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Needle-free jet injection using real-time controlled linear Lorentz-force actuators

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ABSTRACT

Needle-free drug delivery by jet injection is achieved by ejecting a liquid drug through a narrow orifice at high pressure, thereby creating a fine high-speed fluid jet that can readily penetrate skin and tissue. Until very recently, all jet injectors utilized force- and pressure-generating principles that progress injection in an uncontrolled manner with limited ability to regulate delivery volume and injection depth. In order to address these shortcomings, we have developed a controllable jet injection device, based on a custom high-stroke linear Lorentz-force motor that is feed-back controlled during the time-course of an injection.

Using this device, we are able to monitor and modulate continuously the speed of the drug jet, and regulate precisely the volume of drug delivered during the injection process. We demonstrate our ability to control injection depth (up to 16 mm) and repeatably and precisely inject volumes of up to 250 μL into transparent gels and post-mortem animal tissue.

1. Introduction

Needle-free drug delivery can be realized using the principle of jet injection, whereby a liquid drug is pressurized and accelerated through a small orifice, creating a narrow, high-speed fluid jet of sufficient velocity to penetrate skin and tissue. Pressures of ~20 MPa, and forces of ~200 N are required to accelerate the drug to the requisite velocity of 100–200 m/s; the energy required per injection is ~10 J. The principle of jet injection was first discovered in the nineteenth century, and has been utilized for drug delivery since the mid-twentieth century [1].

Currently available commercial devices employ a variety of forms of stored energy, including compressed springs [2–6], compressed gases [5,7–11], or explosive chemicals [12–14]. Because it is not possible to control the actuator during delivery, these techniques provide limited pressure control at best, and poor regulation of injection depth and volume. Piezo-electric actuators offer greater opportunities for active control. Electrically pulsed microjet piezo-electric actuators have been used to deliver injections, albeit to restricted tissue depths (~200 μm) and at slow rates (100 nL/s) [15]. Others [16,17] have used piezo-electric stack actuators [18] to effect jet injection via a piston, but deliverable fluid volumes were <10 μL, and scaling this technology is challenging.

There is an evident need for a jet injection system that affords active control of jet speed or drug pressure, while allowing the injection of precisely metered volumes of the order of 1 mL. We have previously used Lorentz-force actuators driven by voltage waveforms in an open-loop jet injection system to deliver volumes of this magnitude [19–21]. In this paper, we report on the implementation of real-time control of a prototype jet injector that utilizes a linear Lorentz-force motor [21–23]. Using this device, it is possible reproducibly to create the high pressures and jet speeds necessary to penetrate this skin and then transition smoothly to a lower jet speed for delivery of the remainder of the desired dose [20,23,24]. Here, we quantify the performance of our device in terms of its monotonicity, sound production, repeatability and accuracy, and demonstrate its effectiveness in delivering injectate into a tissue analog, and post-mortem animal tissues.

2. Materials and methods

The servo-controlled jet injection system (Fig. 1) described in this paper comprises a hand-held injector, real-time controller, and a linear power amplifier. This prototype system has been designed for initial use in our laboratory, with a view to developing portable, electronically controllable, high-volume, and/or continuous-throughput jet-injection devices suitable for animal and human drug delivery applications. The hand-held jet injector is designed to be light, but sufficiently robust for moderate workloads. The real-time controller is connected to a computer (via Ethernet) when interactive control is required, but can readily be operated in stand-alone mode.

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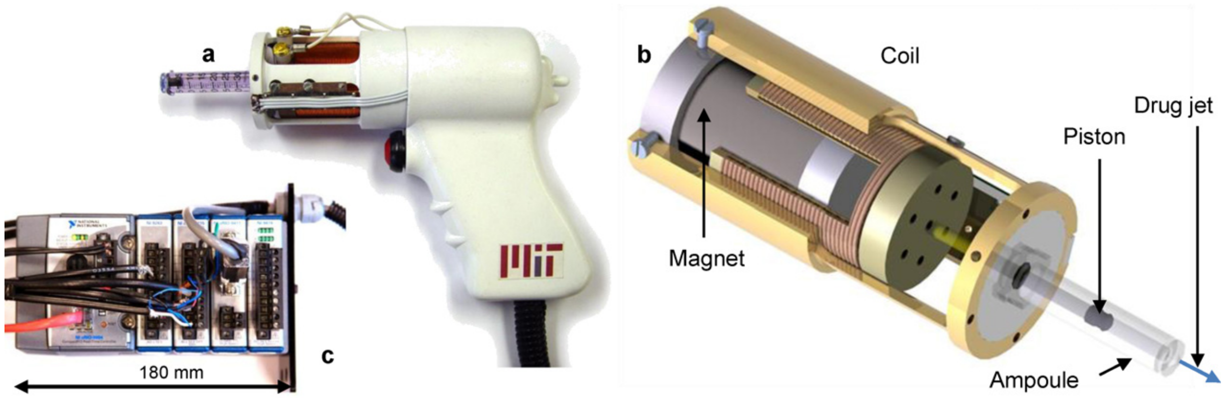

Fig. 1. (a) Handheld-injector. (b) Cutaway view of linear Lorentz-force motor. (c) cRIO controller.

2.1. Jet injector hand-piece

The jet injector hand-piece (Fig. 1(a)) incorporates a linear Lorentz-force motor (Fig. 1(b)), designed and constructed in the MIT BioInstrumentation Laboratory, that propels the piston of a disposable commercially available drug ampoule (Injex Ampoule, part #100100). These ampoules are designed for use in a spring-based jet injector system (Injex 30) and were selected for our device because of their availability, relatively low cost and proven performance. The internal diameter of the ampoule tapers to the tip to form an orifice with a diameter of $220 \pm 5\,\mu$m; a maximum volume of 300 μL can be ejected with 30 mm piston stroke. Although this ampoule is disposable and designed for single-use, we routinely achieve 50–100 injection cycles before the ampoule or piston exhibits noticeable wear and requires replacement.

The custom-made linear Lorentz-force motor [22] consists of a copper coil (582 turns, 6 layers tightly wound on a high-temperature plastic former) and magnetic circuit. A portion of the coil (approximately 8 mm in length) experiences a radial magnetic field (0.6 T flux density). Current in the coil creates an axial Lorentz force of up to ± 200 N, with a force constant of 10.8 ± 0.5 N/A. The total moving mass of the motor is approximately 50 g. A linear slide potentiometer provides a measure of the position of the coil (0.75 V/mm).

2.2. Control system architecture

High-speed position monitoring and servo-control of coil position is achieved using a compact reconfigurable system (Fig. 1(c)) comprising a real-time controller (cRIO-9004, National Instruments, Austin, TX) embedded in a reconfigurable field-programmable gate-array (FPGA) chassis (cRIO-9104). The controller executes a LabVIEW 8.5 Real-Time "host" application that interacts with the FPGA circuitry, performs high-level injection trajectory planning, interprets user commands, and provides real-time and post-injection feedback. The user interface of the host application is broadcast by a web-server running on the controller, and operated from a web-browser on a networked laptop computer.

FPGA code is composed, compiled and downloaded using the LabVIEW FPGA module. Spline points and coefficients describing the desired coil trajectory are generated in the host-code and downloaded to the FGPA at 1 kHz rate. The FPGA uses a fixed-point spline engine to interpolate 63 intermediate position set points that describe the desired coil trajectory and continuously presents these to the FPGA position-control algorithm (64 kHz loop-rate).

Replaceable I/O modules in the FPGA chassis provide four channels of 16-bit analog input and output, six bits of digital input, and eight bits of digital output. A linear power amplifier (LVC5050, Techron, configured in bridged-mono mode) amplifies an analog output and drives the Lorentz force motor with a maximum available peak power output of 4 kW. The amplifier voltage and current waveforms are monitored and digitized by the cRIO system (10 kHz, 16 bit) together with the position of the coil, and transmitted via TCP-IP to the laptop for post-injection analysis and storage.

The host user interface indicates the status of the hand-piece controls, the coil position, and displays data recorded during an injection. The operator can use the rear bidirectional toggle switch to slowly drive the piston forward (in order to expel air bubbles from the ampoule) or backwards (to draw fresh solution into the ampoule, using any of the Injex drug-vial adaptors). Additionally, an auto-load algorithm allows the user to reload the ampoule with a downward click of the toggle switch on the rear of the hand-piece.

2.3. Control strategy

The position-based jet-injector control algorithm has two components: a velocity-driven feed-forward model that predicts the voltage required to achieve a given jet-speed, and a linear proportional-integral (PI) displacement feed-back controller to counteract noise and disturbances to the injector system (Fig. 2). Both components of the control scheme are active during controlled motion of the coil. During injections, the non-linear feed-forward component of the controller dominates the control effort. Between injections, and during low-speed refilling of the ampoule, the control effort is dominated by the feed-back component of the controller. Feed-back control ensures that the correct volume is delivered during the injection, and that the ampoule piston is held stationary in between injections.

The feed-forward component of our jet injector control system relies upon identification of a system model of the jet injector and injectate, together with the load properties of the target tissue. The feed-forward relationship is discovered by an interactive routine in which the user performs a number (usually five) of constant-velocity drug injections into a target tissue or a tissue analog. During this process, the applied coil voltage is increased for each successive injection, resulting in constant jet speeds ranging from about 10 m/s to 200 m/s. After each step experiment, the controller measures the voltage and the displacement response of the coil, from which the steady state jet speed is computed. Having collected the jet speed resulting from each applied voltage the relationship between the two is fit with a third order polynomial and the coefficients are stored for later use (Fig. 3). This model discovery procedure can be completed in a matter of seconds, and need only be executed once for each tissue-type and drug.