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Rapid Prototyping in Biomedical Engineering

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1. Introduction

Tissue engineering has attracted great attention as a key technology for realizing regenerative medicine (Lysaght and Reyes, 2001, Ringe, et al., 2002). In particular, tissue and organ repair are a possible applications owing to recent advances such as the development of induced pluripotent stem (iPS) cells (Takahashi and Yamanaka, 2006). Cell culture on a 3-dimensional extracellular matrix (3D ECM) is required to study differentiation of stem cells into various types and achieve in vitro tissue repair (Cukierman, et al., 2001, Stevens and George, 2005). Therefore, 2D and 3D patterning technologies for developing scaffolds are increasingly required in tissue engineering.

In this context, the role of rapid prototyping (RP) in medicine and biomedical engineering is greatly expanding. Highly precise and fine scaffold patterning has been achieved not only by photolithography (Leclerc, et al., 2004) but also by several RP methods including 3D printing (Kim, et al., 2008, Landers, et al., 2002, Nakamura, et al., 2005, Roth, et al., 2004). In most of these technologies, 2D or 3D scaffold patterns are batchwise or sequentially fabricated, cells are subsequently cultured on the scaffold pattern, and cell viability in the mixture of patterns is evaluated. To investigate the process of tissue repair, interactions between various types of cells on 3D structures have been studied. The pattern complexity of these structures has been found to be increasing.

In biomedical engineering, not only tissue engineering but also the developments of implantable and other prostheses are important applications of RP technology. In biomedical engineering. Commencing with inlays, many implantable prostheses such as total joint prostheses and dental prostheses have been realized based on RP technology. Furthermore, bone regeneration is one of the principal applications of tissue engineering. RP of hydroxyapatite (HAp) is expected to play a significant role in this field. As described above, the application of RP in biomedical engineering is greatly expanding. In this chapter, some applications of RP in medicine and biomedical engineering fields and a systematic collection of the latest achievements in these areas have been described.

2. Materials used in RP techniques for biomedical applications

This section provides a review of the materials used in RP techniques for biomedical applications. For example, hydrogel is one of the important materials used for cell culture. Some advanced biomaterials such as thermoreversible hydrogels have also been discussed below.

Ceramics are also used for orthopedic implants. Especially, porous composites such as HAp are expected to be used for bone tissue regeneration. Furthermore, cells themselves are directly printed or patterned through RP techniques.

2.1 Hydrogels

Hydrogels are a water-containing networks of water-insoluble polymer chains. They are also referred as aquagels and can absorb a huge amount of water. Of note, a hydrogel can contain more than 99% water by weight. By modifying the polymer network, various functionalities of a hydrogel such as biocompatibility and stimulus responsibility can be realized. These hydrogels are often referred as "Smart gels" (Chaterji, et al., 2007) or "Intelligent gels"(Osada and Ross-Murphy, 1993). A hydrogel is widely used for embedding biological samples and/or pharmaceutical agents ecause it is a soft and wet material.

One of the most important applications of hydrogels in tissue engineering is their use as a scaffold for cell culture (Drury and Mooney, 2003, Nowak, et al., 2002). Many natural materials such as agarose, alginate and gelatine are used to produce bioactive materials (Awad, et al., 2004, Ladet, et al., 2008, Raghunath, et al., 2007). Natural materials as well as synthetic polymers are used as biocompatible hydrogels. Fabrication and shaping of the hydrogel scaffold is strongly demanded in tissue engineering (Landers, et al., 2002).

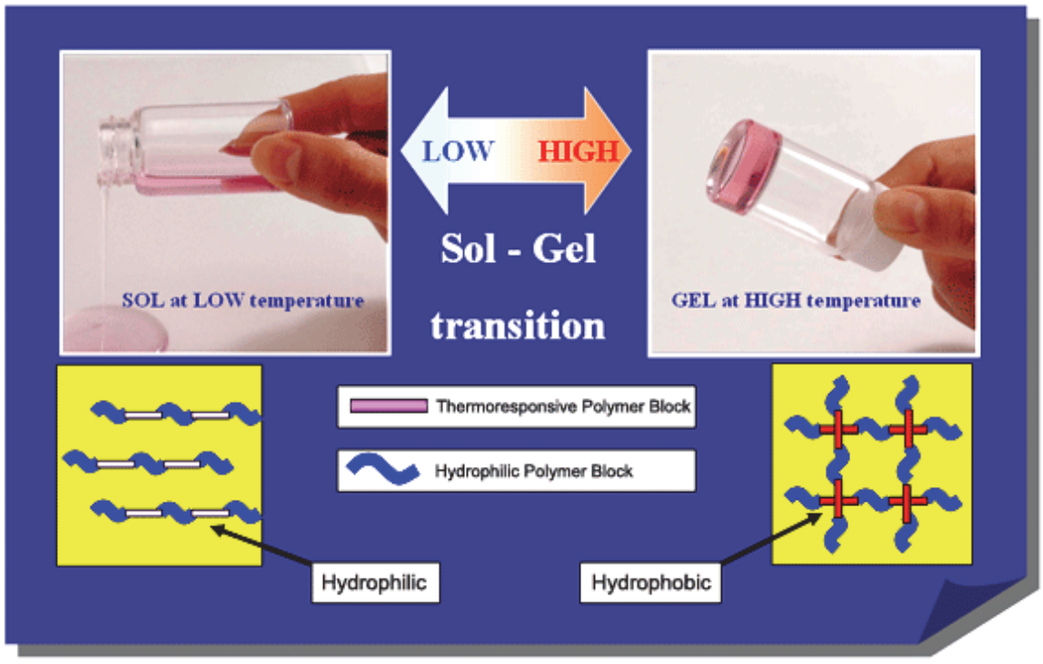

Fig. 1. Mebiol Gel

2.1.1 Thermoreversible hydrogels

Some natural hydrogels such as agarose and gelatin are in a gel state at low temperature, and their transition to the sol state occurs with heating. This property is often unsuitable for tissue engineering because cultured tissues or organs may be damaged during peeling or recovery. To solve this problem, a thermoreversible hydrogel, Mebiol® gel (Mebiol Inc., Kanagawa Japan) has been used (Yoshioka, et al., 1998). The Mebiol® gel MB-10 is composed of N-isopropylamide and polyoxyethylene.

Fig. 1 shows MB-10 in sol and gel states. The sol–gel transition temperature of MB-10 is 22°C. The sol state temperature of the gel is below 15°C. Its viscosity slightly increases with temperature. The sol–gel transition of MB-10 has very little thermal hysteresis. MB-10 is

supplied as a sterile freeze-dried powder (1 g in a glass vial), which is dissolved in 10 ml of sterile water or culture medium.

2.2 Ceramics

Ceramics have been widely used for biomedical applications for a long time. The most common application of ceramics is a mold for fabrication of metal alloy implants. RP has played an important role in this application. A 3-D printed ceramic mold and cast metal alloy used for knee prosthesis are typical examples (Curodeau, et al., 2000).

In addition to molds, ceramics have recently been attracting great interest for use in clinical implants because of increased awareness of the problems associated with metal implants such as corrosion, ion elution, and fatigue cracking (Clarke, 1992). In contrast, ceramics have superior characteristics of chemical stability, bioinertia (alumina and zirconia), bioactivity (HAp), and porosity for tissue ingrowth (HAp and alumina) (Hench, 1991).

Both hard and porous ceramics are used as implants. The most representative examples of the former are alumina and zirconia. Materials containing these compounds such as zirconia-toughened alumina (ZTA) or yttria-stabilized zirconia are also used (He, et al., 2008, Manicone, et al., 2007). Because of their extreme hardness and scratch resistance, alumina and zirconia are often used as loaded implants such as total joint prosthesis and dental prosthesis prosthesesas described in Section 4.1. These hard ceramics are used in bulk, beads, powders, or as coatings (De Aza, et al., 2002, Dorlot, et al., 1989, Oonishi, et al., 2002). Alumina powder is used to form porous structures by sintering packed a powder with proper binder such as silica (Maca, et al., 2001).

2.2.1 Porous ceramics and composites

Because alumina ceramic itself is not bioactive, bone ingrowth is difficult to achieve and implant anchoring becomes challenging. Porous structures and bioactive coatings are often adopted to solve this problem. HAp is one of the most commonly used bioactive coating materials because of its porous structure, and a HAp coating provides favorable sites for cell attachment (Bose, et al., 2002).

3. RP methods

In this section, RP techniques used for biomedical applications have been described. Selective laser sintering (SLS) is used in the development of metal or ceramic implants. Stereolithography (STL) is used to develop 3D structures through both top-down and bottom-up approaches. Many materials are available for fused deposition modeling (FDM) and 3D printing. Some advanced methods such as tissue engineering assisted by laser (TEAL), inkjet-based 3D printing and a combination of extrusion/aspiration/refilling have also been described below.

3.1 Selective laser sintering

Selective laser sintering (SLS) is a method used to sinter thin layers of powdered polymeric or ceramic materials to form solid 3D objects by laser irradiation. CO_2 or YAG lasers are often used. In this method, the object is fabricated layer-by-layer from slices of 3D CAD data files. During single layer fabrication, the laser beam is selectively scanned over the powder surface, following following the designing of cross-sectional profiles by the CAD slice. When the powder is irradiated by the laser, the powder temperature increases and reaches

its melting point. The particles are then fused together and this layer is defined. Subsequent layers are fabricated on the top of previous layers.
The type of material fabricated by SLS ranges from polymers to ceramics. Calcium phosphates including HAp are the best example of the former (Duan and Wang, 2010, Tan, et al., 2003). Other polymers such as polyetheretherketones (PEEK), polylactides and polycaprolactones are also fabricated by SLS (Bukharova, et al., 2010, Williams, et al., 2005). Alumina is an important target for SLS (Maca, et al., 2001). Recently, composites of these materials have been widely studied because they can combine the characteristic advantages of existing materials (Chua, et al., 2004, Eosoly, et al., 2010).

3.2 Stereolithography

Stereolithography is a method used to produce a 3D structure of a UV- or photocurable resin. In this method, similar to SLS, the object is fabricated layer-by-layer. In general, this method has higher accuracy than that of SLS (Melchels, et al., 2010). The range of materials that can be used in this method is not limited to resin. Ceramic 3D structures can be formed by dispersing ceramic particles in resins (Doreau, et al., 2000). This process also offers the ability to form 3D ceramic structures.

3.3 Fused deposition modeling and 3D printing

Fused deposition modelling (FDM) is an RP method based on extrusion of filament through a nozzle. A 3D structure is produced by traversing the nozzle over a substrate. This method is often applied in the manufacturing of scaffolds used in tissue engineering (Zein, et al., 2002). Fig. 3 shows a schematic illustration of scaffold manufacturing by FDM.

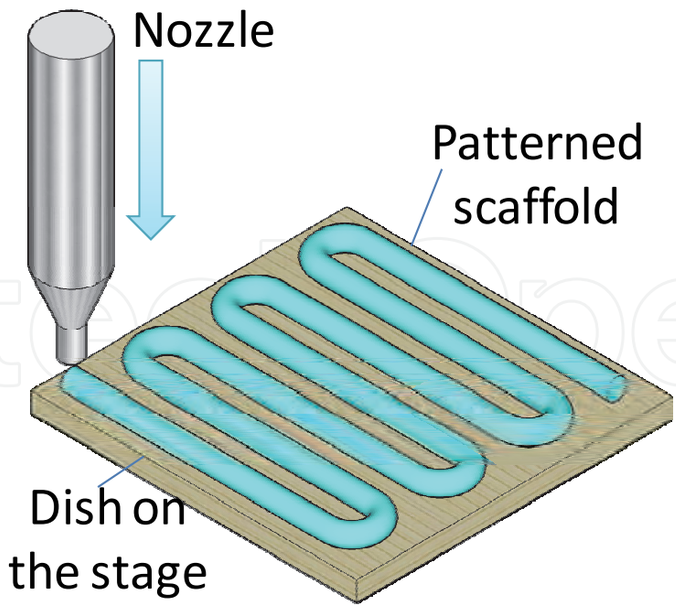

Fig. 3. Schematic of scaffold patterning based on FDM

Polymers are often used for FDM in bioengineering (Hutmacher, et al., 2001). This method can also be used to form polymer-ceramic composites (Kalita, et al., 2003).

3.4 Advanced printing methods

Printing technology is widely used in biomedical engineering. Novel applications of printers in this field include printing images of cells and organs. Conventional inkjet technologies are now applied to cell printing, and patterning and seeding of viable cell have been realized (Mironov, et al., 2003, Nakamura, et al., 2005, Roth, et al., 2004). In these methods, not only 2D but also 3D printing of cell images has been realized using the layer-by-layer scheme. Laser printing is also applied to create cell patterns with higher throughput using pulsed IR laser (Guillemot, et al., 2010).

Another important application of printing technology in this field is 3D printing of hard materials. Porous ceramic scaffolds manufactured by 3D printing are expected to have applications in bone replacement (Seitz, et al., 2005). This method is also applied to fabricate molds for orthopedic implants (Curodeau, et al., 2000).

4. Advanced FDM by extruding/aspirating/refilling of thermoreversible hydrogels

As long as injection- or extrusion-based technologies are used in conventional FDM using hydrogels, it is difficult to locally remove or modify cultured cells. Furthermore, generation of cell patterns with a large-area is difficult because of the low throughput of extrusion patterning. A combination of extrusion and aspiration could provide a solution to this problem. The patterning throughput for a large-area cell is increased by adopting aspiration technology. Furthermore, local modification of the pattern is possible by refilling the previously aspirated groove with a cell-scaffold mixture. This system could have a wide range of applications in tissue engineering. However, such technology has not yet been reported.

To solve this problem, a novel cell–tissue RP method has been developed using a cell–scaffold mixture (Iwami, et al., 2010). This method offers both extrusion of the mixture and aspiration on the basis of Bernoulli suction; extrusion and aspiration can be easily interchanged. This system has broad applications in cell patterning. For example, cell patterns can be filled into another cell matrix. Fig. 4 shows a conceptual drawing of the system.

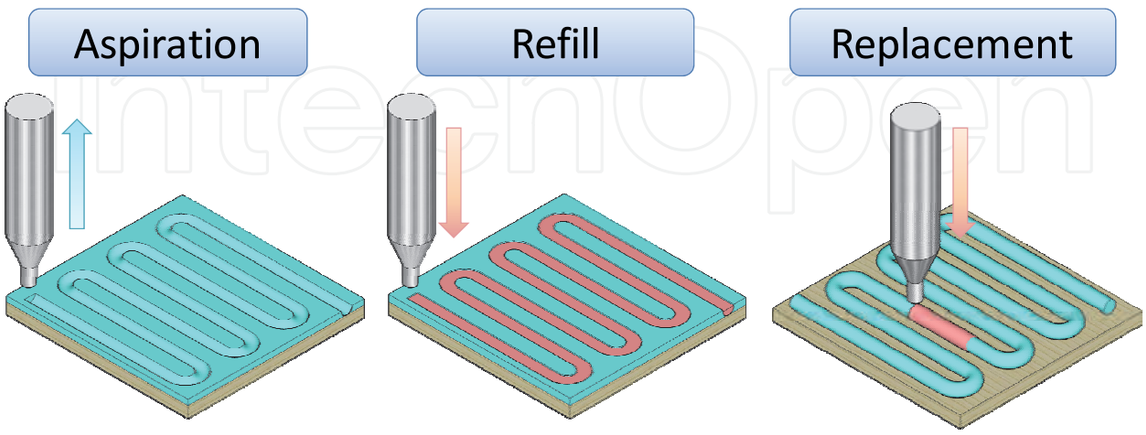

Fig. 4. Conceptual drawing of FDM based on extruding/aspirating/refilling of a thermoreversible hydrogel

Here we show scaffold patterning by combining extrusion and aspiration of a thermoreversible hydrogel, and a culture of Sf-9 insect cells mixed in the patterned gel is illustrated.

4.1 Hydrogel extruding/aspirating/refilling system

The apparatus for the gel patterning system is shown in Fig. 5. The system is based on RP. The nozzle and substrate are placed in an incubator box with controlled internal temperature and humidity. Substrate temperature on the 3D stage can be controlled between room temperature and 90°C.

MB-10 solution is dispensed from a metal nozzle. The solution in the nozzle is retained in the sol state by maintaining the temperature of the nozzle below 10°C using an integrated cooler, which consists of a heat sink, a heat pipe, and a Peltier device (UT3030CE-M, 27W; VICS Co., Tokyo, Japan). The Peltier controller (VPE-10, VICS Co.) maintains the temperature of the device between −10°C and 50°C. In this system, other materials can be used by replacing the nozzle. Because the temperature of this Peltier device ranges from −40°C to 150°C, if the Peltier controller is replaced, other materials that require a higher sol–gel transition temperature (i.e., agar) can be used.

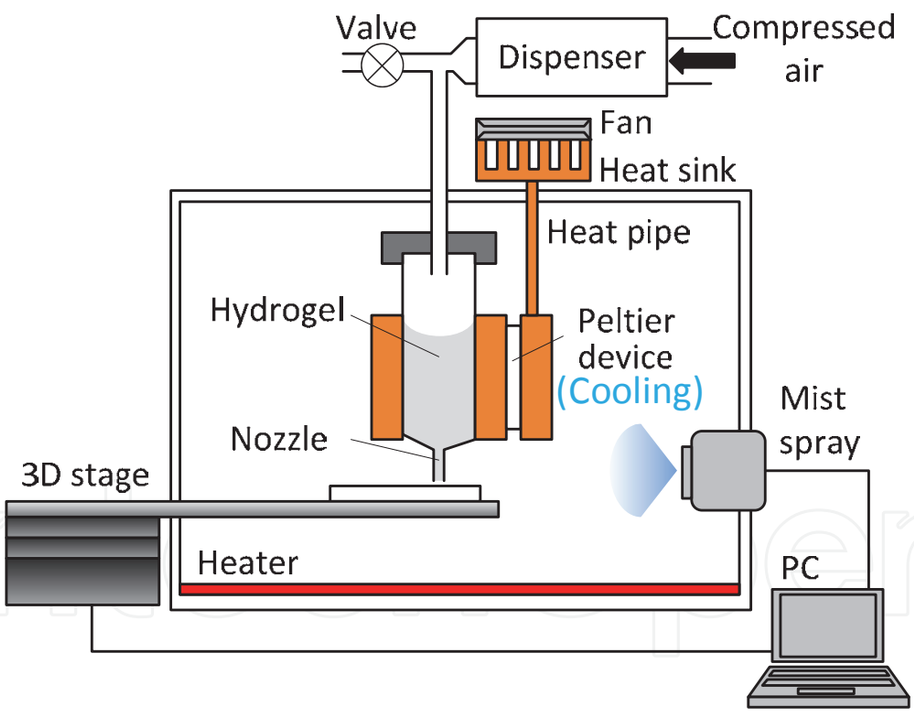

Fig. 5. Experimental setup for the FDM system based on extruding/aspirating/refilling

The bottom of the nozzle is connected to the dispenser and valve. The dispenser regulates the pressure of the compressed air, controlling the air flow. A 0.01-μm air filter (NHM-T8, Kitz Microfilter Co., Tokyo Japan) is placed before the dispenser.

This system operates in 3 modes: extrusion, aspiration, and refilling. These modes are toggled by closing or opening the valve. When the valve is closed, compressed air is supplied to the nozzle, and the MB-10 solution is extruded to the substrate or refilled into

the aspirated groove. When the valve is opened, the compressed air is directed away through the valve, and the MB-10solution is aspirated by Bernoulli suction. The substrate is placed below the nozzle, and the required gel patterns are drawn on the substrate using a computer-controlled 3D stage.

In this system, the medium on the substrate is maintained in the gel state by keeping the temperature in the box higher than the sol–gel transition temperature. The temperature control enables immediate sol–gel transition of the solution extruded from the nozzle. In contrast, when the system is operated in the aspiration mode, the medium in the gel state is cooled by the nozzle and reverted to the sol state, which can then be aspirated. In this system, the gel must be prevented from desiccating to maintain cell viability. This is achieved using a mist spray. And a supersaturated atmosphere is maintained inside the box.

A Labview program was developed to control the stage and dispenser. The control procedure for this program is similar to that used for numerical control (NC) machining. The program toggles the dispenser and moves the stage into the given coordinate with the given feed speed. Therefore, the design of the scaffold is given by a table consisting of stage coordinates, feed speeds, and toggle flags. The width of the gel or groove can be controlled by the feed speed of the stage.

4.2 Experimental

In the extrusion mode, a metal nozzle with 100-μm diameter (SHN-0.1N, Musashi Engineering Inc., Tokyo Japan) was used. Because this nozzle has a large reservoir diameter and a short tapered tip, the temperature of the nozzle tip can be effectively lowered. The distance between the nozzle and substrate was 100 μm. The temperature in the incubator box was maintained at 30°C, and the nozzle was cooled to 12°C. Straight gel lines with a length of 10 mm were formed by varying the pressure applied to the nozzle and the feed speed of the stage. A single line was drawn under each condition. The width of each line was measured by laser microscopy. Patterning of planar gel meshes and a square column were demonstrated.

In the aspiration mode, metal nozzles with diameters of 100, 200, and 500 μm (SHN series, Musashi Engineering Inc.) and a pulled micropipette with a 50-μm diameter were used. The sample covered with an MG layer was prepared by spin-coating. The coating speed and time were 1000 rpm and 20 s, respectively, and the thickness of the MG layer was 17 μm. Time variation of aspirated gel weight was measured to evaluate the aspiration speed. Straight grooves of 10 mm length were formed by aspiration, thereby varying the feed speed. A single groove was drawn under each condition, and the width of the grooves was measured by laser microscopy. Cross-line patterning was demonstrated.

In the refilling mode, a 5 mm square groove pattern was formed on the MG layer with a thickness of 17 μm. Then, 10-μm diameter glass beads were mixed with MG, and used as a pattern indicator. Beads mixed with MG were refilled into the groove by extruding and tracing the trajectory of aspiration patterning. Refilling of the aspirated grooves with the bead-mixed gel was demonstrated in this mode.

Patterning of the cell-mixed gel was demonstrated in the extrusion mode. A 100-μm diameter pulled micropipette was used as the nozzle. An acrylic plate was used as the substrate. The gel pattern was overlaid with 3 ml of the culture medium (Sf-900 III SFM), and its temperature was maintained at 30°C. The patterned cells were cultured in the incubator. Cell viability in the pattern was evaluated by the trypan blue method.

4.3 Results and discussion

The extruded gel line is shown in Fig. 6. The widths of straight lines formed by extrusion mode was obtained by laser microscopy and is shown in Fig. 7. When the feed speed of the stage was higher than 0.5 mm/s with an applied pressure of 30 kPa, the lines were patterned intermittently. Except under these conditions, continuous line patterns were formed. As the feed speed of the stage increased, the line width decreased, except under the condition of 50 kPa and 1.67 mm/s. The line width could be controlled from 114 ± 15 to 300 ± 25 μm by changing the extrusion conditions. The extruded gel was swollen because a 100-μm diameter nozzle was used. The die swell ratio for a circular cross-section nozzle is usually expressed as De/D where De and D are the diameters of the extrudate and nozzle, respectively (Liang, 2004). Table 1 shows the relationship between the applied pressure and swell ratio. The die swell ratio increased linearly with increasing applied pressure.

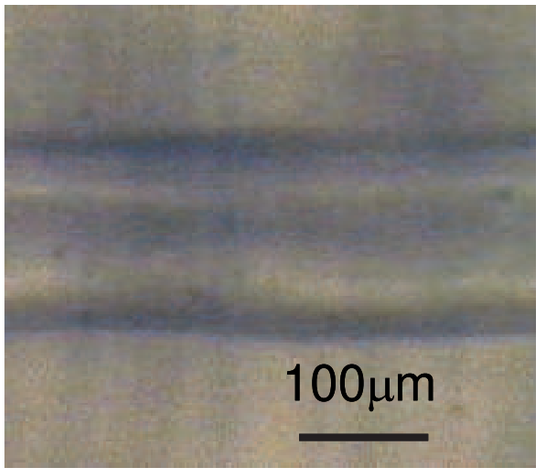

Fig. 6. A gel line extruded through a metal nozzle with 100 μm diameter.

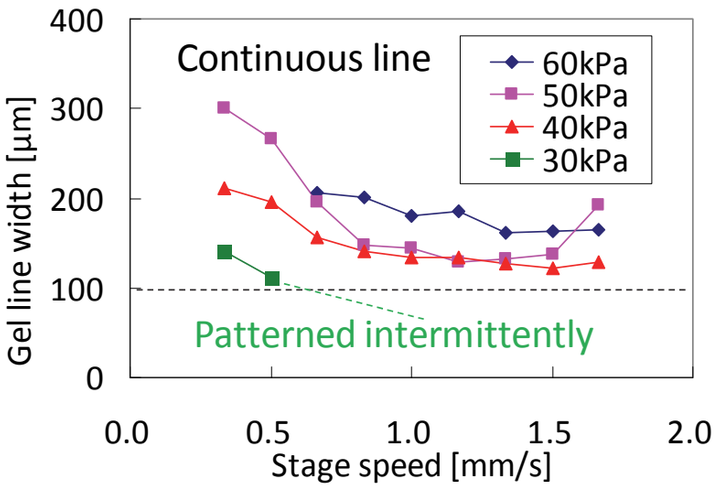

Fig. 7. Width of the extruded gel at different stage speeds and applied pressures (gauge pressure). Error bars indicate standard deviations (S. D.) for each data point (n = 10).

Applied presssure (kPa)	Swell ratio	S. D.
30	1.27	0.21
40	1.50	0.32
50	1.83	0.62
60	1.80	0.18

Table 1. Relationship between applied pressure and the swell ratio

Mesh patterning was demonstrated. In this experiment, the feed speed and applied pressure were 0.83 mm/s and 40 kPa, respectively. Under this condition, the linewidth estimated from the straight-line result was 141 ± 9 μm. Fig. 8 shows the designed trajectory of the nozzle (a) and the extruded mesh pattern of the gel with a period of 300 μm (b). As shown in Fig. 8, gel patterns were well defined. However, the line widths broadened at crossing points. This was considered to be caused by pattern stacking.

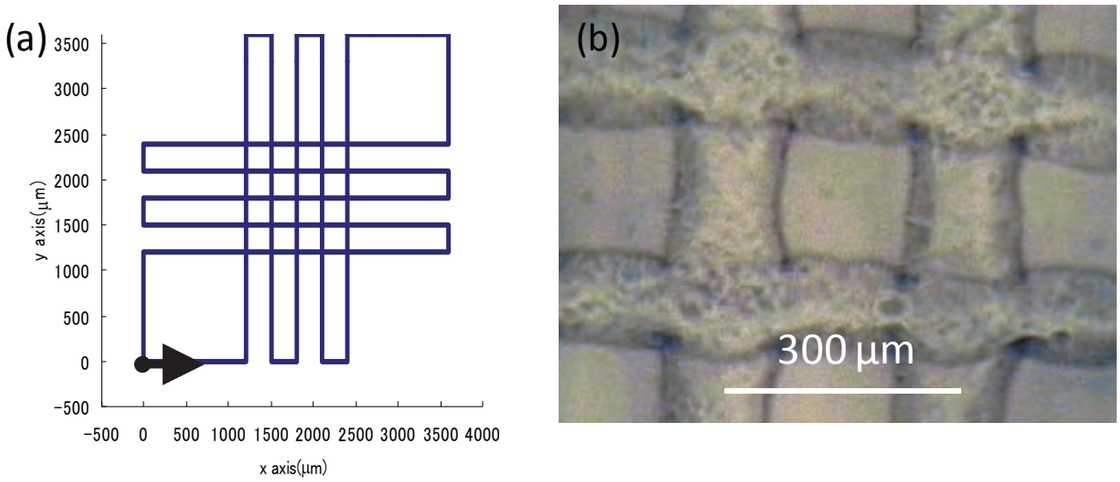

Fig. 8. Designed trajectory of the nozzle (a) and the extruded mesh pattern of the gel with a period of 300 μm (b)

In the aspiration mode, the output pressure of the dispenser was fixed at 0.2 MPa. Time variation of aspirated gel weight with the 500-μm diameter nozzle is shown in Table 2. A constant aspiration speed of 7 mg/s was obtained. However, with diameters of 50, 100 and 200 μm , the measured weights were less than 10 mg after 30 minutes of aspiration. Therefore, the 500-μm diameter nozzle was chosen for the following aspiration patterning. Fig. 9 shows the trajectory of the nozzle (a) and a close-up photograph of the cross-line aspirated pattern (b).

Fig. 10 shows photographs of refilled patterns of gel–bead mixtures (a–d) and their position in the aspirated 5-mm square groove (e). Glass beads obtained in the pattern indicate successful refilling. The height of the refilled surface is 11 μm lower than that of the original gel surface.

Table 3 shows the patterning condition of Sf-9 insect cells produced by extrusion using a 100-μm nozzle diameter. A sinusoidal line pattern with a period of 1 mm was obtained by controlling the stage. Fig. 11 shows the patterned Sf-9 insect cells obtained by extrusion. The

cell pattern had a width of 300 µm. The pattern retained its structure while the temperature was maintained above 30°C. When the substrate was cooled to 10°C, the gel melted and the cell pattern was dispersed in the culture medium.

Time (min.)	Aspirated gel weight (mg)
0	0
5	21
10	71
15	97
20	146
25	184
30	233
35	258
40	296
45	308
50	309

Table 2. Time variation of aspirated gel weight

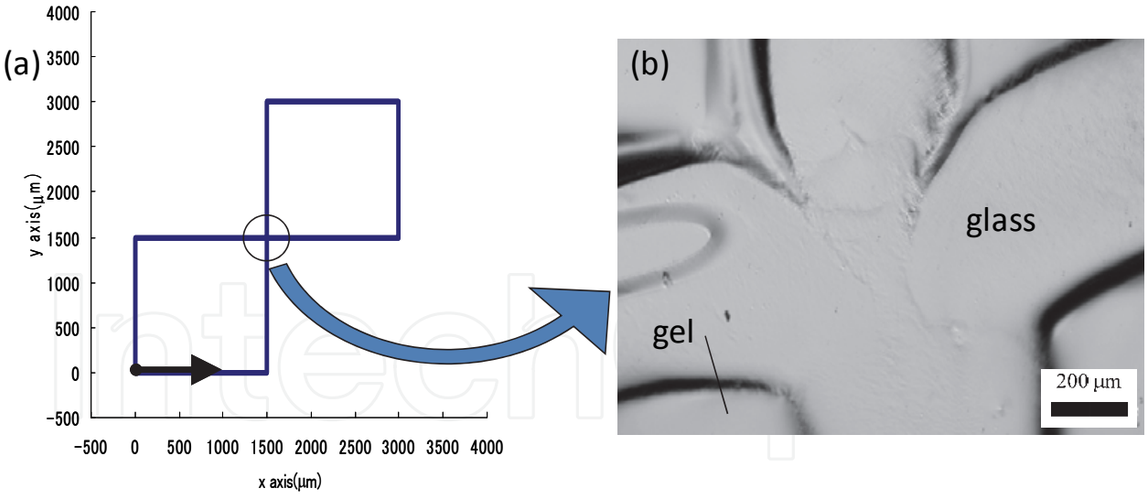

Fig. 9. Designed trajectory of a nozzle (a) and an aspirated cross pattern of a gel developed using a 500-µm diameter nozzle (b).

4.4 Section conclusion

An RP system based on extrusion, aspiration, and refilling was developed and proposed. Cell patterning using this system was demonstrated by extrusion of a mixture of cells and thermoreversible hydrogel. In the extrusion mode, the width of the pattern ranged from 114 ± 15 to 300 ± 25 µm using a nozzle of 100 µm diameter. In the aspiration mode, grooves with a

width of 355 ± 10 and 636 ± 21 µm were obtained using a nozzle with a diameter of 500 µm. Refilling of the aspirated groove with gel was also demonstrated. Cell patterning using this system in the extrusion mode was successfully performed. This system offers a novel procedure for the field of tissue engineering. To enhance this system so that it becomes possible to inject/aspirate/refill multiple materials automatically, further challenges, such as construction of a rotary nozzle changing system, need to be addressed.

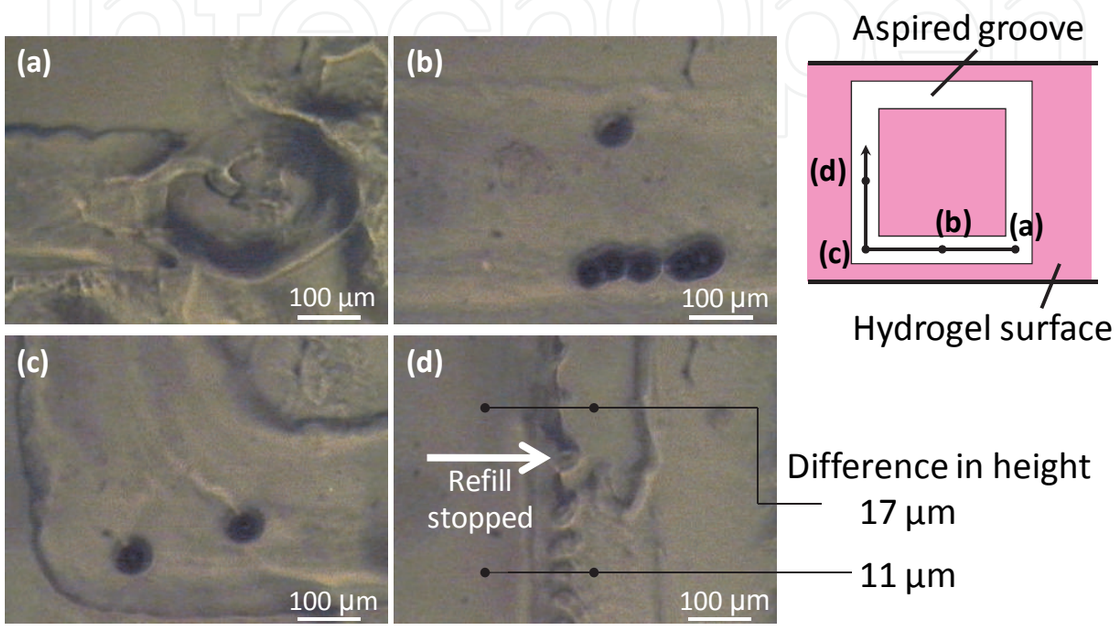

Fig. 10. Photographs of a gel–bead mixture refilled pattern (a-d) and their position in the aspirated groove (e)

Cell	Sf-9 insect cell
Nozzle diameter	100 µm
Gel	Mebiol®, 1g/ml vial
Adhesive	0.1% gum arabic
Binding agent	0.5% methylcellulose
Spray	75% DPBS
Medium	SF-900 SFM

Table 3. Conditions of Sf-9 insect cell patterning

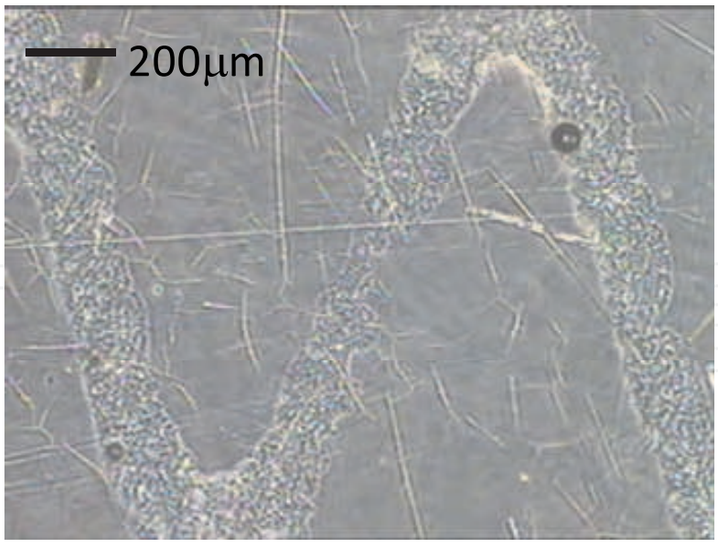

Fig. 11. Sinusoidally patterned Sf-9 insect cells obtained by extrusion

5. Applications

Commencing with inlays, alloys are used for implantable prostheses. Recently, in addition to ceramics, these prostheses as bone replacement materials are fabricated through RP technologies. Furthermore, bone regeneration through RP fabrication of Hap scaffolds will be one of the biggest applications of RP in biomedical engineering. Tissue engineering is another important application of RP. Fabrication of 3D scaffolds mimicking the ECM will make great contributions to the fields of regenerative medicine and in vitro organ regeneration.

6. Conclusion

RP in biomedical engineering is attracting great interest. Although this field had been important for a long time, recent advantages and breakthroughs are opening up research frontiers. Because the range of materials has broadened from hard and dry to soft and wet, proper methods should be designed for the application of each type of material.

7. Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science (JSPS).

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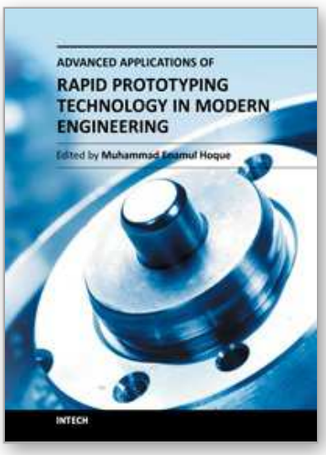

Advanced Applications of Rapid Prototyping Technology in Modern Engineering

Edited by Dr. M. Hoque

ISBN 978-953-307-698-0
Hard cover, 364 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

Rapid prototyping (RP) technology has been widely known and appreciated due to its flexible and customized manufacturing capabilities. The widely studied RP techniques include stereolithography apparatus (SLA), selective laser sintering (SLS), three-dimensional printing (3DP), fused deposition modeling (FDM), 3D plotting, solid ground curing (SGC), multiphase jet solidification (MJS), laminated object manufacturing (LOM). Different techniques are associated with different materials and/or processing principles and thus are devoted to specific applications. RP technology has no longer been only for prototype building rather has been extended for real industrial manufacturing solutions. Today, the RP technology has contributed to almost all engineering areas that include mechanical, materials, industrial, aerospace, electrical and most recently biomedical engineering. This book aims to present the advanced development of RP technologies in various engineering areas as the solutions to the real world engineering problems.

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