ v_{y,n} \ v_{z,n} \ \theta_{r,n} \ \theta_{p,n} \ \theta_{y,n}]^T$$

[0075] Where p and v are calculated from equation 1 and 2 and θ_r , θ_p and θ_y are Euler's angles converted from quaternions, roll, pitch and yaw, respectively.

The acceleration can be assumed constant in short sampling period or a linear approximation can be used.

The ZUPT is applied by using pseudo measurements of the velocity in the observation matrix. The pseudo measurements are zero with some noise added from the acceleration measurement. In addition, the z-coordinate obtained by the pressure sensor is added to this matrix in order to obtain better estimates of p_z . The measurement vector, z , becomes:

$$z = [p_z \ v_{x,pseudo} \ v_{y,pseudo} \ v_{z,pseudo}]^T$$

[0076] The pseudo measurements of velocity are only applied in the period with none or negligible movement, while the correction for p_z is applied at every state. As an alternative, a z velocity component can be calculated from the pressure measurements if the absolute depth (density) is not known, but the density can be assumed constant. If there is no motion at all (i.e. no movement and no rotation), then it is possible to correct the roll and pitch as well, due to the direction of the gravitational acceleration.

The algorithm also resets the position to $p = [0 \ 0 \ p_z]$ on impact with the wall of the fermentation tank, which results in trajectories as output, rather than absolute position.

[0077] Herein relevant references include:

Diebel, J. (2006). Representing Attitude: Euler Angles, Unit Quaternions, and Rotation Vectors. Section 6.

[0078] Abdulrahim, K., Moore, T., Hide, C., Hill, C. (2014). Understanding the Performance of Zero Velocity Updates in MEMS-based Pedestrian Navigation. International Journal of Advancements in Technology, 4: 53-60.

[0079] Welch, G., Bishop, G. (2001). An introduction to the Kalman Filter. University of North Carolina at Chapel Hill. Department of Computer Science.

[0080] Nilsson, J., Gupta, A. K., Handel, P. (2014) Foot-mounted inertial navigation made easy. International Conference on Indoor Positioning and Indoor Navigation

[0081] Colomar, D. S., Nilsson, J., Handel, P. (2012). Smoothing for ZUPT-aided INSs. International Conference on Indoor Positioning and Indoor Navigation

EXAMPLE 2: Test of sensor device in a bioreactor

[0082] The sensor device was the sensor device as shown in Figure 1a comprising (using numbering of block diagram of Figure 1b):

a house (10), wherein the house (10) comprises:

1. (a) a position determination unit (1) comprising an accelerometer and a pressure sensor,
2. (b) a microcontroller unit (3) comprising a software algorithm configured for determining position of the sensor device,
3. (c) a power management unit (5),
4. (d) a process parameter sensor (2), and
5. (e) a communication unit (4) adapted for communicating with a user interface.

[0083] As known in the art - relevant electronic components (e.g. sensors) are commercially available - e.g. at the website of the company Farnell (www.farnell.com).

[0084] In relation to (a) - the accelerometer was a commercially available ADXL375 from Analog devices and the pressure sensor was a commercially available MSS5803-05 from TE Connectivity.

[0085] In relation to (b) - the microcontroller unit (3) was a microcontroller unit comprising a standard MCU with RAM for data and calculation, a ROM for boot, flash for program storage and tables, a CPU for program execution and numerous peripherals for communication with onboard sensors etc. The software algorithm is part of the program and resides in the flash. The timers are used for timing external event, generating event on periodic basis and for generation of PWM signals.

[0086] In relation to (c) - the power management unit (5) was a power management unit comprising battery and several voltage regulators. Generally speaking, the power management unit may be different power units depending on the overall state of the system. Blocks can be powered down individually in order to save power and only power needed sensors, internal devices etc.

[0087] In relation to (d) - the process parameter sensors (2) were two sensors - one capable of measuring temperature and one capable of measuring pH. The temperature sensor was included in the above described commercially available pressure sensor and the pH sensor was a sensor based on pH meter ISFET technology.

[0088] In relation to (e) - the communication unit (4) adapted for communicating with a user interface a unit based on wireless communication. The unit contained a radio transceiver and an antenna for wireless communication with the outside world.

[0089] The sensor device was tested in a 1 m³ bioreactor with a diameter of 0.92 m. The bioreactor was filled with 0.66 m³ of pure water to reach a liquid height of 1 m. The liquid was agitated by two Rushton turbines (i.e. impellers) with a clearance of approximately 0.35 m, a diameter of 0.3 m and a rotation speed of 175 rpm.

[0090] The software algorithm in (b) of the sensor device was an algorithm capable of:

(iia) determining the immersion depth and thereby the vertical position of the sensor device in the liquid medium of the bioreactor based on the sampled pressure data wherein the pressure is correlated to the depth in the sense that higher pressure relates to increased immersion depth of the sensor device in the liquid medium of the container; and

(iib): determining horizontal position of the sensor device in the liquid medium of the bioreactor based on the sampled accelerometer data, wherein a first acceleration profile is derived from the sensor device contacting the agitator/impeller and a second acceleration profile is derived from the sensor device contacting the wall of the container and wherein the first and seconds acceleration profiles are different and the algorithm is capable of identifying this difference and thereby determining when the device contacts the agitator or contacts the wall of the container.

[0091] Herein relevant details of the software algorithm are discussed below.

[0092] The software algorithm was configured to measure acceleration profiles of impacts at 3200 Hz and the pressure at 100 Hz.

[0093] The shock accelerometer profiles were processed to differentiate between impacts with the wall and the impellers. The differentiation was based on a threshold of in the weighted mean, p , given by:

$$p = \frac{\alpha a + \beta b + \gamma c + \delta d}{\alpha + \beta + \gamma + \delta}.$$

The value of p is calculated by a fuzzy logic algorithm in which α , β , γ and δ are weight parameters and a , b , c and d are functions of the shape of the acceleration profile. An example of a measured impact profile is shown in figure 3.

[0094] Figure 4 shows a comparison of impacts with wall and impellers which are theoretically determined by the algorithm and the corresponding impacts which are determined by visual inspection. A correct match of geometric figures indicates a correct determination. The grey line is the measured pressure which can be used to calculate the immersion depth (i.e. vertical position). It can be seen that the algorithm has a fairly high success rate, which can be further optimized by tweaking the algorithm.

[0095] In conclusion - the algorithm of the sensor device was able to determine the horizontal position of the sensor device in the liquid medium of the bioreactor based on the sampled accelerometer data, wherein a first acceleration profile was derived from the sensor device contacting the agitator and a second acceleration profile was derived from the sensor device contacting the wall of the container and wherein the first and seconds acceleration profiles were different and the algorithm was capable of identifying this difference and thereby determining when the device contacts the agitator/impeller or contacts the wall of the container.

[0096] As discussed above, the sensor device comprised two process parameter sensors (2) - one capable of measuring temperature and one capable of measuring pH.

These two parameters were continuously measured and correlated with position of the sensor - i.e. specific temperature/pH parameters were obtained for specific positions of the sensor device within the liquid medium of the bioreactor. It is evident that such information is very useful for optimization of e.g. fermentation/growth conditions of the bioreactor.

REFERENCE LIST

[0097]

1. 1: Thiele et al., "Autonomous sensor particle for parameter tracking in large vessels", Meas. Sci. Technol. vol. 21 (2010) page 085201 (8pp).
2. 2: Reinecke et al., "Macro-mixing characterisation of a stirred model fermenter of non-Newtonian liquid by flow following sensor particles and ERT. Chemical Engineering Research and Design vol. 118, (2016-12-09) pages 1-11.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- **DIEBEL, J.**Representing Attitude: Euler Angles, Unit Quaternions, and Rotation Vectors, 2006, [\[0077\]](#)
- **ABDULRAHIM, K.MOORE, T.HIDE, C.HILL, C.**Understanding the Performance of Zero Velocity Updates in MEMS-based Pedestrian NavigationInternational Journal of Advancements in Technology, 2014, vol. 4, 53-60 [\[0078\]](#)
- **WELCH, G.BISHOP, G.**An introduction to the Kalman Filter.University of North Carolina at Chapel Hill. Department of Computer Science20010000 [\[0079\]](#)
- **NILSSON, J.GUPTA, A. K.HANDEL, P.**Foot-mounted inertial navigation made easyInternational Conference on Indoor Positioning and Indoor Navigation, 2014, [\[0080\]](#)
- **COLOMAR, D. S.NILSSON, J.HANDEL, P.**Smoothing for ZUPT-aided INSsInternational

Conference on Indoor Positioning and Indoor Navigation, 2012, [\[0081\]](#)

- **THIELE et al.**Autonomous sensor particle for parameter tracking in large vesselsMeas. Sci. Technol., 2010, vol. 21, 085201- [\[0097\]](#)
- **REINECKE et al.**Macro-mixing characterisation of a stirred model fermenter of non-Newtonian liquid by flow following sensor particles and ERTChemical Engineering Research and Design, 2016, vol. 118, 1-11 [\[0097\]](#)

Patentkrav

1. Sensoranordning, som omfatter et hus (10), hvor huset (10) omfatter:

- (a) en positionsbestemmelsesenhed (1), der omfatter et accelerometer og en tryksensor,
- (b) en mikrocontrollerenhed (3), der omfatter en softwarealgoritme, som er konfigureret
- 5 til bestemmelse af sensoranordningens position,
- (c) en strømstyringsenhed (5),
- (d) en procesparametersensor (2), og
- (e) en forbindelsesenhed (4), der er tilpasset til at etablere forbindelse med en brugergrænseflade; og

10 hvor softwarealgoritmen i (b) kan bestemme sensoranordningens position i en beholder, der omfatter et flydende medium, en væg og en omrører, hvor algoritmen er en algoritme, der omfatter følgende trin:

(i) prøvetagning af data om tryk og acceleration fra positionsbestemmelsesenheden (1) i komponent (a); og

15 (iia) bestemmelse af nedsækningsdybden og derved sensorens vertikale position i beholderens flydende medium baseret på de i trin (i) prøvetagne trykdata, hvor trykket er korreleret med dybden i den forstand, at højere tryk relaterer til øget nedsækningsdybde for sensoranordningen i beholderens flydende medium; og

(iib): bestemmelse af sensoranordningens horisontale position i beholderens flydende
20 medium baseret på de i trin (i) prøvetagne accelerometerdata, hvor en første accelerationsprofil er afledt fra sensoranordningen, der er i kontakt med omrøreren, og en anden accelerationsprofil er afledt fra sensoranordningen, der er i kontakt med beholdervæggen, og hvor den første og den anden accelerationsprofil er forskellige, og hvor algoritmen er i stand til at identificere denne forskel og derved bestemme, hvornår
25 anordningen er i kontakt med omrøreren eller er i kontakt med beholdervæggen.

2. Sensoranordning ifølge krav 1, hvor positionsbestemmelsesenheden (1) i komponent (a) endvidere omfatter et gyroskop, og hvor softwarealgoritmen endvidere omfatter følgende trin:

- (iii) prøvetagning af data om vinkelhastighed fra gyroskopet i positionsbestemmelsesenheden (1) i komponent (a); og (iv): bestemmelse af sensoranordningens position via mikrocontroller-enheden (3) i komponent (b) ifølge krav 1, hvor i trin (i) ifølge krav 1 prøvetagne accelerometerdata og i trin (iii)
- 5 prøvetagne gyroskopdata kontinuerligt beregner position, orientering og hastighed (retning og bevægelseshastighed) for den bevægelige sensoranordning i beholderens flydende medier via en proces til beregning af sensoranordningens aktuelle position ved hjælp af en tidligere bestemt position, og hvor den tidligere bestemte position er, når anordningen kommer i kontakt med omrøreren, og når anordningen kommer i kontakt
- 10 med beholdervæggen som bestemt i trin (iib) ifølge krav 1.
3. Sensoranordning ifølge et af de foregående krav, hvor huset (10) er i en todelt form.
4. Sensoranordning ifølge et af de foregående krav, hvor huset (10) er fremstillet af et biokompatibelt produkt herunder metal, træ, bambus og plast såsom organisk termoplastisk polymerplast inklusive polyetheretherketon (PEEK) og
- 15 polyaryletherketon (PAEK).
5. Sensoranordning ifølge et af de foregående krav, hvor huset (10) omfatter en datalagringsenhed, og/eller sensoranordningens vægt er 1 g til 500 g.
6. Sensoranordning ifølge et af de foregående krav, hvor procesparametersensoren (2) omfatter en eller flere sensorer valgt fra gruppen bestående af en pH-sensor, en
- 20 oxygensensor, en brydningsindekssensor, en celletæthedssensor og en temperatursensor.
7. Sensoranordning ifølge et af de foregående krav, hvor sensoranordningen er formet som en kugle, og/eller sensoranordningens størrelse er en størrelse med en diameter fra 1 mm til 100 cm.
8. Sensoranordning ifølge et af de foregående krav, hvor tryksensoren er valgt fra
- 25 gruppen bestående af en DMS-tryksensor, kapacitiv tryktransducer, piezoelektrisk tryktransducer, piezo-resistiv SMS-sensor, piezoelektrisk sensor og piezo-resistiv brosensor.
9. Sensoranordning ifølge et af de foregående krav, hvor accelerometeret er valgt blandt en inertisensor såsom en MEMS-inertisensor.

10. Sensoranordning ifølge et af de foregående krav, hvor strømstyringsenheden (5) omfatter et genopladeligt batteri, og/eller hvor forbindelsesenheden (4) er trådløs.
11. Sensoranordning ifølge et af de foregående krav, hvor softwarealgoritmen ifølge krav 1 er en del af et program, der ligger i hukommelsen i mikrocontroller-enheden (3),
5 og som udføres af en centralenhed (CPU) i mikrocontroller-enheden (3).
12. Anvendelse af sensoranordningen ifølge et af kravene 1-11 til måling af position og procesparametre i en beholder, der omfatter et flydende medium, en væg og en omrører.
13. Anvendelse ifølge krav 12, hvor omrøreren er et skovlhjul, og det flydende medium i beholderen omfatter et polypeptid af interesse.
- 10 14. Anvendelse ifølge et af kravene 12-13, hvor beholderen er en bioreaktor, og bioreaktoren omfatter mindst 100 liter flydende medium, og det flydende medium er et fermenteringsvæskemedium, og bioreaktoren anvendes til vækst af mikroorganismer, og hvor væksten af mikroorganismer er til rekombinant produktion af et polypeptid af interesse.
- 15 15. Anvendelse ifølge et af kravene 12-14, hvor beholderen er cylinderformet.
16. Fremgangsmåde til bestemmelse af sensoranordningens position ifølge et af kravene 1-11 i en beholder, der omfatter et flydende medium, en væg og en omrører, som omfatter følgende trin:
- (i) prøvetagning af data om tryk og acceleration fra positionsbestemmelsesenheden (1) i
20 komponent (a); og
- (iia) bestemmelse af nedsænkingsdybden og derved sensorens vertikale position i beholderens flydende medium baseret på de i trin (i) prøvetagne trykdata, hvor trykket er korreleret med dybden i den forstand, at højere tryk relaterer til øget nedsænkingsdybde for sensoranordningen i beholderens flydende medium; og
- 25 (iib): bestemmelse af sensoranordningens horisontale position i beholderens flydende medium baseret på de i trin (i) prøvetagne accelerometerdata, hvor en første accelerationsprofil er afledt fra sensoranordningen, der er i kontakt med omrøreren, og en anden accelerationsprofil er afledt fra sensoranordningen, der er i kontakt med beholdervæggen, og hvor den første og den anden accelerationsprofil er forskellige, og

hvor algoritmen er i stand til at identificere denne forskel og derved bestemme, hvornår anordningen er i kontakt med omrøreren eller er i kontakt med beholdervæggen.

DRAWINGS

Figure 1a

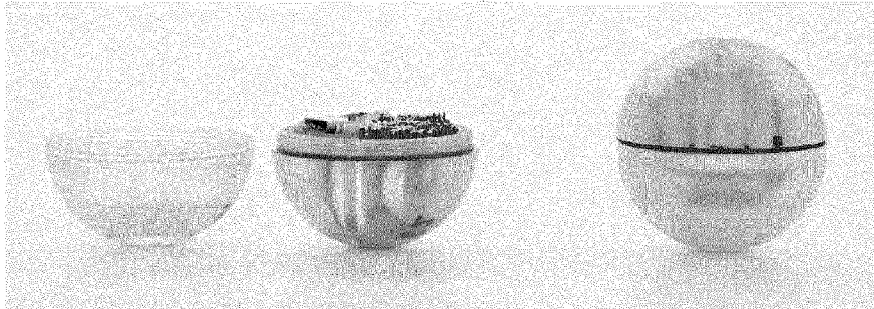
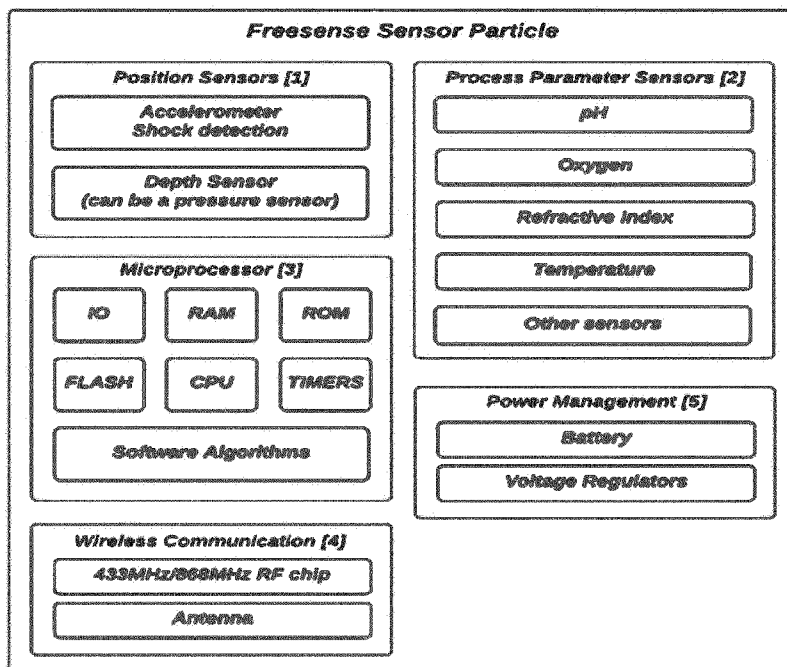


Figure 1b



House 10

Figure 2

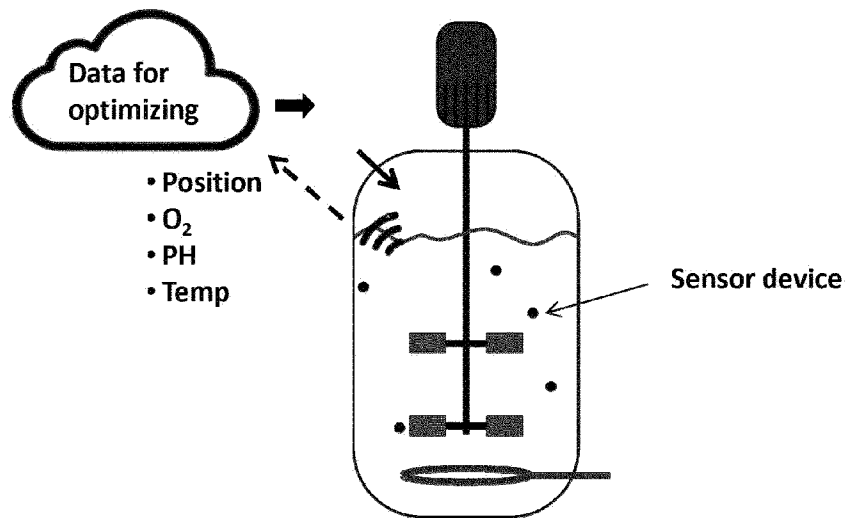


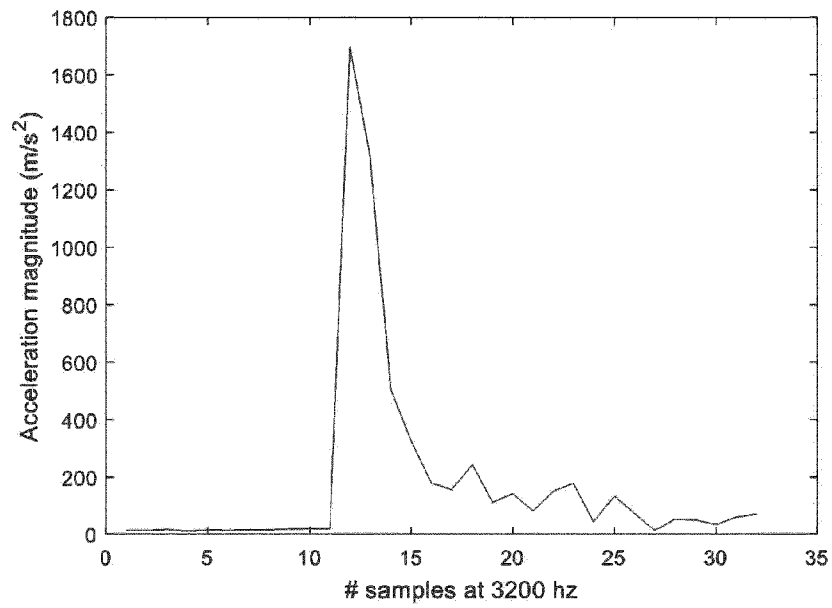
Figure 3

Figure 4

