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(54) **CONTROLLING RELEASE OF A MATERIAL CARRIED BY ULTRASOUND SENSITIVE PARTICLES**

STEUERUNG DER FREISETZUNG EINES VON ULTRASCHALLSENSITIVEN PARTIKELN GETRAGENEN MATERIALS

COMMANDE DE LA LIBÉRATION D'UN MATÉRIAU PORTÉ PAR DES PARTICULES SENSIBLES AUX ULTRASONS

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Description

FIELD OF THE INVENTION

[0001] The present disclosure relates to a method of controlling a release of a material carried by ultrasound sensitive particles.

BACKGROUND OF THE INVENTION

[0002] Ultrasound provides a unique opportunity to deposit energy remotely into inaccessible human tissue for therapeutic purposes. In the past, such approaches have used one of two mechanisms to activate therapeutic interventions. Ultrasonically deposited energy can be manifested through heat for the activation of heat shock proteins (C. Rome, F. Couillaud and C.T.W. Moonen, Spatial and temporal control of expression of therapeutic genes using shock protein promoters. Methods, 2005. 35(2): p. 188-198), or other temperature sensitive therapies. In addition, ultrasound sensitive particles administered through intra-venous or arterial injection can be used through the incorporation of specific pharmaceutical or genetic material into the particle or on particle shell and the remote activation through the use of specially designed single ultrasound pulses (R. Bekeredjian, P.A. Grayburn, and R.V. Shohet, Use of ultrasound contrast agents for gene or drug delivery in cardiovascular medicine, Journal of the American College of Cardiology, 2005. 45(3): p. 329-335). Further, the US-patent US 5,542, 935. discloses a therapeutic delivery system comprising gaseous precursorfilled microspheres comprising a therapeutic (see abstract), where the microspheres have various resonance frequencies. The rupturing of the microspheres is carried out by applying ultrasound of a frequency corresponding to the resonant frequency of the microspheres.

[0003] Typical ultrasound sensitive particles consist of stabilized microbubbles. These microbubbles are usually less than 5 microns in diameter, stabilized with a shell consisting of protein, lipid, and/or polymers, with gaseous interior. These microbubbles possess the ability to interact with the ultrasound field through resonant behavior within the typical diagnostic imaging frequency range. The resonant behavior can be used to drive the bubbles from a resonant regime where the motion of the bubble is stable to a regime where the bubble expands and collapses violently and transiently. In both cases, it has been observed that when the bubbles incorporate genetic and pharmaceutical material on, within or even in close proximity to the bubble, it is possible to deliver the material to the surrounding tissue using ultrasound.

[0004] These prior art methods however suffer from the difficulty that it is impossible to control the rate of release of a material carried by the microbubbles and the spatial location of the released material. As an example, it might be required to deliver material A to a particular tissue, and subsequently material B. Such an operation is not possible with the existing technique. Further, when using ultrasound-mediated gene delivery techniques in vivo or in cell culture, in the past it has not always possible to visualize the presence and the execution of specific instruction sets and the specified outcome of this instruction set.

BRIEF DESCRIPTION OF THE INVENTION

[0005] The ultrasound particles of the invention are defined in Claim 1. A method of controlling a release of a material in cell culture or in vitro is defined in claim 9.

[0006] According to one aspect, the present invention relates to a method (as defined in Claim 9) of controlling a release of a material carried by ultrasound sensitive particles, the release being caused by irradiating the ultrasound sensitive particles with an ultrasonic pulse having acoustic properties selected so as to interact with the ultrasound sensitive particles and thus causing the release of the material in a cell culture or in vitro, wherein the ultrasound sensitive particles comprise sub-groups of ultrasound sensitive particles, the ultrasound sensitive particles within the same sub-group having their respective acoustic activation property causing each respective sub-group to interact independently with the ultrasonic pulse.

[0007] Since the ultrasound sensitive particles comprise sub-groups having different acoustic properties, it is possible to let the ultrasound sensitive particles to act in a "programmed manner", or as a basic Turing machine. Accordingly, the sub-groups of the particles correspond to "data instances" that can be acted upon with ultrasound at a specific frequency or frequencies, amplitude, and other parameters, to enact a computing step. This means that the particles within the same sub-group can be activated, and thus the material carried by the particles can be released based on the acoustic property of the ultrasonic pulse, while the other sub-groups are not activated. Accordingly, by changing the acoustic property of the ultrasonic pulse, the type of material to be released can be changed. The ultrasound can accordingly be used to control the delivery of the material. In the analogy to a computing system, ultrasound acts as the memory controller fetching "instructions", i.e. delivering ultrasound with specific acoustic properties to cause activation i.e. data processing, where data is the biological/genetic material.

[0008] In one embodiment, the adjustment of the ultrasonic pressure amplitude of the ultrasonic pulse is based on selecting the mechanical index of the ultrasonic pulse between 0.7 and 1.1. In one embodiment, the ultrasound sensitive particles within the same sub-group of ultrasound sensitive particles carry the same type of material.

[0009] Thus, the release of a specific material can be controlled accurately, e.g. by releasing the material in a sub-group A, or first releasing the material in a sub-group A and subsequently the material in a sub-group B.

[0010] The sub-groups of ultrasound sensitive parti-

cles comprise microbubbles containing the material therein.

[0011] It is an advantage to use such microbubbles since they can be selectively activated with judicious choice of properties of the ultrasound field.

[0012] The sub-groups of ultrasound sensitive particles comprise microbubbles having a shell structure containing the material therein.

[0013] The shell structure can be made with an extremely narrow size distribution which e.g. resonates over a narrow frequency range. Thus, by using microbubbles having such shell structure, it is possible to produce many sub-groups of microbubbles that have different acoustic properties, e.g. different resonance frequencies.

[0014] The shell structure within the same sub-group has similar physical property, the property being characteristic for the respective acoustic activation property.

[0015] Thus, the property of the ultrasonic pulse may be selected such that it interacts only with a particular group at a time.

[0016] Advantageously, the physical property is selected from:

- the shell thickness,
- the shell size,
- the diameter of the shell,
- geometrical shape of the shell,
- chemical composition of the shell, and
- a combination thereof.

[0017] The acoustic activation property of the sound wave is the pressure amplitude of the ultrasonic pulse.

[0018] In one embodiment, the sub-groups of ultrasound sensitive particles are selected from:

- microbubbles having a shell structure containing said type of material therein,
- microbubbles containing said type of material therein,
- microbubbles in a solution containing the type of material therein,
- nanoparticles,
- liposomes,
- heat shock proteins, and
- a combination thereof.

[0019] In one embodiment, the material carried by ultrasound sensitive particles is a biological material and is selected from:

- pharmaceutical material,
- polysaccharides,
- lipids,
- fatty acids,
- steroids,
- proteins,
- enzymes,
- deoxyribonucleic acid (DNA),
- ribonucleic acid (RNA),
- small interfering ribonucleic acid (siRNA),
- inorganic artificial constructs,
- nanoparticles,
- nanomachines,
- chemicals intended to alter the composition or geometry of existing sub-groups of particles,
- biochemical particles, and
- a combination thereof.

[0020] Preferably, the release of the material is carried out locally in or nearby a target tissue or cell by releasing the material from at least one of the sub-groups of the ultrasound sensitive particles.

[0021] Thus, it is possible to deliver the material, or pre-defined combination of the materials, directly into the tissue, e.g. by first releasing material A carried by a sub-group a, into the tissue and subsequently material B carried by a sub-group b.

[0022] Thus, different possibilities exist to activate the ultrasound sensitive particles for causing the release of the material. As an example, since the ultrasound sensitive particles are microbubbles having shell structure, the shell structure may be made such that the microbubbles resonate over a narrow frequency range and are susceptible to rupture at a sharp pressure threshold.

[0023] The method may be performed in-vivo or in a cell culture, the method further comprising the following steps:

- receiving a program comprising at least one command indicating at least one spatial delivery zone, each command indicating at least one type of material to be released at specific ratios,
- imaging the spatial distribution of the ultrasound sensitive particles, the imaging resulting in data indicting the spatial distribution of the ultrasound sensitive particles, and in response to the spatial data
- irradiating the ultrasound sensitive particles in the at least one delivery zone with an ultrasonic pulse, the property of the ultrasonic pulse being controlled such that the release of the material in the at least one delivery zone is in accordance to the at least one received command,
- repeating steps b) - c) for each subsequent command until the received commands have been completed.

[0024] By imaging the spatial distribution of the ultrasound sensitive particles, it is possible to detect the presence of the various sub-groups in the desired spatial deliver zone. If, as an example, at a particular delivery zone, e.g. a cell or a tissue, the material C carried by a sub-group c was supposed to be delivered to a particular delivery zone, but the imaging shows that there are excessive ultrasound sensitive particles belonging to the sub-group c left, the irradiation will be made to continue until

the imaging shows that the specified amount of the sub-group c is released. Thus, an iteration process is provided that ensures a precise delivery of the material. Since the ultrasound sensitive particles within the various sub-groups may be considered as a set of "instructions", e.g. ultrasound sensitive particles within the same group carry the same set of instructions, this iteration may be considered as a method to monitor step by step the execution of the "instructions".

[0025] The commands may further include information about the amount of the material or the mix of materials to be delivered at a given delivery zone, or about the type of the material to be released, in order to modify the acoustic properties of the remaining ultrasound sensitive particles.

[0026] Thus, the commands may indicate that only half of the ultrasound sensitive particles within the sub-group C is to be delivered at a given delivery zone. Further, the commands may include subsequently releasing another type of material in the same delivery zone.

[0027] The commands can be interpreted as equivalent to an "assignment" statement in a programming language, e.g. A = b. The particles may be floating, and the material by the particles not yet released. When such a simple command is issued, the ultrasonic pulse induces the release of the material. Therefore, the material can be considered to be absorbed into the tissue/environment (similar to an assignment statement), the tissue "gets" a new value.

[0028] The commands may be 'conditional', meaning that there is an evaluative command, i.e. an "if' condition, and only when this is true, an ultrasonic pulse is delivered to activate e.g. A particles. Otherwise, based on a read-out, the system executes a B command to activate B particles.

[0029] The commands may also be 'looping', meaning that a command will be executed, or a set of commands such as assignment or conditional or other looping commands, while a condition holds true, based on a read-out/imaging.

[0030] The ultrasound sensitive particles having the same acoustic property can be considered as abstract instruction units that interact simultaneously to the same ultrasonic pulse of a particular acoustic property.

[0031] According to still another aspect, ultrasound sensitive particles comprise sub-groups of ultrasound sensitive particles carrying material, the ultrasound sensitive particles within the same sub-group having their respective acoustic property.

[0032] In one embodiment, the diameter of the ultrasound sensitive particles is less than 100 nm, such as less than 50 mm, such as less than 25 nm, such as less than 10 nm, such as less than 5 nm.

[0033] However, for certain applications, it might be preferred to use particles having larger diameters.

[0034] In one embodiment, the particles within the same group carry the same type of material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] Embodiments of the invention will be described, by way of example only, with reference to the drawings, in which

Figure 1 shows an apparatus for controlling a release of a material by ultrasound sensitive particles,

Figures 2-4 depict the scenario where commands received by a user include delivering the material carried by the ultrasound sensitive particles to a tissue or a cell,

Figure 5 (a) and (b) show mono-dispersed microbubbles detected in a scanning electron micrograph and measured with a particle sizer,

Figure 6 shows the number of microbubbles destroyed as a function of ultrasonic pressure amplitude.

Figure 7 shows the force needed to "destroy" and deliver the payload for three different sub-populations, and

Figure 8 shows a flow chart of one example of a method.

DESCRIPTION OF EMBODIMENTS

[0036] Figure 1 shows an apparatus 101 for controlling a release of a material carried by ultrasound sensitive particles 116-118, comprising a control unit 102 and an ultrasound transducer 103 coupled to the control unit 102. In response to a control signal from the control unit 102, the ultrasound transducer 103 irradiates the ultrasound sensitive particles 110-112 with an ultrasonic pulse 108 having acoustic properties selected so as to interact with the ultrasound sensitive particles and thus causing the release of the material. The ultrasound sensitive particles are divided into sub-groups 110-112 of ultrasound sensitive particles, each of the sub-groups 110-112 having their respective acoustic property. As illustrated graphically, the number of sub-groups is three, where the ultrasound sensitive particles within the same sub-group A, B and C are marked with the letters "A", "B" and "C".

[0037] The material to be released may be an inorganic material such as silicon based nanomachines, an organic material or a biological material selected from a pharmaceutical material, proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), small interfering ribonucleic acid (siRNA) and the like. The material within the microbubble or particulate delivery agent can be thought of as "instructions" to the cell to perform a function such as manufacture of a protein or suppression of a particular protein or a metabolic pathway. Accordingly, by incorporating multiple "instructions" onto different sets of microbubbles, each having its own activation property, it is possible to design a "program" consisting of a complex set of instructions that can be "executed" using ultrasound with both spatial and temporal control.

[0038] The apparatus may be applied in vitro, in vivo or in a cell culture such as for medical or non-medical treatment.

[0039] In response to a control signal from the control unit 102, the ultrasound transducer 103 emits a sound wave of a particular acoustic property selected such that it interacts with a particular group 110-112 of ultrasound sensitive particles (USP) 116-118. The interaction causes that the ultrasound sensitive particles within this particular group become activated, which causes a release of the material by the ultrasound sensitive particles 116-118 within this particular group. As an example, the acoustic property of the ultrasonic pulse 108 may the frequency of the pulse 108 and the properties of the different groups may be different resonance frequencies. Thus, the control signal from the control unit 102 may be to tune the frequency of the ultrasound transducer 103 to a frequency that corresponds to a resonance frequency of a particular group, e.g. group B. Instead of using the resonance frequency as a property, the property may as well be the duration of the (duty cycle) of the ultrasonic pulse or the pressure amplitude.

[0040] Accordingly, the process described here above may be considered as bio-computation where the ultrasound acoustic properties and ultrasound sensitive particles may be thought as computing instructions, wherein the software and the biochemical particles (BCP) material may be thought of as "data". By delivery of ultrasound pulses for activating and thus releasing the BCP material using the ultrasound sensitive particles is thus the enabling hardware. The bio-computing consists therefore of activating different ultrasound sensitive particles with the delivery of ultrasound pulses.

Begin example:

INPUT

[0041] Instructions: encoded as combined effect of the ultrasonic pulse having acoustic properties as to interact with the ultrasound sensitive particles: frequency (F), duty cycle (D), pressure amplitude (P), waveform (W), location (L), USP particles. An "instruction" is the quadruple: I = (F, D, P, W, L,USP).

Data: Biochemical payload, BCP. For a give bioparticle there is a range of USPs that can carry the load or can be in the close proximity of the BCP.

OUTPUT

[0042] Output: Reading the output is performed using the imaging apparatus which forms part of the whole ultrasound biocomputing system. The reading could be using ultrasound imaging modality as well as optical imaging modality. One possibility is to have a fluorescently tagged molecule that is activated as part of a reporter construct.

[0043] This method creates an artificial genetic construct that couples the regulatory region of a transcript of interest to the coding sequence of a light-excitable bioluminescent (fluorescent) protein. They "report on" or act as a proxy for the expression of the transcript whose regulatory region has been fused to the DNA sequence coding for the fluorescent protein. The transcript abundance of a particular gene can be indirectly inferred because the amount of protein product is understood to be indicative of transcript abundance. If there are more transcripts, then there is more protein which results in more fluorescence. By measuring the intensity of the fluorescence after excitation with the appropriate wavelength of light, we have readable (in imaging sense) data that reflects how the native gene would behave under the conditions within the cell.

PROGRAMMING CONSTRUCTS

Starting Statement

[0044] This is the execution of the first instruction in the set of programming instructions. In many cases, specific starting instruction are not required.

[0045] One possibility is to have a specific initializing statement. The goal is the release of the facilitation of the first set of BCP type of particles via executing a pulse having a set of parameters (F,D,P,W, L, USP) that verifies that the system is operational.

Assignment Statement

[0046] Single release of ultrasound pulse at a particular set of parameters (F,D,P,W, L, USP) that causes release and activation of BCP is therefore equivalent to a basic "assignment statement" of the form "A=value". In this case, F stands for a particular frequency, D for duty cycle, P for amplitude pressure, W for a particular waveform, L for location where the ultrasound is going to be delivered, and USP for ultrasound sensitive particles, i.e. specific molecular species.

Conditional Statement

[0047] The conditional statement has the generic form of:

if (A) then
perform (B)
else
perform (C)
end

[0048] Here, the conditional statement A could be releasing of a BCP which is inducing a biological response, where a reporting molecule is activated and available for a read-out. Conditional statement A could consist of a reporter gene to assay for the expression of the gene of interest (for example ErbB2). It is desirable to obtain an

in vivo diagnosis of ErbB2 positive patients instead of taking biopsy and performing fluorescent in situ hybridization and separately taking ultrasound imaging diagnostic test of the breast.

[0049] A construct is used that is directly attached to the gene of interest to create a gene fusion: GFP + ErbB2. The fused genes are going to be under the same promoter and are transcribed together. The product is a single polypeptide chain. It is preferred that both proteins are properly translated and form proteins that fold properly into active conformations. It is also assumed that both proteins will be active and dock with their substrates even though they are part of the fusion protein. In the present case, when building the DNA construct, a segment of DNA is inserted that codes for a flexibly polypeptide linker region between the GFP and ErbB2. In this manner, the reporter (GFP) and the gene product (ErbB2) will interact in a minimal way.

[0050] Conditional statement A is executed, then, upon reading the outcome of the GFP reporter construct, it will be apparent whether ErbB2 is overabundant. It is known that the growth promoting signals from ErbB2 are constitutively transmitted, thus promoting invasion, survival and angiogenesis of cells. If yes, then statement B is executed: the payload for B- BCP species is released. The payload could be a drug that counteracts over expression of ErbB2: Trastuzumab, also known under the trade name Herceptin (a well known breast cancer drug). This is a humanized monoclonal antibody that acts on the HER2/neu (erbB2) receptor. Else, a generic drug is released via activation of statement C. It is important to know whether herceptin or another drug is to be released, because it is a very expensive drug and only about 30% of the patients respond to it.

Looping Constructs

[0051] While loop: The statement of the form:

while (D)
perform (E)
end

[0052] This type of statement can be given as multiple ultrasonic pulses executing the E statement(s), until the readout of the instructions (statement D) evaluates to true.

[0053] One example is executing type of instructions in E, which corresponds to administering of a particular drug until the diagnostic molecule is present (i.e. D evaluates to true).

Stopping construct

[0054] It is important to have an instruction that will stop any type of computation and abort the overall execution of the program, if certain readout is indicating that proceeding is not producing the intended results. This instruction can be executed with a particular instruction (F,D,P,W, L, USP) in combination with biochemical particles that act in a ubiquitous manner.

End example

[0055] In one example, the apparatus 101 further comprises input means 104 and imaging means 105. The input means 104 may comprise means for receiving commands from a user 113 relating to e.g. desired spatial delivery zones and the type of material to be released at the desired spatial delivery zones 120. This may be done via e.g. keyboard commands, mouse commands, a speech recognition system, or the like. The input means 104 may also comprise a disk drive, a hard disk and the like having, stored therein, a software code or receiving pro-programmed instructions 114 from e.g. a CD for instructing the control unit 102 to carry out the releasing of the material at various spatial zones. These instructions may include the amount of material to be delivered to a given spatial location, the mix of different materials to be given at a given location, etc.

[0056] These command codes are then implemented as control commands of the control unit 102. The imaging means 105 is used to detect the spatial distribution of the ultrasound sensitive particles, wherein the detection may be based on the use of lower mechanical index (low pressure) ultrasound. These spatial data will be used as input data for the control unit 102 in order to provide controlling, depending on whether the ultrasound sensitive particles 116-118 are located at said given location 120. Thus, if the commands from a user indicate that the material B carried by group B (ultrasound sensitive particles B) is to be released at zone X, and subsequently material A carried by group A (ultrasound sensitive particles A), the imaging means 105 will initially detect whether the ultrasound sensitive particles of these two groups are located at zone X 120 using a unique signal 109. If the answer is yes, the ultrasound transducer 103 irradiates the ultrasound sensitive particles located near zone X 120 with an ultrasonic pulse that has e.g. frequency that corresponds (or within a narrow frequency interval) to the resonance frequency of group B, and after e.g. all the material A has been released, the control unit 102 instructs the ultrasound transducer 103 to tune its frequency to a frequency that corresponds to the resonance frequency of group A. Clearly, this requires that the ultrasound sensitive particles within the different sub-groups should be constructed with pre-defined properties, such that e.g. the ultrasound sensitive particles within group A have "property A" (e.g. resonance frequency within a given frequency range that is preferably narrow), ultrasound sensitive particles within group B have "property B", etc.

[0057] Advantageously, the imaging means 105 continuously monitors whether the commands have been followed. Referring to the example here above, the imaging means 105 will monitor whether all the ultrasound sensitive particles within group B have been dissolved

(assuming that the commands state that all the particles B at delivery zone X are to be dissolved). It is not until the data from the imaging means (Im_M) 105 indicate that all the ultrasound sensitive particles within group B have been dissolved that the control unit instructs the ultrasound transducer 103 to tune its frequency to a frequency that corresponds to the resonance frequency of group A.

[0058] Figures 2-4 depict the scenario addressed here above, where the commands include delivering the material such as a tissue or a cell 120. Figure 2 shows three groups located near the tissue/cell 120. Fig. 3 shows that material carried by the group B has been delivered to the tissue, and Fig. 4 shows that subsequently material carried by the group A has been delivered to the tissue.

[0059] The ultrasound sensitive particles may be mono-dispersed microbubbles. The advantages of using such particles are that they can be made with an extremely narrow size distribution (Shi WT, Böhmer M, de Winter S, Steenbakkers J, Emmer M, van Wamel A, de Jong N, Hall CS. Ultrasonic characterization of novel monodispersed contrast agents. Proceedings of 2006 IEEE Ultrasonics Symposium. pp 301-304 (Session 2D-5).

[0060] Figures 5 a and b show mono-dispersed microbubbles detected in a scanning electron micrograph (Figure 5 a) and measured with a particle sizer (Figure 5 b), where the x-axis indicates the particle diameter. Two different preparations of microbubbles are shown, plga microbubbles hat are prepared using the methodology described in the reference by Shi WT et al, as well as a similar population of microbubbles that have been freeze-dried (lyophilized) and reconstituted in a solution. Accordingly, the particle diameter or the particles in Fig. 5 (a) is around 12-13 μm. This mono-dispersity provides that the population of the microbubbles resonates over a narrow frequency range. Thus, by producing different groups having different sizes, it is possible to define said subgroups having different properties, namely in this particular case having different resonance frequencies. A second advantage is careful control over the shell thickness of the microbubbles. By carefully controlling the size distribution and having specified the amount of a shell material, it is possible to control the shell thickness to a very tight tolerance (see Shi WT et al.). The thickness of the shell then controls the threshold of an external acoustic pressure that causes the entire population of the microbubbles to transition sharply from stable to destruction (i.e. release of the material).

[0061] Figure 6 shows the number of microbubbles destroyed as a function of ultrasonic pressure amplitude (x-axis is the mechanical index of the pulse and y-axis is the event count). The microbubbles show a sharp transition at a specific pressure.

[0062] Figure 7 shows the force needed to "destroy" and deliver the payload for three different sub-populations (marked with circles, triangles and squares, respectively) of microbubbles as a function of the thickness of the surrounding shell. Due to careful selection of the shell thickness, discrete ultrasonic pressure fields can be chosen to deliver the payload. Accordingly, the destruction of the microbubbles can then be used to deliver e.g. any associated drug or genetic material to a particular delivery zone, e.g. tissue. Thus, ultrasound can be used to administer time-varying pressure field to the sub-groups of microbubbles to control the designated spatial and temporal delivery of any attached therapy, as an example.

[0063] Figure 8 shows a flow chart of an exemplary method.

[0064] In this case, steps (S1) 801 - (S2) 803 may be considered as preparing the sub-groups of ultrasound sensitive particles, wherein the step (S1) 801 relates to providing said sub-groups of ultrasound sensitive particles, wherein the particles within the same sub-group share a common acoustic property, the step (S2) 803 relates to "attaching" or "incorporating" the material into the ultrasound sensitive particles, preferably such that the particles within the same sub-group carry the same type of material. The ultrasound sensitive particles are microbubbles having a shell structure, where the physical property of the microbubbles is selected from the shell thickness, the shell size, the diameter of the shell, geometrical shape of the shell, and a combination thereof. The ultrasound sensitive particles may also be selected from nanoparticles, liposomes, heat shock proteins and the like. The material carried by ultrasound sensitive particles may be a biological material selected from a pharmaceutical material, proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), small interfering ribonucleic acid (siRNA), and a combination thereof. Other materials may include artificial constructs such as nanoparticles, nanostructures, or autonomous or guided nanomachines.

[0065] In one example, the respective acoustic activation property of the ultrasound sensitive particles within the same sub-group is a common resonance frequency or resonance frequency range. Thus, the acoustic activation properties of the ultrasound sensitive particles at a specific frequency or limited frequency range correspond to instruction codes that can be given according to a pre-specified "program". There is a defined grammar that encapsulates the syntax and the semantics of this programming paradigm. In a programming language, syntax refers to the ways, symbols may be combined to create a well-formed program. Syntax provides a structural description of the various expressions that make up proper instructions. In this particular case, syntax will refer to the proper formation of the instructions through predefined properties of the ultrasound sensitive particles and the properties of the ultrasonic pulse. Semantics describes the behavior of the computer when executing a program. This behavior can be described by the relationship between the input and output of a program. An example is provided below.

[0066] In step (S3) 805, the ultrasound sensitive particles are administered either simultaneously or subse-

quently e.g. via an intra-venous or arterial injection.

[0067] In steps (S4) 807, commands are received from a user indicating at least one spatial delivery zone and the type of material to be released at the at least one spatial delivery zone.

[0068] In step (S5) 809, the spatial distribution of the ultrasound sensitive particles is imaged. When the imaging data indicate that the ultrasound sensitive particles are localized nearby the spatial delivery zone, the ultrasound sensitive particles are irradiated in accordance to the received commands (S6) 811.

[0069] Iteration 813 is performed, wherein the imaging is utilized to check whether the commands have been completed. The imaging apparatus could receive image from ultrasound as well as from optical reading e.g. in the case of optoacoustic imaging. As an example, if the user commands that material B and subsequently material A (see Figs. 2-4) is to be delivered to a target tissue at a given delivery zone, the image will show whether there are still some ultrasound sensitive particles comprising material B left. If there are some left, step (S6) 811 is repeated, otherwise the first set of commands is completed (S7) 815, and the subsequent set of the received commands is performed, e.g. delivering material A to the target zone (see also Fig. 4).

[0070] The specification of the present disclosure is not limiting for the scope of the claims.

Claims

1. Ultrasound sensitive particles (116-118) for use in a method of *in vivo* release of a material carried by the ultrasound sensitive particles (116-118), the release being caused by irradiating the ultrasound sensitive particles (116-118) with an ultrasonic pulse (108) having acoustic properties selected so as to interact with the ultrasound sensitive particles (116-118) and thus causing the release of the material,

   - wherein the ultrasound sensitive particles (116-118) include micro bubbles having a shell structure containing the material to be released therein,
   - wherein said micro bubbles comprise different sub-groups,
   - wherein the shell structure within the same sub-group has similar physical property characteristic for a respective acoustic activation property, causing each respective sub-group to interact independently with the ultrasonic pulse (108),
   - wherein the acoustic activation property is an ultrasonic pressure amplitude, so that rupture of said micro bubbles is provided above a sharp acoustic pressure threshold within the same sub-group,
   - wherein different sub-groups have different physical properties of their shell structure in respect of said acoustic activation property,
   - so that the release of the material is controlled spatially and temporally based on the pressure amplitude of the ultrasonic pulse.

2. Ultrasound sensitive particles according to claim 1, wherein the ultrasound sensitive particles (116-118) within the same sub-group (110-112) of ultrasound sensitive particles carry the same type of material.

3. Ultrasound sensitive particles according to claim 1, wherein the material carried by ultrasound sensitive particles (116-118) is a biological material and is selected from:

   - a pharmaceutical material,
   - polysaccharides,
   - lipids,
   - fatty acids,
   - steroids,
   - proteins,
   - enzymes,
   - deoxyribonucleic acid (DNA),
   - ribonucleic acid (RNA),
   - small interfering ribonucleic acid (siRNA),
   - inorganic artificial constructs,
   - nanoparticles
   - nanomachines,
   - chemicals intended to alter the composition or geometry of existing sub-groups of particles,
   - biochemical particles, and
   - a combination thereof.

4. Ultrasound sensitive particles according to claim 1, wherein the release of the material is carried out locally in or nearby a target tissue or cell (120) by releasing the material from at least one of the sub-groups (110-112) of the ultrasound sensitive particles.

5. Ultrasound sensitive particles according to claim 1, the *in vivo* release method further comprising the following steps:

   a. receiving at least one command (807) indicating at least one spatial delivery zone, each command indicating at least one type of material to be released at specific ratios,
   b. imaging the spatial distribution (809) of the ultrasound sensitive particles, the imaging resulting in data indicating the spatial distribution of the ultrasound sensitive particles, and in response to the spatial data
   c. irradiating the ultrasound sensitive particles (813) in the at least one delivery zone with an ultrasonic pulse, the property of the ultrasonic pulse being controlled such that the release of the material in the at least one delivery zone is

in accordance to the at least one received command,

d. repeating steps b) - c) for each subsequent command until the received commands have been completed.

6. Ultrasound sensitive particles according to claim 5, wherein the at least one command further includes information about the amount of the material to be delivered at a given delivery zone or the mix of materials to be delivered at a given delivery zone, or about the type of the material to be released, in order to modify the acoustic properties of the remaining ultrasound sensitive particles (116-118).

7. Ultrasound particles according to claim 1, wherein the physical property of the shell structure is selected from the shell thickness, the shell size, the diameter of the shell, geometrical shape of the shell chemical composition of the shell, and a combination thereof.

8. Ultrasound sensitive particles according to claim 1,

- wherein the shell structure provides resonance of micro bubbles over a narrow frequency range within the respective sub-group, and
- wherein the acoustic property furthermore comprises an ultrasonic frequency corresponding to the resonance frequency of at least one of the sub-groups.

9. A method of controlling a release, in a cell culture or *in vitro,* of a material carried by ultrasound sensitive particles (116-118),

- the release being caused by irradiating the ultrasound sensitive particles (116-118) with an ultrasonic pulse (108) having acoustic properties selected so as to interact with the ultrasound sensitive particles (116-118) and thus causing the release of the material,
- the release being caused by irradiating the ultrasound sensitive particles (116-118) with an ultrasonic pulse having acoustic properties so as to interact with the ultrasound sensitive particles (116-118), thus causing the release of the material,
- wherein the ultrasound sensitive particles include micro bubbles having a shell structure containing the material therein,
- wherein the micro bubbles comprise different sub-groups,
- wherein the shell structure within the same sub-group has similar physical property characteristic for a respective acoustic activation property, causing each respective sub-group to interact independently with the ultrasonic pulse (108),
- wherein the acoustic activation property is an ultrasonic pressure amplitude, so that rupture of said micro bubbles is provided above a sharp acoustic pressure threshold within the same sub-group,
- wherein different sub-groups have different physical properties of their shell structure in respect of said acoustic activation property,
- so that the release of the material is controlled spatially and temporally based on the pressure amplitude of the ultrasonic pulse.

10. A method according to claim 9, wherein the ultrasound sensitive particles (116-118) within the same sub-group (110-112) of ultrasound sensitive particles carry the same type of material.

Patentansprüche

1. Ultraschallempfindliche Partikel (116-118) zur Verwendung in einem Verfahren zur In-vivo-Freisetzung eines von den ultraschallempfindlichen Partikeln (116-118) transportierten Materials, wobei die Freisetzung durch die Beschallung der ultraschallempfindlichen Partikel (116-118) mit einem Ultraschallimpuls (108) bewirkt wird, der akustische Eigenschaften aufweist, die so ausgewählt werden, dass er mit den ultraschallempfindlichen Partikeln (116-118) interagiert und somit die Freisetzung des Materials bewirkt,
wobei die ultraschallempfindlichen Partikel (116-118) Mikroblasen mit einer Hüllenstruktur beinhalten, die das freizusetzende Material enthält,
wobei die genannten Mikroblasen unterschiedliche Teilgruppen beinhalten,
wobei die Hüllenstruktur innerhalb derselben Teilgruppe ähnliche physikalische Eigenschaften aufweist, die für eine entsprechende Schallaktivierungseigenschaft charakteristisch sind, sodass jede entsprechende Teilgruppe veranlasst wird, unabhängig mit dem Ultraschallimpuls (108) zu interagieren,
wobei die Schallaktivierungseigenschaft eine Ultraschalldruckamplitude ist, sodass das Platzen der genannten Mikroblasen innerhalb derselben Teilgruppe oberhalb eines deutlichen Schwellenwerts des Schalldrucks erfolgt,
wobei unterschiedliche Teilgruppen unterschiedliche physikalische Eigenschaften ihrer Hüllenstruktur in Bezug auf die genannte Schallaktivierungseigenschaft aufweisen,
sodass die Freisetzung des Materials anhand der Druckamplitude des Ultraschallimpulses räumlich und zeitlich gesteuert wird.

2. Ultraschallempfindliche Partikel nach Anspruch 1, wobei die ultraschallempfindlichen Partikel (116-118) innerhalb derselben Teilgruppe (110-112)

von ultraschallempfindlichen Partikeln dieselbe Art von Material transportieren.

3. Ultraschallempfindliche Partikel nach Anspruch 1, wobei das von den ultraschallempfindlichen Partikeln (116-118) transportierte Material ein biologisches Material ist und aus den folgenden Materialien ausgewählt wird:

eine pharmazeutische Substanz,
Polysaccharide,
Lipide,
Fettsäuren,
Steroide,
Proteine,
Enzyme,
Desoxyribonukleinsäure (DNA),
Ribonukleinsäure (RNA),
kurze interferierende Ribonukleinsäure (siRNA),
anorganische künstliche Gebilde,
Nanopartikel,
Nanomaschinen,
chemische Substanzen, die für die Veränderung der Zusammensetzung oder Geometrie vorhandener Teilgruppen mit Partikeln bestimmt sind,
biochemische Partikel und
eine Kombination aus diesen Substanzen.

4. Ultraschallempfindliche Partikel nach Anspruch 1, wobei die Freisetzung des Materials lokal in oder nahe einem Zielgewebe oder einer Zielzelle (120) durch die Freisetzung des Materials von zumindest einer der Teilgruppen (110-112) der ultraschallempfindlichen Partikel erfolgt.

5. Ultraschallempfindliche Partikel nach Anspruch 1, wobei das Verfahren zur In-vivo-Freisetzung ferner die folgenden Schritte umfasst:

a. Empfangen zumindest eines Befehls (807), der zumindest einen räumlichen Abgabebereich angibt, wobei jeder Befehl zumindest eine Art von in bestimmten Anteilen freizusetzendem Material angibt,
b. Abbilden der räumlichen Verteilung (809) der ultraschallempfindlichen Partikel, wobei sich aus der Abbildung Daten ergeben, die die räumliche Verteilung der ultraschallempfindlichen Partikel angeben, und als Reaktion auf die räumlichen Daten
c. Beschallen der ultraschallempfindlichen Partikel (813) in dem zumindest einen Abgabebereich mit einem Ultraschallimpuls, wobei die Eigenschaft des Ultraschallimpulses derart gesteuert wird, dass die Freisetzung des Materials in dem zumindest einen Abgabebereich in Übereinstimmung mit dem zumindest einen empfangenen Befehl erfolgt,
d. Wiederholen der Schritte b) - c) für jeden nachfolgenden Befehl, bis die empfangenen Befehle abgearbeitet sind.

6. Ultraschallempfindliche Partikel nach Anspruch 5, wobei der zumindest eine Befehl ferner Informationen über die Menge des in einem vorgegebenen Abgabebereich abzugebenden Materials oder über die Mischung des in einem vorgegebenen Abgabebereich abzugebenden Materials oder über die Art des freizusetzenden Materials umfasst, um die akustischen Eigenschaften der verbleibenden ultraschallempfindlichen Partikel (116-118) zu verändern.

7. Ultraschallempfindliche Partikel nach Anspruch 1, wobei die physikalische Eigenschaft der Hüllenstruktur aus Hüllendicke, Hüllengröße, Hüllendurchmesser, geometrischer Form der Hülle, chemischer Zusammensetzung der Hülle und einer Kombination dieser Eigenschaften ausgewählt wird.

8. Ultraschallempfindliche Partikel nach Anspruch 1, wobei die Hüllenstruktur innerhalb der entsprechenden Teilgruppe für Resonanz der Mikroblasen in einem schmalen Frequenzbereich sorgt und
wobei die akustische Eigenschaft ferner eine Ultraschallfrequenz umfasst, die der Resonanzfrequenz von zumindest einer der Teilgruppen entspricht.

9. Verfahren zur Steuerung der Freisetzung in einer Zellkultur oder *in vitro* eines Materials, das von ultraschallempfindlichen Partikeln (116-118) transportiert wird,
wobei die Freisetzung durch die Beschallung der ultraschallempfindlichen Partikel (116-118) mit einem Ultraschallimpuls (108) bewirkt wird, der akustische Eigenschaften aufweist, die so ausgewählt werden, dass er mit den ultraschallempfindlichen Partikeln (116-118) interagiert und somit die Freisetzung des Materials bewirkt,
wobei die Freisetzung durch die Beschallung der ultraschallempfindlichen Partikel (116-118) mit einem Ultraschallimpuls (108) bewirkt wird, der akustische Eigenschaften aufweist, sodass er mit den ultraschallempfindlichen Partikeln (116-118) interagiert und somit die Freisetzung des Materials bewirkt,
wobei die ultraschallempfindlichen Partikel (116-118) Mikroblasen mit einer Hüllenstruktur beinhalten, die das Material enthält,
wobei die Mikroblasen unterschiedliche Teilgruppen beinhalten,
wobei die Hüllenstruktur innerhalb derselben Teilgruppe ähnliche physikalische Eigenschaften aufweist, die für eine entsprechende Schallaktivierungseigenschaft charakteristisch sind, sodass jede entsprechende Teilgruppe veranlasst wird, unabhängig mit dem Ultraschallimpuls (108) zu interagie-

ren,
wobei die Schallaktivierungseigenschaft eine Ultraschalldruckamplitude ist, sodass das Platzen der genannten Mikroblasen innerhalb derselben Teilgruppe oberhalb eines deutlichen Schwellenwerts des Schalldrucks erfolgt,
wobei unterschiedliche Teilgruppen unterschiedliche physikalische Eigenschaften ihrer Hüllenstruktur in Bezug auf die genannte Schallaktivierungseigenschaft aufweisen,
sodass die Freisetzung des Materials anhand der Druckamplitude des Ultraschallimpulses räumlich und zeitlich gesteuert wird.

10. Verfahren nach Anspruch 9, wobei die ultraschallempfindlichen Partikel (116-118) innerhalb derselben Teilgruppe (110-112) von ultraschallempfindlichen Partikeln dieselbe Art von Material transportieren.

Revendications

1. Particules sensibles aux ultrasons (116-118) destinées à être utilisées dans un procédé de libération in vivo d'un matériau porté par les particules sensibles aux ultrasons (116-118), la libération étant provoquée par l'irradiation des particules sensibles aux ultrasons (116-118) par une impulsion ultrasonore (108) présentant des propriétés acoustiques sélectionnées de manière à interagir avec les particules sensibles aux ultrasons (116-118) et ainsi provoquer la libération de la matière :

où les particules sensibles aux ultrasons (116-118) comprennent des microbulles comportant une structure en forme de coque contenant le matériau à libérer à l'intérieur de celle-ci ;
où lesdites microbulles comprennent différents sous-groupes ;
où la structure en forme de coque à l'intérieur du même sous-groupe présente une caractéristique de propriété physique similaire pour une propriété d'activation acoustique respective, amenant chaque sous-groupe respectif à interagir indépendamment avec l'impulsion ultrasonique (108) ;
où la propriété d'activation acoustique est une amplitude de pression ultrasonore, de sorte qu'une rupture desdites microbulles se produise au-delà d'un seuil de pression acoustique fine à l'intérieur du même sous-groupe ;
où différents sous-groupes présentent des propriétés physiques différentes de leur structure en forme de coque par rapport à ladite propriété d'activation acoustique ;
de sorte que la libération du matériau soit régulée dans l'espace et dans le temps sur la base de l'amplitude de pression de l'impulsion ultrasonore.

2. Particules sensibles aux ultrasons selon la revendication 1, où les particules sensibles aux ultrasons (116-118) à l'intérieur du même sous-groupe (110-112) de particules sensibles aux ultrasons portent le même type de matériau.

3. Particules sensibles aux ultrasons selon la revendication 1, où le matériau porté par les particules sensibles aux ultrasons (116-118) est un matériau biologique et est sélectionné parmi:

un matériau pharmaceutique ;
des polysaccharides ;
des lipides ;
des acides gras ;
des stéroïdes ;
des protéines ;
des enzymes ;
un acide désoxyribonucléique (ADN) ;
un acide ribonucléique (ARN) ;
un petit ARN interférent (petit ARNi) ;
des structures inorganiques artificielles ;
des nanoparticules ;
des nanomachines ;
des substances chimiques destinées à altérer la composition ou la géométrie des sous-groupes de particules existants ;

- des particules biochimiques et
- une combinaison de ce qui précède.

4. Particules sensibles aux ultrasons selon la revendication 1, où la libération du matériau est effectuée localement à l'intérieur ou à proximité d'un tissu ou d'une cellule cible (120) en libérant le matériau provenant d'au moins l'un des sous-groupes (110-112) des particules sensibles aux ultrasons.

5. Particules sensibles aux ultrasons selon la revendication 1, le procédé de libération in vivo comprenant en outre les étapes suivantes :

a. la réception d'au moins un ordre (807) indiquant au moins une zone de livraison dans l'espace, chaque ordre indiquant au moins un type de matériau à libérer à des taux spécifiques ;
b. l'imagerie de la répartition dans l'espace (809) des particules sensibles aux ultrasons, l'imagerie engendrant des données indiquant la répartition dans l'espace des particules sensibles aux ultrasons et, en réponse aux données dans l'espace ;
c. l'irradiation des particules sensibles aux ultrasons (813) dans l'au moins une zone de livraison par une impulsion ultrasonore, la propriété de

l'impulsion ultrasonore étant régulée de sorte que la libération du matériau dans l'au moins une zone de livraison soit conforme à l'au moins un ordre reçu,

d. la répétition des étapes b et c pour chaque ordre suivant jusqu'à ce que les ordres reçus soient tous exécutés.

6. Particules sensibles aux ultrasons selon la revendication 5, où l'au moins un ordre présente en outre des informations sur la quantité de matériau à livrer dans une zone de livraison donnée ou le mélange de matériaux à livrer dans une zone de livraison donnée ou sur le type de matériau à libérer afin de modifier les propriétés acoustiques des particules sensibles aux ultrasons (116-118) restantes.

7. Particules ultrasonores selon la revendication 1, où la propriété physique de la structure en forme de coque est sélectionnée parmi l'épaisseur de la coque, la taille de la coque, le diamètre de la coque, la forme géométrique de la composition chimique de la coque et une combinaison de ce qui précède.

8. Particules sensibles aux ultrasons selon la revendication 1,
où la structure en forme de coque fournit une résonance de microbulles sur une étroite plage de fréquences à l'intérieur du sous-groupe respectif ; et
où la propriété acoustique comprend en outre une fréquence ultrasonore correspondant à la fréquence de résonance de l'au moins un des sous-groupes.

9. Procédé de régulation d'une libération, dans une culture de cellules ou in vitro, d'un matériau porté par des particules sensibles aux ultrasons (116-118) :

la libération étant provoquée par l'irradiation des particules sensibles aux ultrasons (116-118) par une impulsion ultrasonore (108) présentant des propriétés acoustiques sélectionnées de manière à interagir avec les particules sensibles aux ultrasons (116-118) et provoquant ainsi la libération du matériau ;
la libération étant provoquée par l'irradiation des particules sensibles aux ultrasons (116-118) par une impulsion ultrasonore présentant des propriétés acoustiques permettant une interaction avec les particules sensibles aux ultrasons (116-118), en provoquant ainsi la libération du matériau ;
où les particules sensibles aux ultrasons comprennent des microbulles comportant une structure en forme de coque contenant le matériau à l'intérieur de celle-ci ;
où les microbulles comprennent différents sous-groupes ;
où la structure en forme de coque à l'intérieur du même sous-groupe présente une caractéristique de propriété physique similaire pour une propriété d'activation acoustique respective, amenant chaque sous-groupe respectif à interagir indépendamment avec l'impulsion ultrasonore (108) ;
où la propriété d'activation acoustique est une amplitude de pression ultrasonore, de sorte qu'une rupture desdites microbulles se produise au-delà d'un seuil de pression acoustique fine à l'intérieur du même sous-groupe ;
où différents sous-groupes présentent différentes propriétés physiques de leur structure en forme de coque par rapport à ladite propriété d'activation acoustique ;
de sorte que la libération du matériau soit régulée dans l'espace et dans le temps sur la base de l'amplitude de pression de l'impulsion ultrasonore.

10. Procédé selon la revendication 9, où les particules sensibles aux ultrasons (116-118) à l'intérieur du même sous-groupe (110-112) de particules sensibles aux ultrasons portent le même type de matériau.

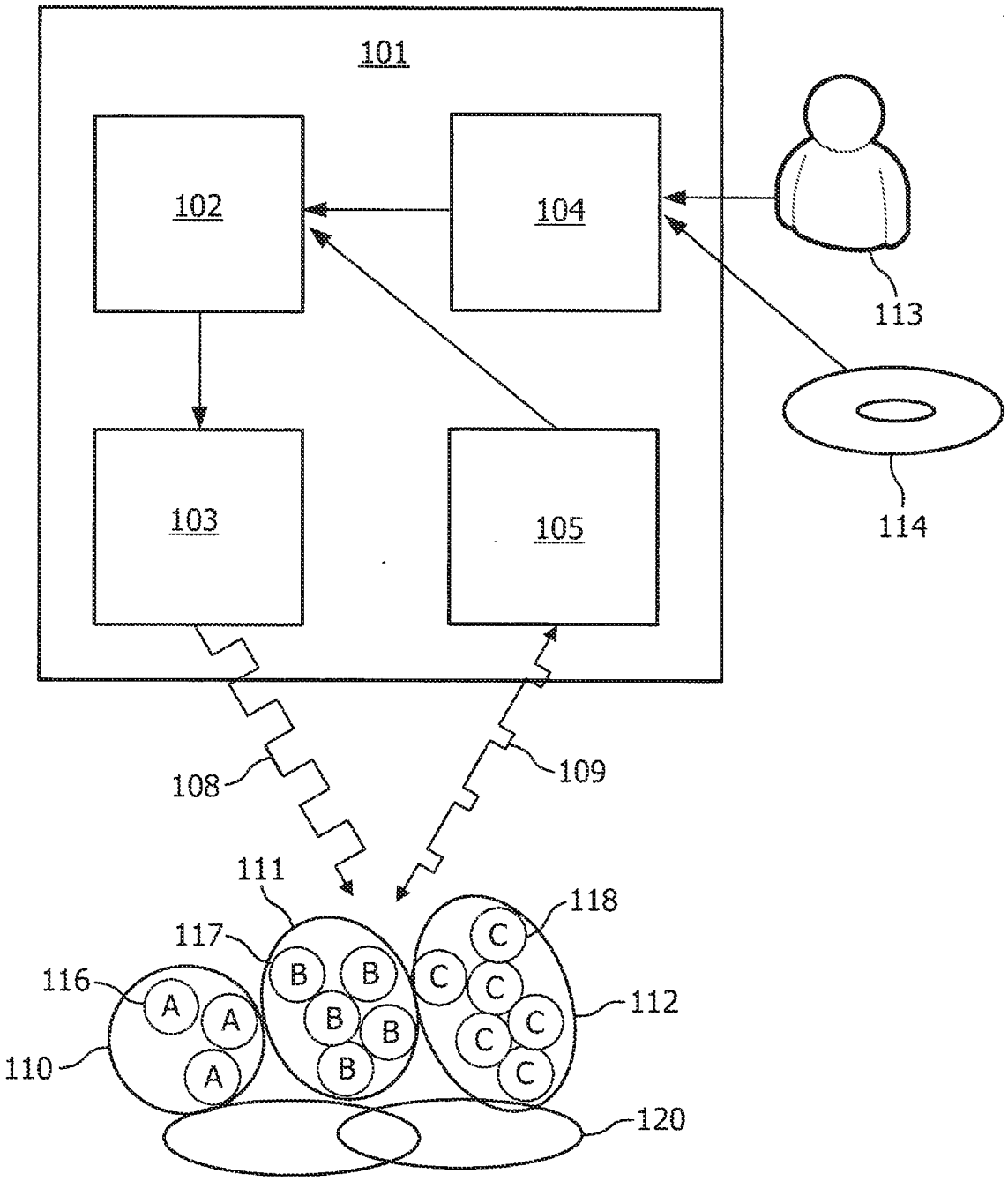

101
102
104
103
105
113
114
108
109
111
117
118
116
112
110
120
A
B
C

FIG. 1

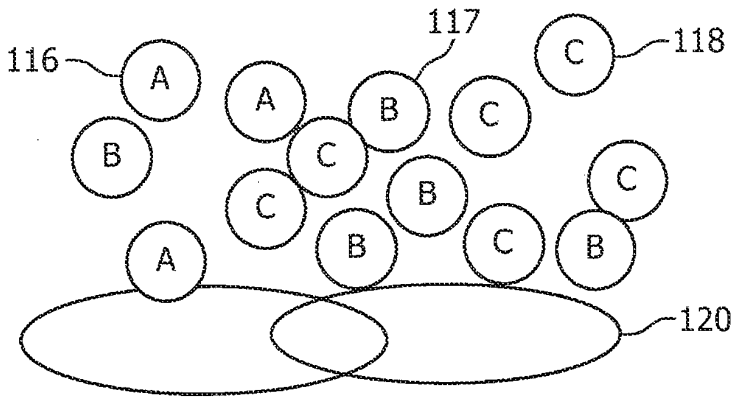


FIG. 2

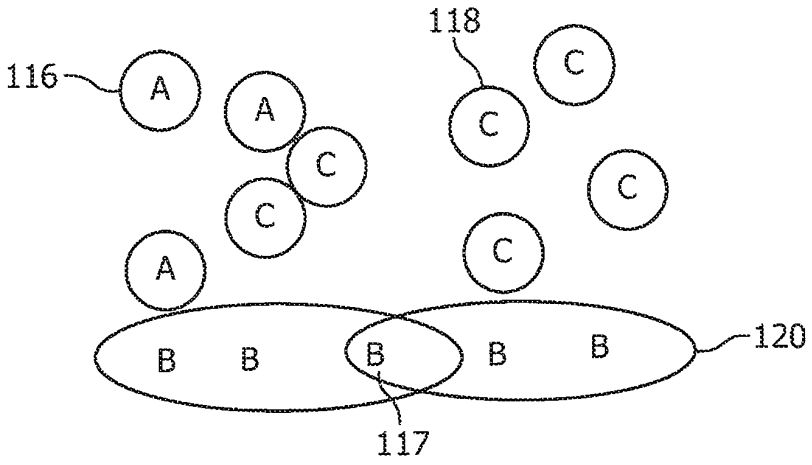


FIG. 3

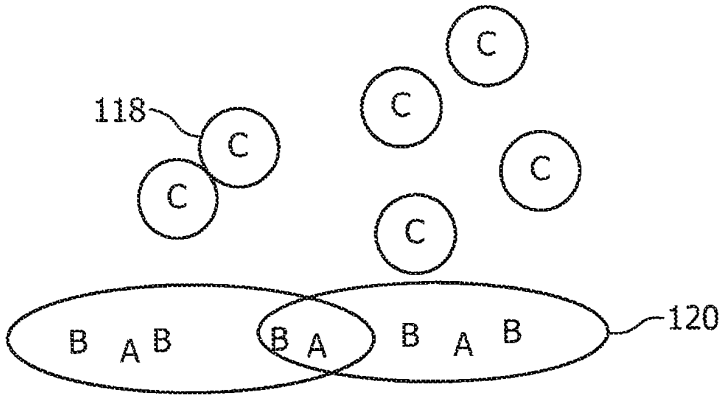


FIG. 4

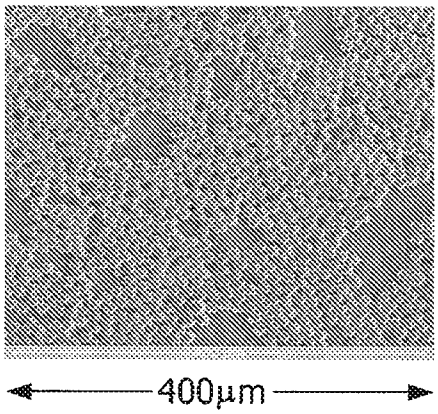

400µm

FIG. 5a

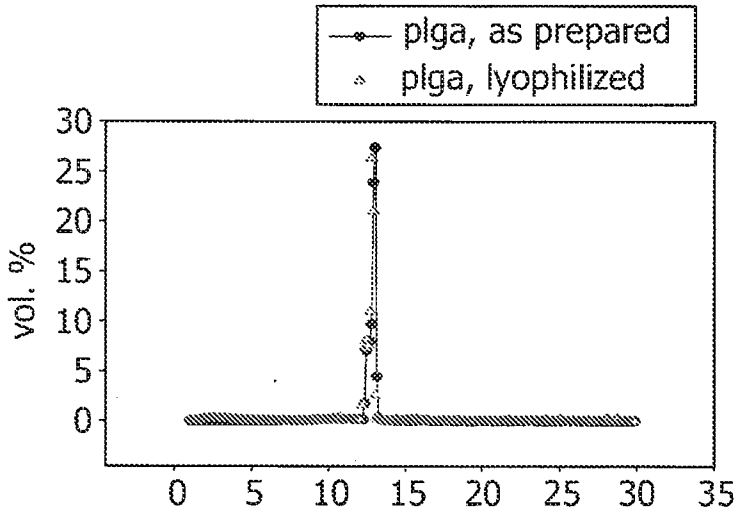

plga, as prepared
plga, lyophilized
vol. %
0
5
10
15
20
25
30
0
5
10
15
20
25
30
35

FIG. 5b

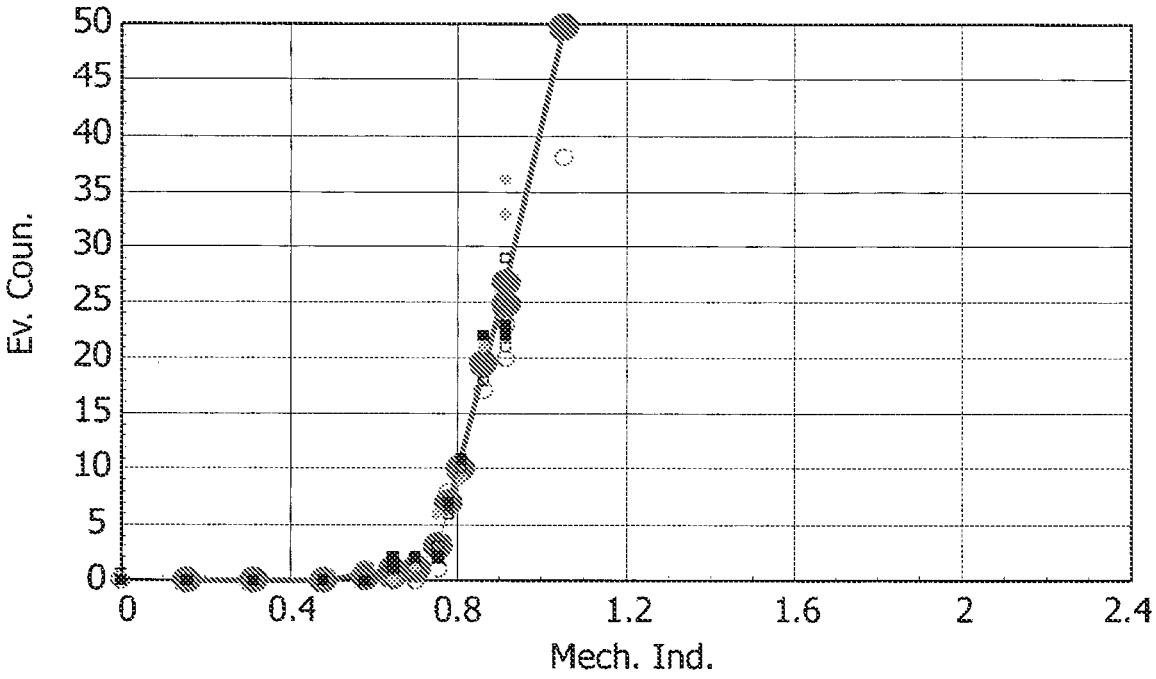
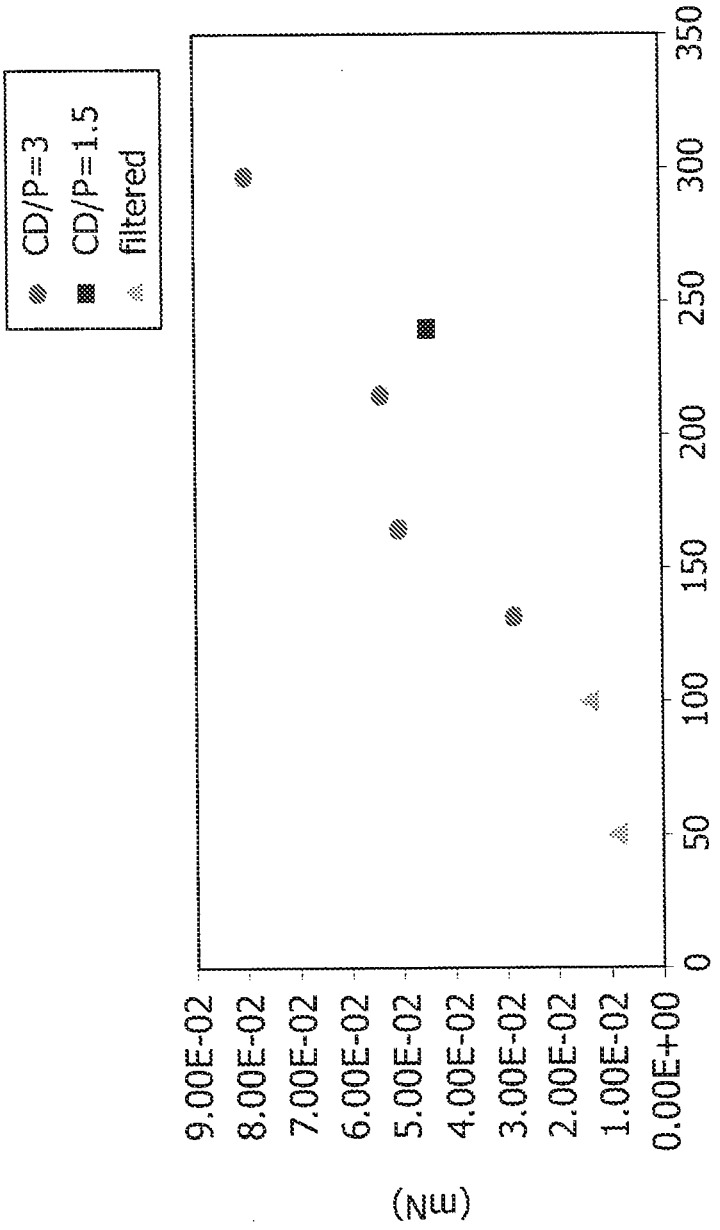


FIG. 6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4.00E-02
3.00E-02
2.00E-02
1.00E-02
0.00E+00
(#/cm³)
0
50
100
150
200
250
300
350
(nm)

FIG. 7

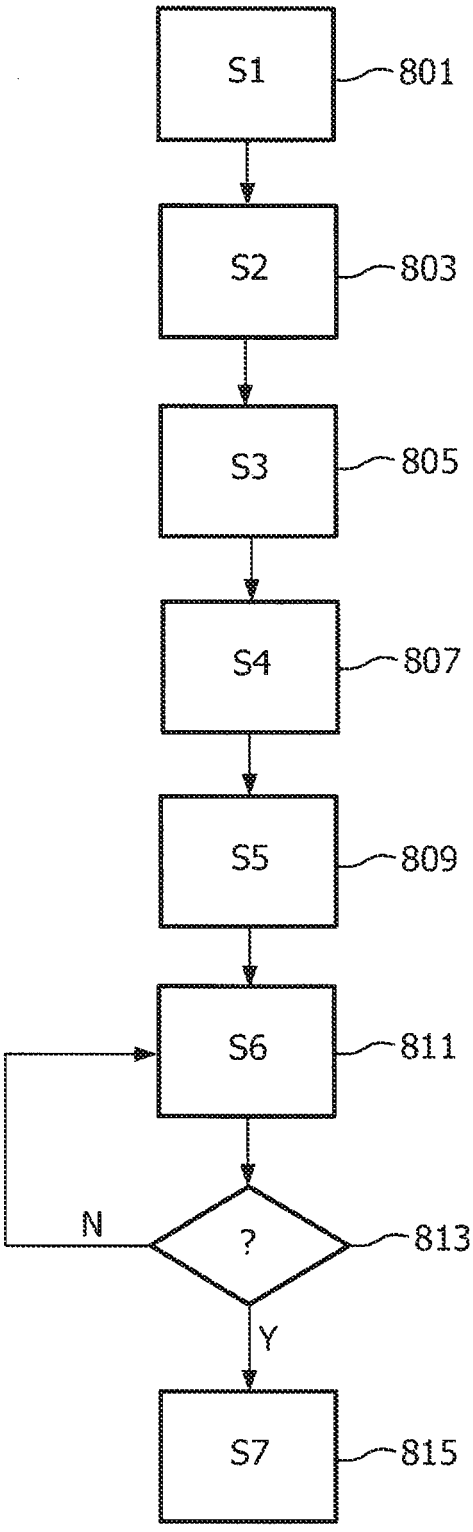

FIG. 8

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	控制超声敏感颗粒携带的材料的释放		
公开(公告)号	EP2120722B1	公开(公告)日	2014-05-07
申请号	EP2008719539	申请日	2008-03-03
[标]申请(专利权)人(译)	皇家飞利浦电子股份有限公司		
申请(专利权)人(译)	皇家飞利浦电子N.V.		
当前申请(专利权)人(译)	皇家飞利浦N.V.		
[标]发明人	DIMITROVA NEVENKA HALL CHRISTOPHER S CHIN CHIEN T		
发明人	DIMITROVA, NEVENKA HALL, CHRISTOPHER, S. CHIN, CHIEN, T.		
IPC分类号	A61B8/00 A61K9/00 A61K41/00 A61K47/48 A61K49/22 A61M37/00 G01S15/89		
CPC分类号	A61B8/481 A61K9/0009 A61K41/0028 A61K47/6925 A61M37/0092		
代理机构(译)	kroeze antonius，约翰		
优先权	60/893916 2007-03-09 US		
其他公开文献	EP2120722A1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种控制由超声敏感颗粒携带的材料的释放的方法和设备，该释放是通过用超声脉冲照射超声敏感颗粒引起的，所述超声脉冲具有选择的声学特性以便与超声敏感颗粒相互作用并且从而导致材料的释放。超声敏感颗粒包括超声敏感颗粒的子组，同一子组内的超声敏感颗粒具有其各自的声学特性，使得每个相应的子组独立地与声波相互作用。

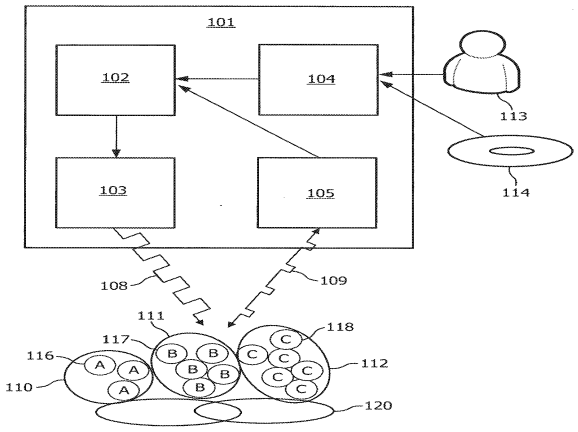

FIG. 1