Medical devices obtained with nanoprinting: elements for risk analysis

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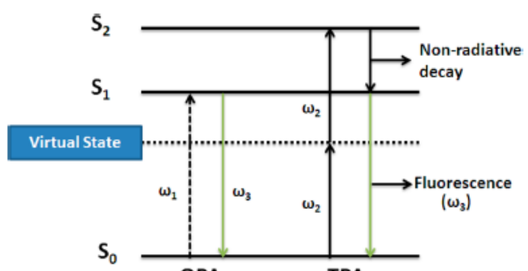
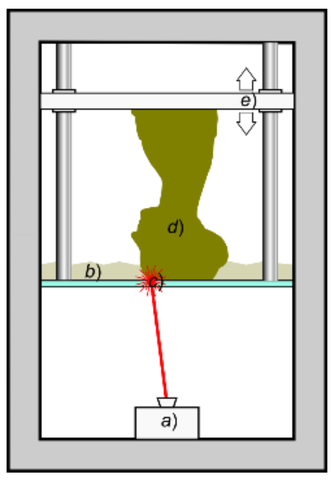
Additive manufacturing (AM) is gaining diffusion also in the field of medical devices (MDs). Recent advances in nanoprinting make use of additive multiphoton polymerization (MPP) [1], which enables to use light at wavelenghts at which a polymer is transparent, in order to obtain a polymerization at designed locations, with sub-diffraction limit resolution (a feature size of few tens of nm has been obtained [2]).



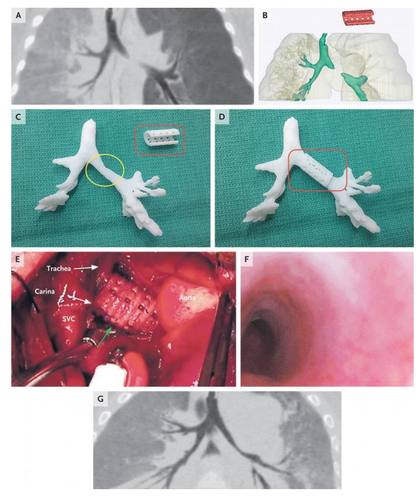
The photoinitiator needs to be set in an excited state in order to trigger polymerization. The simplified Jablonski diagram shows one-photon absorption (OPA) and degenerate (one color) two-photon absorption (TPA) excitation processes. S_0 is the ground state and S_1 is an excited state reached directly by OPA or indirectly by TPA via a very short-lived higher energy state (S_2); ω_1 and ω_2 are incident light frequencies, and ω_3 is a fluorescent emission frequency. Copyright 2008 Elsevier.

Additive manufacturing (AM)



Stereolithography *- A light-emitting device a) selectively illuminate the bottom of a tank b) filled with a liquid photo-polymerizing resin; the solidified resin d) is progressively dragged up by a lifting platform e). Adapted form Scopigno et al, DOI:10.1111/cgf.12781.*

3D printed medical devices



An infant with tracheobronchomalacia (a disease characterized by excessive collapsibility of the lower airways) was implanted with a customized, bioresorbable 3D printed tracheal splint, based on a computed tomographic image of the patient's airway, to treat this life-threatening condition [3].

MPP is dependent on multiphoton absorption, which requires a high photon density to drive a transition from the ground state to an excited state via a short-lived intermediate virtual state (see diagram above left). This implies that the effect can only occur in the narrow focal volume of the laser beam, thereby reaching nanometric scale.

The Regulation (EU) 2017/745 on MDs [4] (MDR) does not address specifically the MDs obtained with AM. Such MDs can be considered as series-made or as custom-made devices. In either case, the product must be assessed with regard to the possible risks, carrying out a risk analysis as per the international standard EN ISO 14971. According to the latter, each hazardous situation must be identified, and the associated risk(s) shall be estimated using available information/data. Also the MDR imposes that the risk management be a key part of the assessment of a MD, in order to demonstrate conformity to the General Safety and Performance Requirements (GSPR).

MDR, Annex I

3. Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:

(a) establish and document a risk management plan for each device;

(b) identify and analyse the known and foreseeable hazards associated with each device;

(c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;

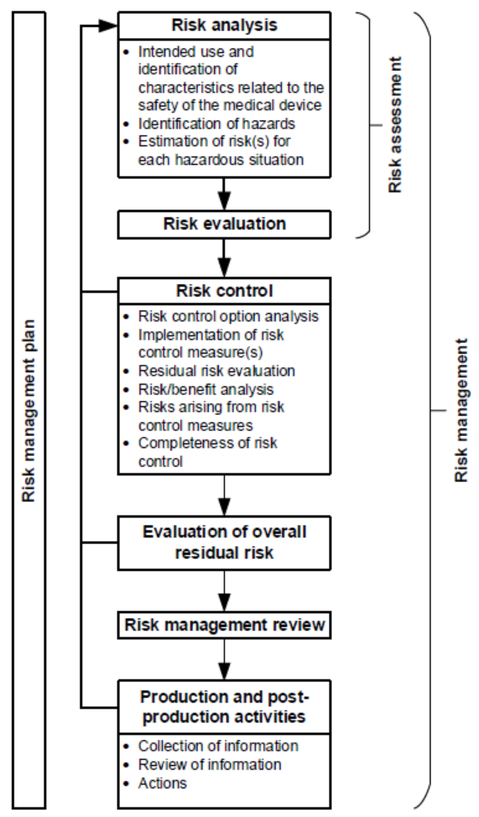
(d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4; […]

4. Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, Manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:

(a) eliminate or reduce risks as far as possible through safe design and manufacture;

(b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and

(c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.



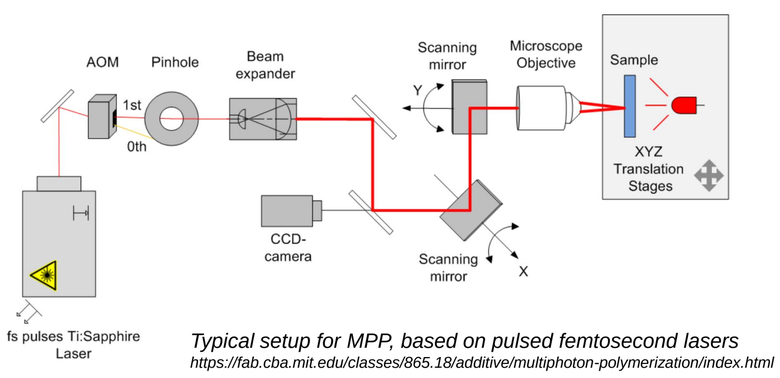
Schematic representation of the risk management process, as per EN ISO 14971:2019

Due to the peculiar AM fabrication techniques, appropriate qualification of biological hazards should always be carried out.

Additive MPP has hitherto generally leveraged on consumables (polymers and photoinitiators) not specifically designed for biological applications, typically adapting materials from stereolithography. The mechanism itself of polymerization in MPP typically involves the photoinitiator-enabled creation of free-radical species, which may be evidently toxic.

As already observed with more traditional AM techniques (FDM, Fusion Deposition Modeling), the quite high temperature which the polymer undergoes to could pose hazards. Actually, it has been observed that the consumable material after FDM printing may have different chemical and physical signatures in its extracts with respect to the same material before printing, leading to possible contact of body parts with undesirable substances leached from the printed MD [5].

It is essential to evaluate all these hazards, in order to obtain safe MDs obtained with nanoprinting, and to exploit the capabilities offered by this innovative technology.



Typical setup for MPP, based on pulsed femtosecond lasers
https://fab.cba.mit.edu/classes/865.18/additive/multiphoton-polymerization/index.html

References

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4. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

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