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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *the filing date of the international application is within two months from the date of expiration of the priority period (Rule 26bis.3)*

(54) Title: HIGH TEMPERATURE MODULE FOR A 3D BIOLOGICAL PRINTER DEPOSITION SYSTEM

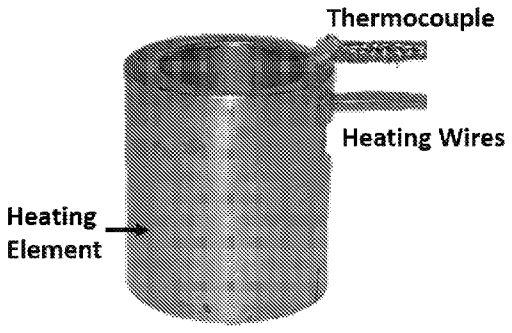

Figure 1. A round heating element with heating wires enclosed within the walls.

(57) Abstract: This present invention provides a high temperature module for a 3D biologies printer's deposition system. This module is designed to be adaptive and integrative to current biological printers while providing the ability to maintain a "hot" environment within the fabrication head. A "hot" environment is defined as changing and maintain the temperature within the printer's fabrication system of at least one degrees Celsius (1 degree C) above ambient temperature.

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HIGH TEMPERATURE MODULE FOR A 3D BIOLOGICAL PRINTER DEPOSITION SYSTEM

BACKGROUND

Researchers in the field of tissue engineering and regenerative medicine have begun to realize that complex, multicellular systems are needed for improved testing and growing large organs and tissues (have been difficult to develop due to lack of a blood supply to transport oxygen and nutrients). Conceptually, 3D printing could print complex structures required to transport oxygen and nutrients and could print cells, extracellular matrix, and growth factors precisely to create samples that better mimic *in vivo* tissue. The key of successfully building a functional tissue construct, is having the right tool. In order to assemble cells into a functional array, the material delivery system must sustain cell life and have full control of the fluid/bio-suspension being printed. Most importantly, a printer's deposition system must have the capabilities to handle and/or utilize an expansive library of biologically compatible materials. This library will increase the printer's abilities to fabricate more complex physiologically relevant tissue constructs. Due to the nature of many biological materials, cells, and the design of many biological printers; there is a need for a temperature module. One that can adapt to current fabrication system. This temperature module will be primarily responsible for heating of the fabrication head. Heat can be used to maintain a cell friendly temperature or even heat polymers such that its viscosity changes, making it printable.

This article presents a high temperature module for a 3D biologics printer's deposition system. This module is designed to be adaptive and integrative to current biological printer while providing the abilities to maintain a "hot" environment within the fabrication head. A "hot" environment is defined as changing and maintain the temperature within the printer's fabrication system of at least one degrees Celsius (1°C) above ambient temperature.

BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction

with the accompanying drawing figures wherein like reference characters denote corresponding parts throughout the several views and wherein:

Figure 1 depicts a round heating element with heating wires enclosed within the walls;

Figure 2 depicts a rectangular heating element with a ceramic heating wire embedded at the corner;

Figure 3 depicts the configuration of the PID controller with the heating element;

Figure 4 depicts the heating system with all its components;

Figure 5 depicts the heating element mounted on a 3D Printer's fabrication heat;

DETAILED DESCRIPTION

This high temperature module has two classification, namely; 1) heating and maintaining a "hot" environment up to forty degrees Celsius (40 °C), and 2) heating and maintaining a "hot" environment up to five hundred degrees Celsius (500 °C).

The first classification of heating and maintaining a "hot" environment up to forty degrees Celsius (40 °C) is and will be referred to in this article as the cell-friendly temperature. Human cells prefer an environment where the temperature is 37 °C, however, some cells can survive an environment where is about 40 °C. Due to this, the first classification is referred to the cell-friendly temperature.

The second classification of heating and maintaining a "hot" environment up to five hundred degrees Celsius (500 °C) is and will be referred to the hot-melt temperature. When using this process of the high temperature module there will not be any cell in the fabrication system. Any living organism used with temperature setting of the hot-melt settings will die. The hot-melt processes are primarily used to change the viscosity of the bio-polymer within the fabrication system, rendering it printable. Most bio-polymer are rigid at ambient temperature and cannot be printed on a biological printer. Some processes used to make these material printable are chemical synthesis. Most chemical process will change the material properties, or even worst, introduce hard toxins, making it useless for the use of cells. Introducing a hot-melt system directly to the fabrication system provides new incentives to use a wider range of material to fabricate more complex physiologically relevant tissue constructs.

Figure 1 and Figure 2 shows two designs of the heating elements. Figure 1 is a round heating element with the heating wires enclosed within its walls. This design is best for fast heating, high heating, and limited space applications. Figure 2 is designed with a ceramic heating wire that conducts heats thru the heating block. This design is for relatively low heating applications. Figure 3 shows the system configuration and the closed-loop feedback PID controller.

The design and operation of the cell-friendly and hot-melt high temperature module is the same. The major difference between the two, is the range of operational temperature. This high temperature module for a 3D biological printer's deposition system has a proportional-integral-derivative (PID) temperature control unit, thermocouple, relay system, heating element, heating body, and mounting apparatus.

The PID temperature control unit is integrated with the biological printer such that all settings and processes can be controlled by the end-user and/or with the printer's control system. The PID system provides a unique feedback control system that reduces error and over-shooting temperature settings. Over-shooting temperature can create an environment that is too hot, hence causing cell dead or burning the material in the fabrication system. Coupled with the PID system is the relay system. Together these two systems provides and maintain thermal equilibrium (set by the end user). Figure 4 shows the heating elements and its system components.

The heating element is designed based on the operator's main objectives. If the desire is for hot-melt, a high wattage heating element will be used. If the desire if for cell-friendly temperature, a low wattage heating element will be used. The heating element is a thermal electric system that generates heat from electricity. This heating element is place inside the heating body where it heats the heating body. The heating body will conduct and uniformly transfer and maintain the heat (energy) onto the fabrication system. The heating body is fabrication from high conductive bio-compatible material. Also on the heating body is a thermocouple. The thermocouple reports current conditions about the heating body back to the PID controller. The thermocouple provides real-time temperature monitoring. To maintain a tight fit on the fabrication system, a mounting apparatus is used. Figure 5 shows an image of the heating element mounted onto the fabrication head of an existing 3D cell printer.

CLAIMS

1. A method of changing and maintain the temperature within a 3D biological printer's fabrication system of at least one degrees Celsius (1 °C) above ambient temperature.
2. The method of claim 1, provides a cell-friendly environment (temperature of up to 40 °C).
3. The method of claim 1, provides a hot-melt environment (temperature of up to 500 °C).
4. The method of claim 1, wherein the extruded bioactive filament maintains cell viability of at least 70%.
5. The method of claim 1, wherein the extruded bioactive filament includes one or more selected from the group consisting of: a polymer, a solution, a cell-lade solution, a chemically reactive solution, an aqueous solution, sodium alginate solutions, a sacrificial support material, a cell, alginate, a cross-linker, a cross-linking solution, a calcium chloride solution, and a hydrogel.
6. The method of claim 1, wherein the extruded bioactive filament is produced by uniform mass flow rate.
7. The method of claim 1, wherein the extruded bioactive filament is produced by a gradient mass flow rate.
8. The method of claim 1, wherein the extruded bioactive filament is produced by backwards mass flow rate.
9. The method of claim 1, wherein the extruded bioactive filament in-part comprised of one or more living cells.
10. The method of claim 1, wherein the extruded bioactive filament has no living biologics.
11. The method of claim 1, wherein the extruded bioactive filament is symmetrical along a longitudinal axis
12. The method of claim 1, wherein the extruded bioactive filament is asymmetrical along a longitudinal axis.
13. The method of claim 1, wherein the extruded bioactive filament has one-dimensional pattern.

14. The method of claim 1, wherein the extruded bioactive filament has two-dimensional pattern.
15. The method of claim 1, wherein the extruded bioactive filament has three-dimensional pattern.
16. The method of claim 1, wherein the extruded bioactive filament has a largest cross-sectional dimension less than about 1 mm.
17. The method of using one of more fabrication head using the method in claim 1: producing methods of claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16.
18. The method of claim 1, wherein the bioactive filament is used to produce: microfluidic tissue constructs, tissue scaffolds, tissue-on-chip, organ-on-a-chip.

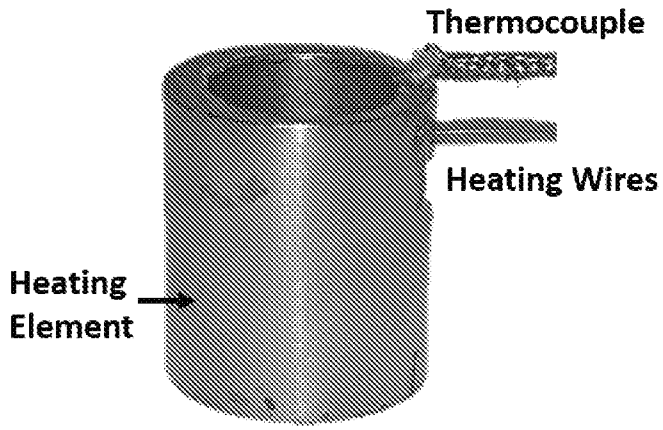

Figure 1. A round heating element with heating wires enclosed within the walls.

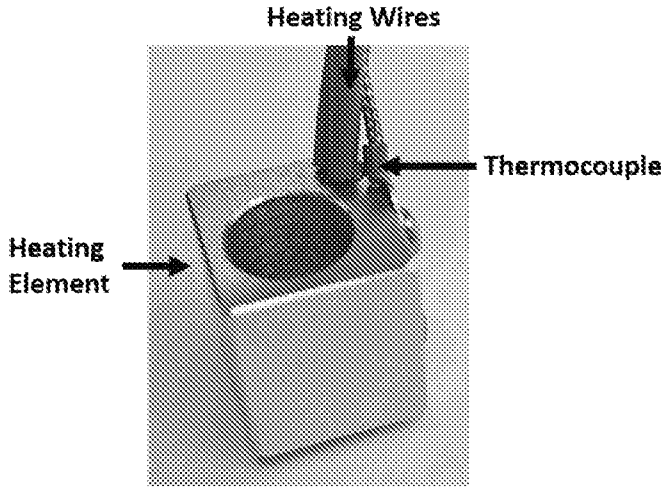

Figure 2. Rectangular heating element with a ceramic heating wire embedded at the corner.

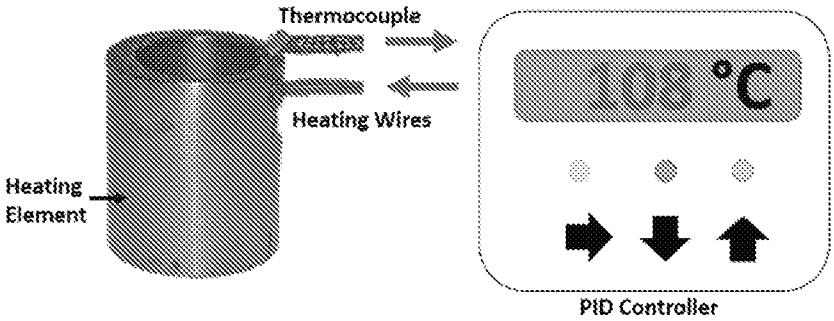

Figure 3. Configuration of the PID controller with the heating element.

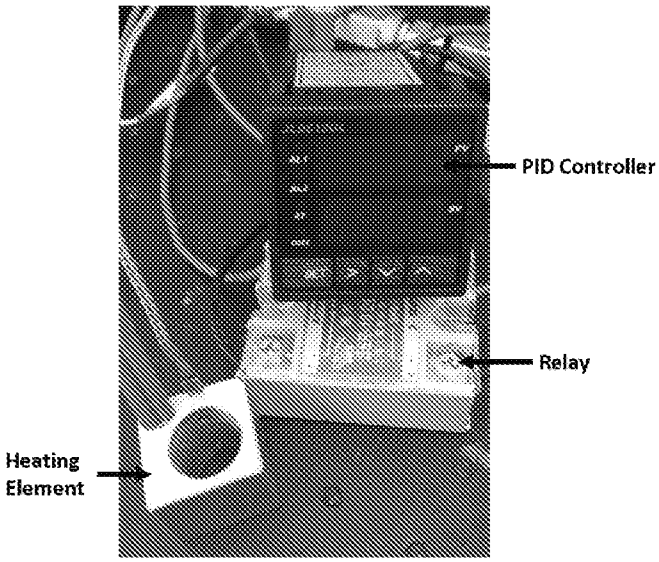

Figure 4. Heating System with all its components.

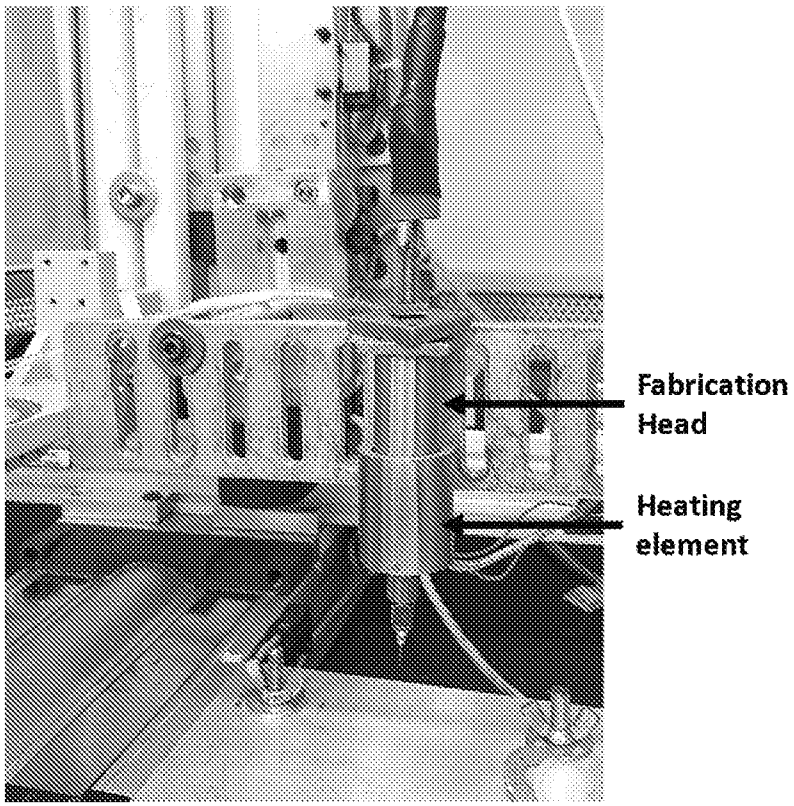

Figure 5. Heating element mounted on a 3D Printer's fabrication heat.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/21270

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61F 2/02, 2/04, 2/06; A61L 27/40, 27/54; B29C 64/10 (2017.01)
CPC - A61F 2/02, 2/04, 2/06, 2/062; A61L 27/40, 27/54; B29C 67/0051, 67/0085; B33Y 10/00, 30/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0089238 A1 (KANG, H-W et al) 12 April 2012; figure 9; paragraphs [0013]-[0014], [0025], [0029], [0035]-[0037], [0050]-[0053], [0069], [0071], [0075]-[0078], [0087], [0112]	1-5, 9, 13-16, 18 --- 6-8, 10-12
Y	US 6,372,178 B1 (TSENG, AA) 16 April 2002; column 3, lines 16-25; column 7, lines 3-6, 53-58; column 9, lines 21-24	6
Y	WO 2015/077262 A9 (GUILL TOOL AND ENGINEERING) 28 May 2015; page 6, lines 24-25; page 7, lines 14-22; page 29, lines 23-27; page 40, lines 21-24; page 41, lines 4-15)	7-8
Y	US 5,490,962 A (CIMA, LG et al) 13 February 1996; column 6, lines 57-68; column 9, lines 53-61; column 11, line 66 – column 12, line 14; column 13, lines 21-27	10
Y	US 2006/0195179 A1 (SUN, W et al) 31 August 2006; paragraphs [0060]-[0062]; claim 7	11-12
A	US 2015/0035206 A1 (SARTORIUS STEDIM BIOTECH GMBH) 05 February 2015; entire document	1-16, 18
A	US 2014/0328963 A1 (MARKFORGED, INC) 06 November 2014; entire document	1-16, 18
A	WO 2013/123049 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 22 August 2013; entire document	1-16, 18
A	CN 105012060 A (UNIV SHANGHAI) 04 November 2015; entire document	1-16, 18

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2017 (24.04.2017)	09 JUN 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571 273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/21270

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.