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PROSPECTS OF 4D PRINTING IN PHARMACEUTICALS

Arpita Roy[1], Md. Sakhawat Hossain[2], Aditi Bhowmick[3] Nisarat Nizhum[4], Shadhan Kumar Mondal[4], Tushar Saha[1*]

[1]Department of Pharmaceutical Technology, University of Dhaka, Bangladesh

[2]Department of Pharmacy, Daffodil International University, Dhaka-1207, Bangladesh.

[3]Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh.

[4]Department of Pharmacy, World University of Bangladesh, Dhaka, Bangladesh.

tushar.saha21@yahoo.com

Abstract

4D printing is a fledgling technology with enormous potential that may bring revolution to the future manufacturing industry along with pharmaceuticals. MIT's Self Assembly Lab and Stratasys education and R&D department first developed this concept jointly in 2013. 3D printing has already proved its competence and achieved wide acceptance after being invented in 1984. 4D printing is an up-gradation of 3D printing technology. 4D printing adopts time as the 4th dimension. It allows the fabrication of stimuli-responsive 3D structures that can independently change its morphology over time. External stimuli such as light, pH, magnetic field, moisture content, etc. can trigger the shape-changing event. 4D printing technology can be applied to develop site-specific, controlled release as well as a customized drug delivery system. Researchers are also optimistic about its application in the biomedical sector. This paper presents a comprehensive review of the basic mechanism of 4D printing technology and its possible future application and prospects in the pharmaceuticals and biomedical fields.

Keywords: 4D printing, stimuli, pharmaceutical, biomedical.

Introduction

4D printing technology is an up to the minute concept, which will substantially influence the modern manufacturing industries. It is an up-gradation of the novel 3D printing technology. 3D printing, one of the revolutionary advancements of the 20th century, has allowed us to fabricate objects in three dimensions according to a digital model. The idea of 4D printing embraces time as a fourth dimension and allows the printed structure to change its structural morphology upon any external stimuli [1].

The idea of printing objects considering four dimensions was first conceptualized by a research group of MIT [2]. 4D printing deals with structural as well as functional development of 3D printed objects. So, 4D printing is the incorporation of time as a fourth dimension in the 3D printing technology. [3].

4D printing technology allows fabrication of structures that are not static and fixed rather capable of altering their shape, property, and functionality with time [4].4D printed objects have some brilliant features which include self-assembly, self-repair, and capability of multitasking. Moreover, time dependency and printer independence made the technology more rational.

Programmable activity and intellectual sensitivity allow 4D printed materials to respond against stimuli like heat, pH, light, magnetic field, etc. [5]. The foundation of this new technology relies on three pillars- smart material, smart machine, and the geometric 'program' [6].

3D printing has already proved its intelligence in various engineering and biomedical fields. Although 4D printing is now in its infancy, it has the potential of changing the face of the future manufacturing industry. The application of 4D printing may open the way for personalized 'smart' formulation of 4D printing may open the way for personalized 'smart' formulation.

Basic of 4D Printing Technology

United States Government Accountability Office (GAO) defines 3D printing as a procedure that produces a 3D object according to a digital model in a layer-by-layer fabrication manner [7]. 3D printing requires mainly three building blocks: Raw materials, digital design software, and the 3D printer.

On the other hand, 4D printing technology relies on appropriately combining 'smart materials' in three-dimensional space according to a very sophisticated mathematical model [8]. The end product possesses a dynamic conformation with adjustable shape, property, and functionality. Both 3D and 4D printing technology are an additive manufacturing process which results in the formation of a new product. The only difference is 'time', which is an extra dimension in the case of 4D printing.

Advantages of 4D printing technology [6]:

1. 4D printing allows the fabrication of programmed products with self-actuation and sensing property.
2. It allows the manufacturing of smart products that do not rely on external devices or any electromechanical system for activation.
3. Requires the use of minimum components for developing a product or system.
4. Requires the least time for post-fabrication assembly.
5. Cost-efficient and time-efficient.
6. Reduces the number of error-prone products.
7. High productivity and sensitivity.

Building Blocks for 4D printed products

Stimulus Responsive Smart Materials. Stimulus responsive smart materials are the most critical component of 4D printing technology. External stimuli such as water, pH, light irradiation, magnetic field, etc. are supposed to act as a driving force of distortion of these responsive materials. These are the feedstock of 4D printing technology.

Hydrogels. Hydrogels are mostly used smart materials in 4D printing. Several types of hydrogels like peptide hydrogels, natural polymeric hydrogels, and synthetic polymeric hydrogels with their responsive properties can be applied in formulating 4D products for biomedical purposes [9].

Hydrogels have some brilliant characteristics that make them one of the most important candidates for 4D printing materials. For example,

1. Hydrogels are a network of polymeric chains that are hydrophilic in nature. Diffusion of water into the scaffold of hydrogel results in specific and localized swelling. As a result,

the morphology of the structure is distorted in a predicted manner [1].

2. Viscous matrix and high water content of soft hydrogels make them able to respond against external stimuli like temperature, light, pH, etc. [10].
3. Interconnectivity and porosity of the polymeric network allow controlled permeation of gas and nutrition to cells in the case of 4D bioprinting [11].
4. Hydrogels also exhibit unique self-healing properties [12, 13].
5. Self-assembly is also observed in stimuli-responsive hydrogels [14].

The researchers of MIT has printed a linear product by combining rigid waterproof material and hydrogel. Hydrogels were placed at the hinges of the structure. The structure when immersed in water, contorted to create a 3D structure. Water absorption into the hinge **Shape Memory Polymers.** Shape memory polymers (SMPs) or alloys are thermo-responsive materials that can transform into different shapes at various temperatures. Upon exposure to an external stimulus, they can hold on a temporary structure and are capable of recovering their permanent shape when they return to the original environment [1].

An interaction mechanism is generally required to make shape-memory polymers appropriate to use in 4D technology. For instance, constrained-thermos-mechanics is one of the most used interaction mechanisms. In this mechanism, at first, an external load at a high temperature deforms the shape memory material. Next, the temperature is lowered but the external load remains the same. Then, the external load is removed at the low temperature and the desired shape of the material is achieved. This desired shape is actually a temporary morphology of the polymer. This is because; the original shape can be recovered after heating the material again. Thus shape memory effect is achieved which can be used in 4D technology [3].

SMPs have already been used to make stents for cardiovascular patients, which can change its shape in response to changing temperature. Because of its sophisticated geometrical structure, it is very time consuming and expensive to manufacture stents by conventional manufacturing methods. 4D printing can solve this issue by fabricating stents in a time and cost-efficient manner.

Again, shape memory alloy, for example, 'Nitinol' that is an alloy of nickel and titanium has potential applications in the biomechanical sector. Having a corrosion resistance similar to stainless steel it can be used in manufacturing stents for veins [24].

Smart Model. The success of 4D printing technology depends on appropriate mathematical modeling [25]. The necessity of a mathematical model in 4D printing:

- To predict the shape evolution of the final product.
- To smoothen self-assembly function
- To manipulate the design of the structure and orientation of the smart materials.
- To customize the deposition of materials and their anisotropic behaviour.
- To reduce the number of trial and error experiments.

Problems associated with 4D printing mathematics can be divided into two categories [25]:

Forward problem: to determine the final desired shape of the final product when material structures, material properties, and stimulus properties are given.

Inverse problem: To determine the structure of the materials/print paths/nozzle sizes when the desired shape of the final product, materials properties, and stimulus properties are given.

Several mathematical models developed by researchers like [26, 27, 28, 29, 30] can be applied in 4D printing technology.

Along with the sophisticated mathematical model, an appropriate theoretical model is also important for 4D printing technology. The theoretical model should include information about four major components [3]:

1. The desired shape of the final product including bending angle, twisting angle, length, the volume of the structure.
2. Material structure including filament size, orientation, interfilamentous spacing, anisotropy.
3. Material properties including shear modulus, Young`s modulus, glass transition temperature, and swelling ratio, etc.

4. Stimulus properties such as temperature value and light intensity.

By applying the theoretical model and some mathematical computation, the desired shape of the final product can be predicted more accurately and quickly for a given material structure, material properties, and stimulus properties.

Printing machine

Initially, researchers used a 3D printing facility to create 4D printed structure.

Stratasy's Connex multi-material printer allows printing of static as well as dynamic structures using smart materials. It can work with a variety of materials ranging from rigid to a soft plastic or transparent materials. It has high-resolution control over dot deposition. Again, it can be used to fabricate Digital Materials (DMs) that hold distinct combinations of both components in different proportions and spatial arrangements [6].

However, researchers faced some problems while constructing a 4D structure using smart materials in a 3D printing machine. Feedstocks can get agglomerated and cause clogging of the nozzle. As a result, productivity could significantly be hampered. To solve this issue, many research groups have developed specific 4D printers. For example, Choi has introduced a smart printer with a significantly longer nozzle, coated with polytetrafluoroethylene to reduce friction. This machine can be used to print smart materials like thermal polyurethane (TPU) [31].

Again, Ge Q has developed another specific 4D printer, which is an upgraded version of micro SLA printer, capable of creating structure up to 1μm resolution [32].

Opportunities of 4D printing in pharmaceutics and healthcare

Although the 4D printing concept is at its infancy, it has a huge potential for future manufacturing revolution. However, there is still much research required to proceed from proof-of-concept to real-life applications. 4D printing is a promising technology that may add a new dimension in the field of personalized medication manufacturing as well as site-specific drug delivery. It may take micro-robotics and bio printing to the next level and make our health care system smarter. Scientists over the world are concerned about novel drug delivery system and 4D printing has the capability to offer that novelty.

pH guided drug delivery system. Using smart materials that respond specifically to pH change, it is possible to fabricate 4D printed pH guided controlled release drug delivery system. He et al. designed a mucoadhesive drug delivery device using pH-sensitive hydrogel that contorts its shape when reaches to the small intestine (pH 6.5) and grip on to the gut wall. This self-folding device demonstrated longer residence time, minimum drug exposure to intestinal fluid and increased drug absorption through the mucosal epithelium [33].

Self-deformation property of 4D printed products can be utilized for biomedical applications also. For instance, 4D printed microcapsules can be developed to treat the gastric ulcerous condition that will deform itself upon exposure to gastric acid and thus will cover the wound and prevent further damage [34].

Magnetically activated drug delivery system. Magneto-restrictive materials that are stimulated by an external magnetic field can be used to fabricate a 4D printed device, which may aid in targeted drug delivery ensuring the least side effect and optimal dosing.

For example, Li et al. developed a micro-robot by a conventional lithographic technique that has a hydrogel bilayer. One of the layers exhibited pH-responsive properties and aided in drug release by changing its morphology upon exposure to specific pH [18]. On the other hand, another layer with iron oxide particles in it enabled the device to be guided magnetically and ensured site-specific drug delivery. This particular finding can be utilized in the targeted delivery of anti-cancer drugs. Tumor tissue microenvironment, low oxygen partial pressure, and specific pH of tumor tissue can act as stimuli for drug release [35, 36].

Such a device can maximize the therapeutic efficacy of drugs whilst minimizing the associated side effects. However, this device needs more advanced research before clinical application.

Micro-grippers. Micro-grippers are microsystem devices developed by researchers using smart feedstock materials. Based on actuation stimuli like thermal, electrostatic, electromagnetic, or piezoelectric there can be several types of micro-grippers. This 4D printed micro-device can be used for localized cell probing, measurement as well as site-specific drug delivery.

Thera-grippers are a kind of micro-grippers that are responsive to temperature change. It is a multi-tipped drug delivery device, which grips onto tissue when exposed to a temperature above 32°C. The porous layer of thera-gripper then allows sustained release of the drug following first-order kinetics for up to 7 days. For example, in vitro study of doxorubicin thera-grippers exhibited an enhanced sustained-release property than control [37].

Magnetically responsive smart materials can be used to fabricate micro-grippers that can be guided by an external magnetic field. Incorporation of iron oxide nanoparticles onto a porous hydrogel layer makes them able to respond against magnetic stimuli [20]. Such micro-grippers has potential application in surgical invasions. Researchers have already proved its capability by excising cells from a fibroblast cell clump.

Encapsulation devices. 4D printing offers a formulation of a product that has self-folding or unfolding capacity. This unique feature can be utilized to create encapsulation devices for controlled drug delivery.

For example, researchers have printed a multi some, consisting of a mixture of DOPE and oleic acid, which encapsulated a droplet containing Ca2+ and dextran-conjugated-fluo-4. Upon exposure to a certain pH, the multi some released its inner content and the signal was measured by fluorescence microscope [38].

Such a multi-compartmental structure can also be programmed to fold/unfold their complex framework upon a change in osmolarity gradients, temperature, ionic environment, etc. Furthermore, surface modification of multisomes can be done by attaching membrane proteins with them. This may allow rapid electrical communication between multisomes [39]. Again, such functionalization may enhance the circulatory time of multisomes, cell tracking property as well as targeted drug delivery.

Not only pharmaceutical ingredients but also living cells can be enclosed within a 4D printed structure. For example, researchers have encapsulated fibroblast and pancreatic beta-cell onto such structure, and cells were reported to display viability even after 7 days of encapsulation [40].

4D bioprinting. 4D printing allows the formation of products with self-assembly and self-healing properties which makes it an important emerging technology in the biomedical field. Hydrogels are preferred for 4D bioprinting and been used to create a scaffold-free bio-printed structure. It is now possible to print nature mimicking cell-based structures without any scaffold, mold support, or liquid delivery medium by 4D printing technology [1].

A study has displayed the deposition of chondrocytes inside a hydrogel cylinder. The latticed tissue strand exhibited post-printing maturation and created a patch containing viable tissue, which could be used for implantation [41]. The proliferating nature of the depositing cells makes them able to act as smart feedstock material for bioprinting.

Researchers have already developed tissues that demonstrate muscle-like movements by using ion responsive smart hydrogels. Muscle contraction was noticed in such tissues upon the influx of Ca2+ ion like natural muscles [41].

Tissue engineering using 4D printing technology is showing signs of future success in the field of vascular treatment. Artificial vascularization can be achieved by using this technology. For example, researchers have embedded multiple cell types (like fibroblasts, ECs, MSCs, etc) in a hydrogel matrix and thus printed a cylinder-shaped structure in a layer-by-layer manner [42, 43]. This cylindrical structure resembles natural blood vessels. Upon activation of the maturation factors, vascular cells can get matured and form an integral vascular structure.

4D printing can also be used to fabricate artificial hard tissues e.g. bone graft. Scientists have printed a grid-patterned polymeric bone graft and coated it with human nasal inferior turbinate tissue-derived MSCs to facilitate graft mineralization. The printed bone graft exhibited post-printing maturation after a short culture period. In vitro as well as in vivo investigation demonstrated improved osteoconductive and osteoinductive property of the graft. However, the mechanical strength of the synthetic graft was less than the natural bones. Therefore, this creation requires more improvisation before a real-life application [44].

4D bioprinting can be used to prepare mini tissues, which integrate and develop onto larger tissue over time. Shortly, this technology may be promoted to a level, where it would be possible to print mature tissue and complex organs like physiological organs [45].

Conclusion

4D printing is a novel concept, which allows the advancement of 3D printing technology to formulate smart time-dependent products. This concept aims to produce products with features like self-assembly, self-repair, and multi-functionality. It has greater potential applications in the field of pharmaceutical and biomedical sectors. It is possible to fabricate customized smart pharmaceutical formulation using this technology. However, it is still in its dawning phase and requires more research regarding software, mathematical modeling, mechanical and chemical issues. A few numbers of self-assembling and multi-responsive materials have been investigated for 4D printing technology. More extensive research should be done to enlist raw materials that meet the requirements to be feedstock of 4D printing technology. Biodegradability and biocompatibility of the printed product as well as in vivo microenvironment should be considered in case of biomedical use. Researchers are working hard to make 4D printed biomedical products to be clinically applicable. We can certainly expect that 4D printing will bring revolution to the manufacturing industry and will open a plethora of unexplored dimensions that will make our future smarter.

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Table 1: List of potential stimuli responsive hydrogels.

Composition of Hydrogels	Stimuli	Observation	Possibility	Reference
Melamine and poly(vinyl alcohol)	Ultrasound	Change in shape	Useful for therapeutic and diagnostic purpose	[15]
Ferrocene-modified chitosan hydrogel	pH	Change in physical phase	Useful for controlled release dosage form	[16]
Poly(N-isopropylacrylamide-co-acrylamide) and nanoclay	Temperature	Change in shape	Useful for soft robotics	[17]
Hydroxyethyl methacrylate and poly (ethylene glycol) acrylate with Fe_3O_4	pH, magnetic field	Exhibit self-folding property	Useful for controlled release dosage form	[18]
N, N′-methylenebisacrylamide, N-isopropylacrylamide and polyether-based polyurethane	Temperature	Change in shape		[19]
Poly(N-isopropylacrylamide-co-acrylic acid), polypropylene fumarate, PPF), and Fe2O3 nanoparticles	Temperature, magnetic field	Change in shape	Useful for site specific drug delivery	[20]
N-isopropylacrylamide and N,N-dimethylacrylamide	Temperature	Change in gel structure	Useful for bioprinting	[21]
Ionic dimethylacrylamide and dimethylacrylamide	pH	Change in gel structure	Useful for bioprinting	[21]
2-vinyl-4,6-diamino-1,3,5-triazine, acrylic acid, polyethylene glycol diacrylate	Change in Ion concentration	Change in gel volume	Useful for nondestructive cell harvesting	[22]
Acrylamide +Irgacure 819, spiropyran and lightresponsive poly(N-isopropylacrylamide)	Light	Change in gel structure		[23]

Table 2: Other promising smart materials for 4D printing technology [24].

Material type	External stimuli	Output	Application
Piezoelectric material	Stress, electric field	Electric charge, mechanical strain	Optical tracking device, dot matrix printer.
Magneto-restrictive material	Magnetic field	Mechanical strain	Site specific drug delivery
pH-sensitive material	Change in H^+ conc.	Change in color and structure	Diagnostic purpose, controlled release dosage form
Electrochromic material	Voltage change	Change in color and opacity	Diagnostic purpose
Photochromic material	Change in light	Change in color	Diagnostic purpose
Optical fiber	Temperature, pressure, mechanical strain	Change in opto-electronic signal	Diagnostic purpose, useful as sensor

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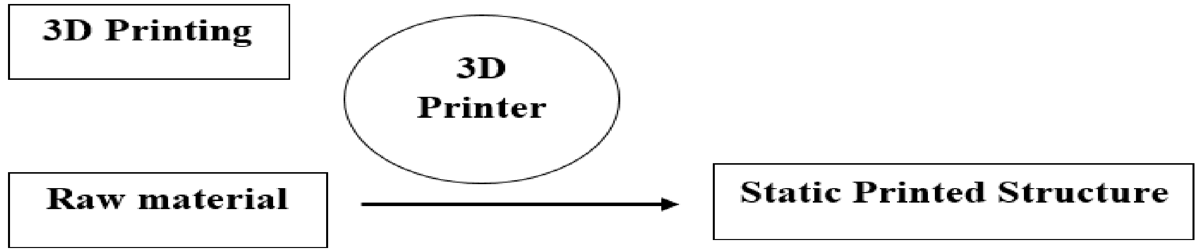

Fig. 1: Basic mechanism of 3D printing.

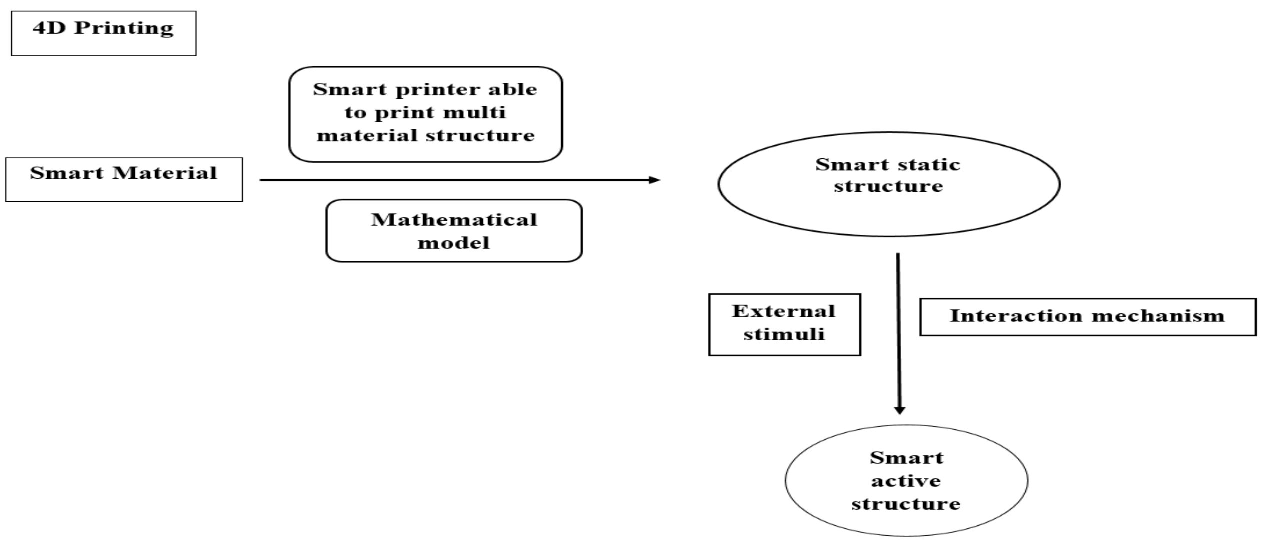

Fig. 2: Basic mechanism of 4D printing.

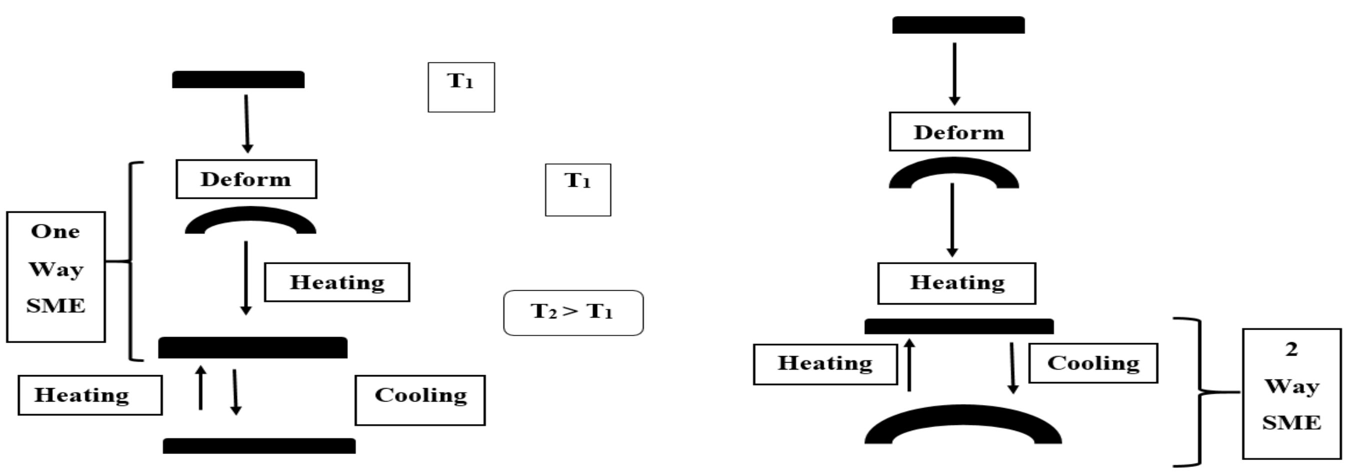

Fig. 3: One way and two way shape memory effect.

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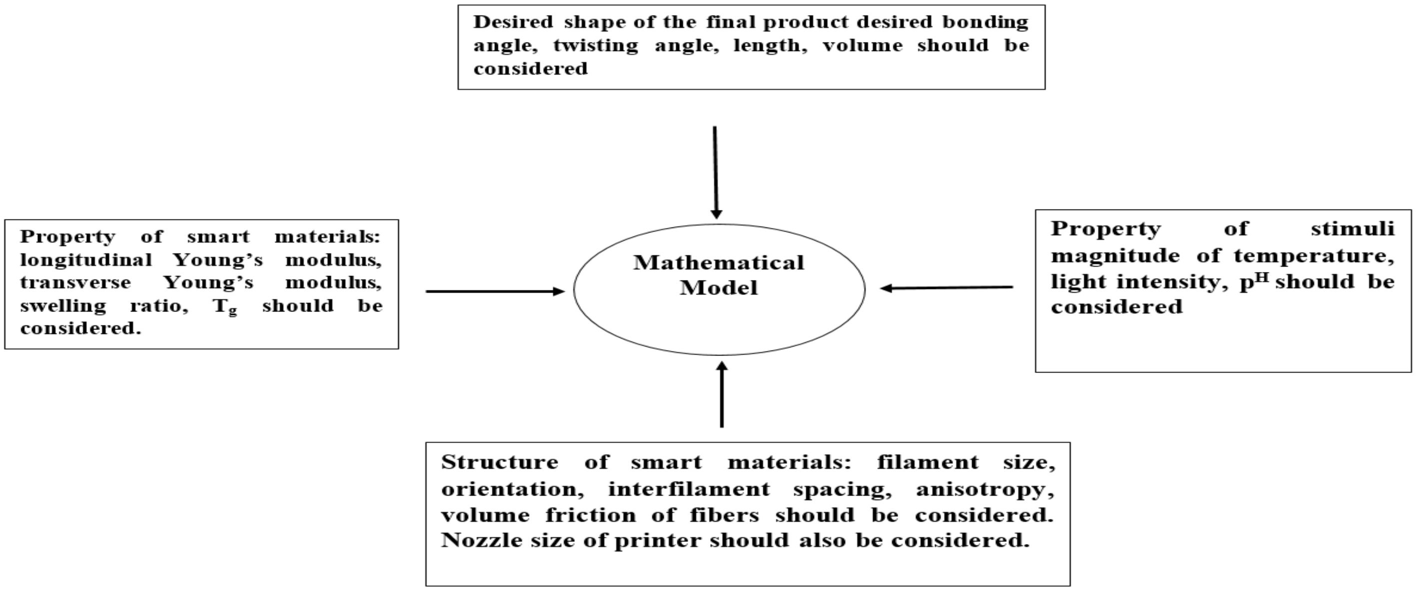

Fig. 4: Mathematical model of 4D printing.

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