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Miniature Articulated Device for Electroporation (‘*MADE*’): A Novel Design

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Abstract: *One of the novel domains of Physics that has emerged in recent past with a technological niche is Electroporation or Electro-permeabilization. The technology of elctroporation is fast creating a deployment arena by virtue of its process that gets stimulated through indigenously-made miniature device(s). Thus, design and hardware implementation of a compact-volume articulated device for electroporation is snatching research attention in a global perspective. Such designs of electroporation devices are built hitherto by means of extended structure and comparatively large controller, by and large. However, a large upliftment of dexterity as well as manoeuvrability can be achieved through the novel technology of miniature manufacturing via metal 3D printing of the device. In this technology break-through, traditional electroporation technology is freshly conceived as miniature delivery system, equipped with either single or multiple nozzles. The present paper dwells on design characteristics of a novel Miniature Articulated Device for Electroporation (MADE) for the purpose of delivery of liquids, e.g. drug, vaccine, skin therapy etc. The prototype ‘MADE’ can be categorized as a novel creation in the domain of Miniature Compliant Robotics (MCR).*

1. Introduction

The ever-changing manifold of *compliant robotics* does provide ample scope of novel research in almost all of the constituent members and sub-assemblies of a compliant robot, preferably in miniature ensemble. The domain of Miniature Compliant Robotics (MCR) is poised to grow at a fast pace in near future, owing to its multi-dimensionality of application in service sectors. Whether it is the in-situ compliance of the device hub (body) or the protruding members, miniature compliant robot can be designed *ab initio*. Truly speaking, inherent compliance of the MCR-devices is slighly different from its ‘sister’-group, namely, flexible robots in a sense that run-time vibration is somewhat controllable in case of compliant robots. Irrespective of the inherent compliance & run-time vibration, all MCR devices can be made very useful in typical application scenarios, such as *Electroporation* or *Electro-permeabilization.* Although the scientific basis of Electroporation is related to the theory of electric spark generation, the technology of elctroporation is highly dependent on the advancements of miniature manufacturing as well as instrumentation. Thus, the very domain of electroporation is rapidly boosting up several potential deployment scenarios, which calls for integration of indigenously-made miniature device(s). In fact, design and firmware of a compact-volume articulated device for electroporation has been an important research manifold all over the world in the past 5-10 years. It may be mentioned that such designs of electroporation devices have been realized hitherto by means of extended structure and comparatively large controller, by and large. The present device, namely, the would-be prototype of novel Miniature Articulated Device for Electroporation (MADE) is a sort of miniature compliant robot that has its motion defined by the ejection of the liquid drug through orifices in a time-spanned manner.

One of the vital parameters for the time-spanned develiery of any liquid through one miniature orifice is the size of the said liquid module. No matter whether this liquid is a drug or vaccine or any other similar therapaeutic substance, the delivery mechanism will have similar articulations. This very ‘flow of liquid molecules’ in the form of liquid-jet through a pre-designed orifice is a novel technology by itself. We will exploit this technology of fluid flow through miniature device in fabricating our prototype ‘MADE’. The fundamental building block of our MCR-based prototype, MADE is the process of ‘electroporation’. It may be mentioned that the basic facet of ‘electroporation’ process is the time-stamped flow of liquid through pre-designed articulated orifices into the target permeable substatrate. In the case of our would-be prototype ‘MADE’, this ejection of liquid will be finally penetrating into the human skin. The prime technological aspect of ‘electroporation’ process is the moderate enlargement of the epithelial cells of human skin through generation of electric spark & vibration using electric-based technology. Thus, the liquid molecues do penetrate through these enlarged pores of the human skin and perform further chemical assimilation inside the human body. Although the scientific paradigms of ‘electroporation’ are not new, it has wide applications in the vast domains of drug delivery, vaccination (especially the larger DNA-molecules), cancer treatment, quick preservation of agri-hoticulture produces, beautification products and finally, various cosmetic skin therapy.

The technological brilliance of this very process of electroporation is such that we can create a consortium of electric spark at the boundary of any live cell. This electric spark generates high frequency that gets controlled in real-time. As a matter of fact, this high frequency electric spark becomes very effective for the smooth penetration of liquid molecules of comparatively larger dimensions. The electric spark, so produced through electroporation process, can be easily instrumented via modern electronics using a customized MOSFET[1] circuitry. Finally, the requisite transfer of liquid molecules take place from one distinct location to another using the process of electroporation, as customized in the encapsulation of the prototype 'MADE'.

Active research is going on in various countries of the world towards harnessing the process of electroporation economically for the desired benefit of targetted delivery of the liquid molecules in real-time. It may be noted here that application-specific customized technology of electroporation can differ based on the specific application that it is aiming at, without altering its basic scientific principles of operation. In fact, in the current era of pandemic of COVID-19, various medical reports of *World Health Organization* and allied scientific information [1] catalyzed to have a robust foundation for active research in the domain of deployability of electroporation for vaccine. It may be noted that multiple manufacturing companies[2] of different countries in the world are currently engaged with the development of working prototype of an electroporation device, few of which may be suitable for the said vaccination. Emily Walltz [2] reported some of these available technologies of electroporation in commerical market as on date that can be deployed for DNA (Deoxyribonucleic Acid)-based vaccine for SARS-CoV2 (COVID-19) virus. The hardware details and technical specifications of the exisiting electroporation devices may be obtained from the web-portals of the respective companies ([3] to [10]). Lissandrello et al [11] discussed on the concept of 'cellular therapy manufacturing' in the context of the design of a continuous-flow type electroporation device, working on the principles of micro-fluidics. Authors have claimed high throughput for this device that is entrusted to be effective on human T cells. Schmitt et al [12] reported on a low-cost portable electroporation device that will be effective for various gene transfer research in the broad domains of biotechnology as well as biomedical engineering. A comprehensive review on the various commercially available technologies for electroporation-based *in-vivo* cellular delivery can be obtained in [13]. Xia et al [14] reported a so-called econmic version of the electroporator for SARS-CoV2 vaccination having micro-needles. All of these literature essentially rely on intra-cellular electroporation, be it for delivery of DNA-based vaccine or something else. Although this is a comparatively longer and time-consuming route so far as prototyping of the final device is concerned, but, at the end, this customization of the electroporation process is the right as well as effective avenue for future R&D.

It is needless to state that any compact small-volume design of electroporator must undergo 3D printing technology so far its manufacturing is concerned. Roy [15] described vividly the strictures of fabricating miniature 'robotics' devices, using the principles of additive manufacturing, in general. The concept therein was successfully adapted for the manufacturing of a miniature device, suitable for electroporation [16]. The author's research group has been instrumental in bringing up the '*Application Note*' for the prposed prototype of 'MADE' subsequently [17], [18].

Unfortunately, majority of the present-day electroporation devices that are avialble commercially are quite large in size and not cost-effective either. Most of these devices are not very effective in easy vaccination for various reasons, although these are perfect from engineering stand-points. Hence, the main bottleneck in mass utilization of those electroporation devices is nothing but proper use of the manufacturing technology. In fact, market has a great demand for the protottye development of a miniature low-cost electric spark-generating device, based on the scientific principles of electroporation. Thus, we badly need a niche prototype of an affordable miniature electroporation device in near future. And, our proposed prototype of 'MADE' is the perfect culmination of this customization of basic electroporation process.

The paper has been organized in six sections. An overview of the design philosophy of the proposed prototype 'MADE' will be presented in the next section. The technical details of the mechanical sub-assembly as well as the ensemble control system design of 'MADE' are repoered in section 3. Section 4 addresses the achievements towards successful prototyping of the

[1] The Metal Oxide Semiconductor Field Effect Transistor

[2] Lonza®, Mirusbio®, Maxcyte®, Novo Engineering®, Thermofisher®, Bio-Rad®, Minnetronix Medical®, Wavemed®

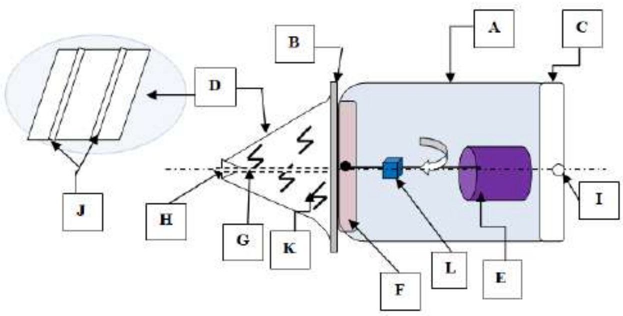
housing of 'MADE', using the state-of-the-art metal 3D printing technology. The attributes of the available technology for achieving a working prototype of MADE will be delineated in section 5. Finally, section 6 will conclude the paper.

2. Design Philosophy of the Proposed Prototype

We will now look at the basic design philosophy of the would-be prototype, 'MADE', with specific reference to the array of internal components and sub-assemblies. The outer casing of the prototype 'MADE' has been conceived as hollow metallic cylindrical-shaped ensemble. It may be pointed out that most of the commercially available electroporation devices do have a non-metallic casing, mainly for the ease of manufacturing. However, in our case, we have mastered the technology of 3D metal printing through full-fledged indigenous effort that ushers in a miniature device ('*AM-BOT*' prototyope of Intech Additive Solutions®, Bengaluru, India) [18]. Besides novelty in mechanical miniaturization, the would-be prototype of 'MADE' becomes functional by means of a custom-made pulse generating circuit through MOSEFET.

By external appearance, the would-be prototype of 'MADE' is a miniature-spaced tapered cylindrical vessel, which is manufactured using complete in-house expertise and indigenous technology. This very manufacturing of the vessel was possible due to the niche application of rapid prototyping technology, namely, through metal 3D printing. Figure 1 illustrates the functional schematic of this characteristic external ensemble of 'MADE' as created through Computer Aided Design (CAD). The device has been designed in the form of two hollow chambers, namely, front & back and both of these chambers have been designed for mololithic fabrication (refer 'A' & 'D'). We may note that the tapered angular front chamber of the device (refer 'D') is destined for two important tasks, namely: a] generation of electric spark & b] ejection of liquid. These two tasks get accomplished by the rotation of the D.C. servomotor (refer 'E') that is housed in the back chamber of the device. The most exciting metric of this design is obviously the tapered front chamber, through which the episode of electric saprk / pulse will be accomplished. It may be noted that we will be able to alter this tapered front chamber as per the need and accordingly, it will be possible for us to get preapred for the next cycle of generation of electric spark as well as exit-route for the liquid through the orifice (refer 'H'). Almost simulataneous to the generation of electric saprk, we will need another crucial technology for the successful prototyping of 'MADE'. This is none other than guidance towards the micro-pathaways for the ejection of the liquid. For this, we need proper manufacturing technology for the micro-machining of the miniature channels, engraved over the internal surface of the tapered front chanber (refer 'J').

As a matter of fact, real technological brilliance for the manufacturing of the tapered angular front chamber lies exclusively on the creation of these micro-grooves & channels. The design for manufacturing of the internal suface of the front chamber is made to accommodate four micro-sub-channels, which will be responsible for the supply of liquid drug / vaccine/ cosmetics. The real-time continuous flow of the liquid mixture will finally reach the underneath of human skin via the main miniature-channel (refer 'G').



A: Cylindrical Back Chamber; **B**: Liquid Holding Annular Chamber; **C**: Replacabale End Shield; **D**: Tapered Front Chamber; **E**: D.C. Servomotor; **F**: Electric Spark Generating Unit; **G**: Miniature Main Channel; **H**: Output Orifice for the Liquid; **I**: Output Orifice for the Tether; **J**: Miniature Sub-Channels (one pair); **K**: Electric Spark; **L**: Coupler of the Motor

Fig.1: Conceptual Schematic of the Would-be Prototype of 'MADE' and its 3D Model

We can find the basic 3D model view as well as super-finished exterior of the proposed prototype of 'MADE' (alongwith the 3D printed end-shield) in fig. 2 below.

Fig. 2: 3D Model View & Super-finished Exterior of the Would-be Prototype of 'MADE'

3. Mechanical Sub-Assembly and Control System Architecture

The crucial-most mechanical sub-assembly of the proposed prototype of MADE is the liquid holding hexagonal-shaped annular chamber (refer 'B' of fig. 1). Figure 3 schematically highlights the design details of the sub-assembly of this annular chamber, alongwith the design details of the tapered front chamber of the proposed device. The part-drawings of fig. 3 are helpful in understanding the modality of the exit-route for the liquid in an easy way. Figure 3A details out the novel design of the heaxagonal-shaped miniature containment for the liquid that can be splitted up in two equal & symmetric portions. The liquid material can be stored as well as retained at two nearly circular spaces inside this hexagonal containment. It is to be noted that the miniature main channel for the ejection of the liquid is constituted by four parallel sub-channels that are engraved at the inner curve surface of the tapered angular front chamber of the device (refer fig. 3B for the detailed schematic). In fact, fig. 3B illustrates the monoplanar architecture of these four sub-channels so far as the angular positioining and allied design are concerned.

It is crucial to note that manufacturing of the hexagonal miniature containment in two equal parts will be challenging because of the sub-thin thickness and we can rely upon 3D metal printing technology for the manufacturing. Likewise creation of the near-circular spaces inside this containment will also call for utmost attention during this manufacturing. The other criticality will be the engraving of the sub-channels over the inner surface of the tapered front chamber of the proposed prototype of 'MADE'.

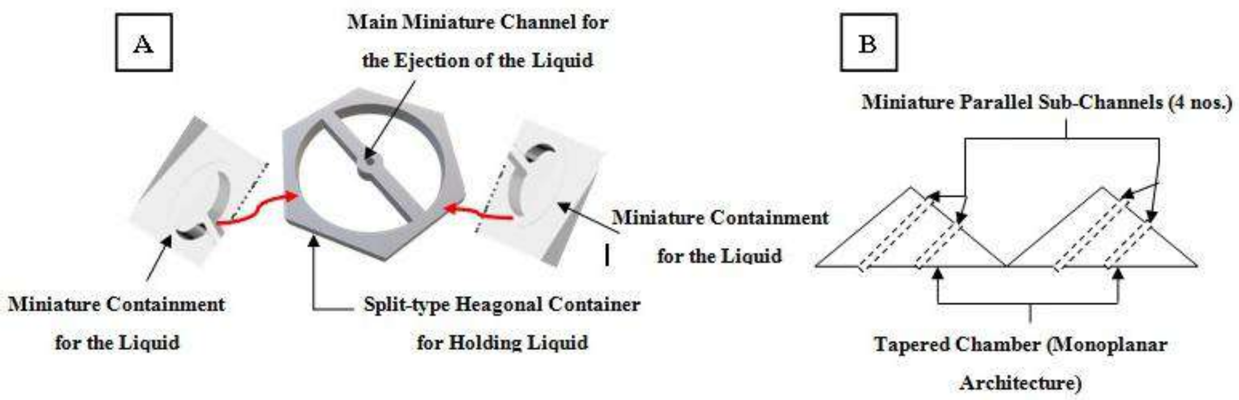


Fig. 3: Schematic Design of the Tapered Angular Front Chamber of 'MADE': [A] Containment for the Liquid; [B] Locations of the Sub-Channels

One of the most exciting features of this proposed device is the episode of spark generation. The electronic circuit diagram for the intended process of spark generation inside the proposed prototype 'MADE' is shown in fig. 4.

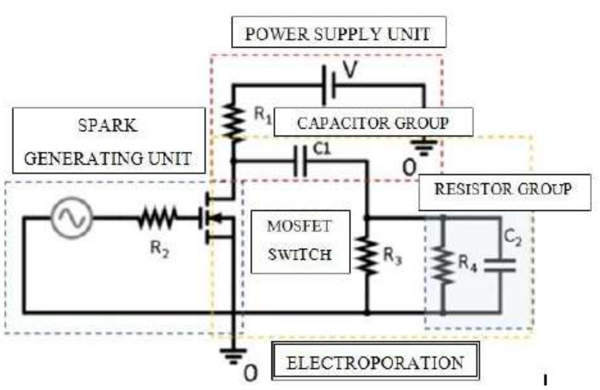


Fig. 4: The Electronic Circuit Design for the Spark Generation Process inside the Proposed Prototype 'MADE'

There are three basic units of this electronic circuitry for the generation of electric spark & vibration thereof, namely: i] power supply unit; ii] MOSFET switch and iii] spark generating unit. As can be seen in fig. 3, two other complementary electronic controller-groups are helping these three basic units to create an unseparable circuitry. The first one is the capacitor group, comprising of two pre-designed capacitors (C1 & C2). The second of these two groups is the resistor group, which has four resistors of unequal resistances (R1, R2, R3 & R4) as its prime constituents. The entire electrinic circuit is getting powered through +V volt D.C. supply. It goes without saying that this very controler, conceptualized from scratch and to be developed indigenously, is the main pillar behind the process of electroporation.

We will now take a look over the usefulness of the creation of electric spark over the human skin, through the schematic of fig. 5. The creation of electric spark of certain pre-defined frequencies inside the tapered vertex of our proposed prototype 'MADE' causes quick breakdown of the exterior membrane of the uppermost epithelial cells of the skin of human body. And, this helps the liquid material to enter the cell.

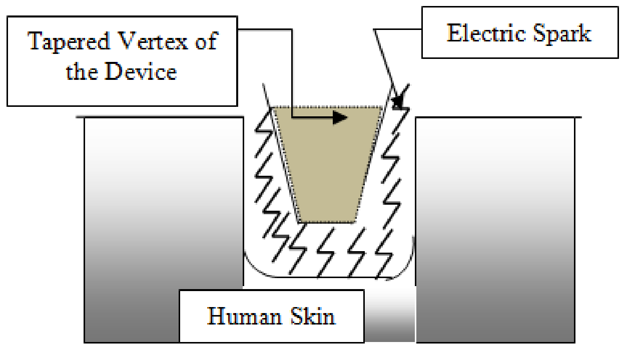


Fig.5: Schematic Showing the Effectivity of the Tapered Vertex of the Prototype Device in Generating Electric Spark on Human Skin

We will now discuss on the various types of electric spark that are required for the process of electroporation. Figure 6 shows the representative time-spanned plots of three main types of waves that may be obtained as a consequence of electric spark / vibration. These are: a] Exponential decay-type wave; b] square wave and c] constant time wave. These representative graphs indicate the spread of the amplitude of the waves with respect to time-instant of operation of the electroporation process

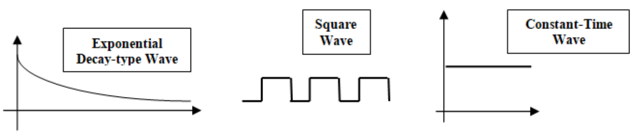


Fig. 6: Graph of Three Main Types of Electric Waves to be Produced in the Device

4. Achievements on Miniature Manufacturing of 'MADE'

The emerging domain of miniature manufacturing and miniature metal components, to be specific, has several critical applications. These applications are branching out especially in the field of miniature robotics (e.g. bio-robots) and in customized electroporation devices (such as for drug delivery, pre-treatment of food, cosmetic therapy of skin etc.).

In contrast to the traditional unconventional machining processes, metal 3D printing, with its design freedom, is a technology that can be leveraged to print fully functional monolithic miniature components with relative ease & sophistication. As a matter of fact, metal 3D printing is the ideal process for manufacturing miniature, intricate and semi-sculptured components, such as those in the proposed design of 'MADE'. None of the existing manufacturing technologies (e.g., wire-cut EDM) used hitherto can be a match for metal 3D printing of the components of 'MADE' so far as reproducibility of the design and the economic feasibility are concerned.

The Metal 3D printed monolithic miniature component, 'MADE' has an overall length of 33 mm with a cylindrical housing (OD: 11.6 mm; ID: 10 mm) and a tapered front. The crucial part of the manufacturing process was in the printing of a tiny portion, the "retainer ring", having a thickness of 1.5 mm and a central hole of diameter 0.9 mm. The crux of this entire ensemble manufacturing is the printing of the retainer ring. Ensuring the workability of the printed retainer ring is essential for the actuation of the component. This component was to be assembled with another part, the "end-cover", having a height of 6.5 mm. The completed assembly of the component is now fully functional and can be used for a variety of applications post further instrumentation.

The engineering details of three crucial constituent members & sub-assemblies of the proposed prototype 'MADE' have been illustrated in fig. 7. These are: A] Removable End Cap (outer diameter: 12.8 mm; inner diameter: 11.8 mm); B] Hexagonal Retainer Ring: container for the liquid (angular span: 20 mm.; diameter of the main channel for the ejection of liquid: 0.9 mm) and C] Tapered Front Chamber & Cylindrical Back Chamber in a combined design paradigm (external diameter: 11.6 mm; internal diameter: 10 mm; height: 33 mm). The 'tinyness' of the proposed device can be ascertained from these dimensions.

Fig. 7: Engineering Details of the Three Crucial 'Components of the Proposed Prototype MADE'

Figure 8 presents the photographic view of the indigenously-designed outer casing assembly of the proposed device, 'MADE' (with end-cover). We may appreciate that the miniaturization of the device is the ideal for the practical implementation of the principles of electroporation. This outer casing assembly has been manufactured successfully through 3D metal printing technology using SS316L material.

Fig. 8: The Developed Prototype of the Miniature Outer Casing of the Proposed Device 'MADE'

The miniature outer casing assembly can now act as a path-breaking attribute towards realizing the final prototype of 'MADE'. The salient technical aspects will be fittment of the servomotor inside the internal cavity and split-up of the hexagonal retainer ring. Once we can achieve these two milestones in the ensemble process the rest of the prototyping is within reach of indigenous development.

5. Technology Available for the Prototyping

If we now rewind back the entire philosophy of practical utility of the electroporation process, we can certify that a good amount of technical knowhow for the development of prototype 'MADE' is available already. Besides command over metal 3D printing, the prototyping of 'MADE' can be entrusted with the following technologies *at hand*, viz.:[I] Test-run of the miniature D.C. servomotor system with in-house instrumentation; [II] Full-fledged design & development of the system controller for the device; [III] Driver circuitry for the servomotor system and finally, [IV] Instrumentation for the on-board computer system alongwith Graphical User Interface.

Figure 9 schematically details out the overall functioning of the proposed prototype of this spark-producing electroporation-enabled device, 'MADE'. The exterior of the device ('A') is shape-specific and as it is hollow cylindrical in shape, it could accommodate two important enginnering elements inside its inner space, viz.: 1] chamber for the D.C. servomotor ('B') and 2] driver circuitry for the servomotor , having electric spark generation capability ('D'). It may be mentioned here that the element 'D' is the prototype-form of the electronic circuit design of the device-controller using MOSFET-switch (refer fig. 4).

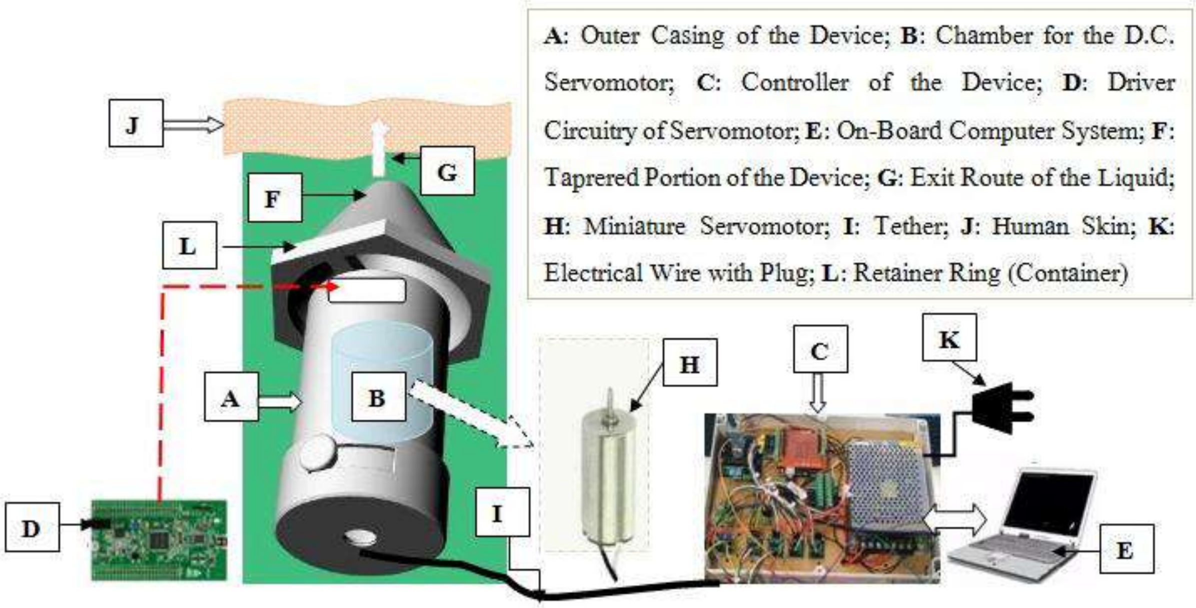


Fig. 9: Overall Functional Scheme of the Proposed Prototype 'MADE'

In order to make the prototype device functionalized, we require a miniature D.C. servomotor 'H' that is kept subsumed in 'B'. The electronic controller of the device, 'C' has been designed by the author from fundamental concepts and it is developed with complete indigenously technology. This controller is equipped with a power supply unit, that is instrumental is generating the requisite rotational motion for the servomotor and subsequently, the process of electric spark generation is also being controlled. The communication between the elements inside the device and the system controller gets established through a tether, 'I'.

A critically important aspect of the device is the exit route of the liquid, 'G' and the region of activation of the device, namely, the human skin, 'J'. It is obvious that all operations of the device are getting controlled by the on-board computer system, 'E' and it has bi-directional communication with varios electronic circuitrires that are present inside the system controller, 'C'. It is to be noted that we must need extremely tiny orifice at the back-end of the devoce in order to orchestrate with the electronic instrumentation of the device that should be replacable as per the need. In other words, we should be able to detach the bottom portion of the device with ease and connect the servonotor inside. Naturally, the minute rotation of this miniture servomotor does generate vibrations of various natural frequencies, which become instrumental in the ejectioon of the liquid as well as its injection inside human skin.

6. Conclusions

The ensemble technology for the successful prototyping of 'MADE' is ready for harnessing. The preliminary testing of the performance of the servomotor system and the controller card are supportive enough for ensemble assemblage of the prototype in near future. Proper pathways for extended laboratory-trials and subsequently, field-trials will be chalked out in near future for the development and commercialization of the technology of electroporation, through the proposed prototype of 'MADE'.

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