Original article: 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 utilised 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 utilises 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.

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 ± 5 μm; 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.

The feedback control algorithm is a fixed-point PI controller, implemented in the FPGA at an update rate of 64 kHz, while the feed-forward component is computed in and updated from the real-time host processor at a rate of 1 kHz. The feed-forward component uses the previously discovered polynomial coefficients to interpolate the voltage required to achieve the desired steady-state jet speed, in the range 0-200 m/s. The feedback controller is empirically tuned to minimize following-error and to prevent overshoot.

2.4 Injection-trajectory design

During injection, the control set points describe a smooth coil trajectory that will produce the desired jet-speed and injection volume. The graphical user interface of the host application allows the operator to define and preview a jet-velocity injection trajectory before injection. Analysis of high speed video photography of jet injections into acrylamide gels confirms the multi-phase delivery that has been observed by others [25] with injections performed at approximately constant jet speed (Fig 4). Initially, the fluid jet punctures the gel surface and begins eroding the material, thereby creating a fine channel that rapidly penetrates to a depth proportional to

the initial speed of the jet. This is followed by a dispersion phase, during which the injectate spreads further into the gel surrounding the hole in a manner that is highly dependent upon the local structure and properties of the tissue. This multi-phase delivery phenomenon suggests that high jet speed need only be maintained for a short period of time (< 10 ms in acrylamide gels) after which time the rate of erosion slows considerably, and the fluid disperses into the tissue.

Accordingly, we [19, 24, 26] and others [16] generate our injection trajectories (Fig 5(a)) with two distinct phases of delivery: a brief high-speed phase (during which the jet erodes the target tissue) followed by a lower speed phase (during which the majority of the drug volume is injected). In the initial phase of delivery, the coil is accelerated to a speed (v_{jet}) that achieves the desired jet speed, taking into account the relative cross-sectional areas of the piston and orifice. The coil is maintained at this speed for the user-determined time T_{jet} and then gently decelerated to the desired "follow through" speed (v_{follow}). The trajectory generator then maintains this coil speed until the coil position approaches the displacement at which the desired injection volume (V) will be realized. At this time the coil speed is decelerated gently to a position corresponding to the desired total injection volume. Different rates of acceleration and deceleration can be specified by the user. Limiting the trajectory bandwidth to 50 Hz sufficiently avoids exciting the fundamental mechanical resonance (approximately 400 Hz) while allowing the injectate to be accelerated to the desired injection speed within 1-2 ms (Fig 5(b)).

During controlled reloading and manual control, the software creates and downloads an S-shaped trajectory (typical for motion control systems) with velocity, acceleration and deceleration limited to modest levels.

2.5 Video imaging

During device characterization, the position of the piston tip during the time-course of injection was recorded by a high-speed CMOS video camera (Phantom v9, Vision Research) imaging through a 65 mm macro photo lens (Canon MP-E 65). Images of the piston tip (144 x 1152 pixels, trans-illuminated and viewed through the transparent syringe walls) were captured at a frame rate of 5000 Hz and stored as an uncompressed video recording for post-processing. An analysis application was written in LabVIEW 8.5 to read in the video recording and track the motion of the piston tip during injection. Each frame of the video recording was

successively loaded and the position of the piston tip was estimated using an interpolating edge-detection algorithm. The resulting estimate of piston tip position was time-synchronized with other data measured during the injection and recorded to disk.

Additionally, estimates of the progress of injection into acrylamide gel were obtained by transilluminating the gel while recording video images at a rate of 5000 Hz. The position of the leading edge of the fluid jet was estimated with the same algorithm used to estimate piston-tip position. The erosion depth into the acrylamide was determined from the position of the leading edge of the jet in the video-frame during which rapid jet-penetration ceased and dye dispersion commenced. We estimate an uncertainty of ±2 frames (400 μs) in our choice of the frame during which transition occurs. The concomitant uncertainty in our measure of erosion depth is estimated to be ±5 pixels (~125 μm).

2.6 Materials and tissues

Acrylamide gels are commonly used as convenient models for characterizing jet injection systems [16, 25] because of their transparency, and their skin-like stiffness and damping properties (Chen *et al.*, unpublished results). While acrylamide gels lack the anisotropy [27, 28] and heterogeneity of *in vivo* skin they provide researchers with a convenient tool with which to visualize and quantify the performance of jet-injectors. Gels (10% and 20%) were prepared by mixing an appropriate volume of 40% acrylamide stock (*i.e.* 37.5 acrylamide/1 bis-acrylamide; BioRad Laboratories) with water. Polymerization was initiated by the addition of ammonium persulfate and TEMED. Injection into acrylamide gels was visualized using 0.25% bromophenol blue (Sigma Aldrich) or tissue marking dye (Polysciences Inc.).

Post mortem animal tissue was obtained through the MIT Tissue Harvest Program using procedures approved by the IUCAC and in accordance with the NIH Guide for the Use and Care of Laboratory Animals. Porcine tissue was harvested from the abdomen and shoulder area of Yorkshire pigs approximately 6 months in age and included muscle, subcutaneous fat, and skin. Rabbit tissue included the lumbar muscles and associated skin on either side of the backbone while the entire pelt was removed from adult guinea pigs and mice. Freshly harvested and trimmed tissue was immediately vacuum-sealed in bags and stored at -80ºC. Prior to injection, tissue was equilibrated with room temperature and the hair removed if necessary using a clipper.

All injections into acrylamide and post-mortem animal tissues were conducted by placing the tip of the ampoule in contact with the gel or tissue until completion of the injection. Injections were performed into excised samples of tissue, the size of which varied dependent on the source. Pig and rabbit tissue were cut to fit into clear plastic-sided containers (22 mm x 22 mm (L x W) x 18 mm (H)) which provided support to ensure that tissue layers remained aligned during delivery. Mouse and guinea-pig injections were into the full pelt or into plugs of tissue approximately 18 mm in diameter placed in individual wells of a 24-well tissue culture plate. Post injection, samples were covered and placed at -20 ºC for 15 to 30 minutes after which each sample was cut down the midline of the injection site. Samples injected with a 1:20 dilution of tissue marking dye were splayed injection side up, imaged using a Zeiss Stemi SV11 microscope, and photographed using a Canon EOS-1Ds camera. Depth of injection was estimated using a calibration scale. Other sections were embedded in optical cutting compound and sectioned using a microtome cryostat (Vibratome). The resultant 10 µm sections were counter stained with Mayer's Hematoxylin (DakoCytomation) and imaged through a Nikon E800 microscope fitted with a Canon EOS-1Ds camera. A calibrated ocular reticle was used to estimate depth. The volume of dye delivered was calculated from the change in tissue weight, pre- to post-injection. Any fluid/dye remaining on the surface of the tissue post-injection was blotted with filter paper prior to weighing.

2.7 Validation Experiments

One potential advantage offered by our trajectory-generation and real-time control scheme is the ability to gently increase the pressure being applied to the drug, and thereby avoid exciting the mechanical resonance formed by the motor-drug-ampoule system. In order to test this capability, we used high-speed videography to measure the trajectory of a standard Injex piston-tip being driven by an Injex 30 spring-based actuator. We then utilized our jet injector to propel the same piston with a band-limited trajectory that was designed to achieve the same steady-state jet speed (approximately 160 m/s) as the Injex device, but low-pass filtered to 50 Hz. Both injections were conducted into water. We computed and integrated the power spectral density of both signals using LabVIEW SignalExpress, and identified the power in the dominant frequency in the displacement spectrum using the LabVIEW tone-search algorithm. In addition, we measured the sound pressure generated during a series of eight injections from each device (dBA-weighted, at 1 m distance and 51.2 kHz sample rate,

BK4189 full-field microphone with DeltaTron preamplifier 2671, Brüel and Kjær). The equivalent-pressure and peak-pressure were computed (using SignalExpress Sound and Vibration toolkit) over a time window from 10 ms before initiation of injection to 120 ms after initiation of injection. Pressure measurements were converted to decibels (referred to the threshold-pressure of hearing (20 μPa)) and the mean and standard deviation of each series were computed.

The depth of the erosion hole created by jet injection into acrylamide gel has been shown to be determined by both the jet speed [25] and the time for which jet speed is maintained [16]. The two-phase characteristic of constant-speed jet injection implies that a high speed jet need only be maintained during the process of erosion, after which the jet speed can be decreased while the bulk of the drug is delivered. To verify the relationship between jet speed and injection depth, we performed repeated dyed-water injections into acrylamide gel (10% and 20% concentration) at different jet speeds. High-speed videography through the gel was used to track the progress of injection and determine the depth of the erosion hole as a function of jet speed, while T_{jet} was held constant. In addition, we conducted a series of injections into 10 % acrylamide gel where we varied T_{jet} while holding jet speed constant. The repeatability of the erosion process was quantified by the coefficient of variation (CV) of the erosion depth.

To quantify the repeatability and accuracy of ejected volume we conducted experiments where a fraction of the total ampoule volume was ejected and collected in vials containing dry cotton wool. The specified volume of drug ejected was varied in the range 50 μL-200 μL and the ejected drug volume was determined from the difference between the post- and pre injection weight of the vial. Ejections of 50 μL were conducted in groups of four per ampoule-reload. Ejections of 100 μL were conducted in pairs per ampoule reload. Ejections of 150 and 200 μL were each conducted from a fully loaded ampoule.

Finally, we carried out a series of experiments to quantify the performance of our system when injecting dyed fluid into mammalian tissue. We conducted injections into post-mortem animal tissue obtained from a variety of species (mouse, guinea-pig, rabbit, pig), measured the volume of drug absorbed by the tissue, by weight, and estimated the mean depth of delivery from medially sectioned tissue blocks or plugs. Experiments were conducted at jet speeds (100-200 m/s) and volumes (20 μL, 100 μL) appropriate to the type and thickness

of the target tissue.

3 Results

The ability of our device to accelerate the injectate gently and controllably is illustrated in Figure 6 where piston-tip motion of an Injex ampoule driven by our system (Fig. 6, dashed line) is compared with that of the same ampoule being driven by a standard Injex 30 spring-based injector (Fig. 6, solid line). The spring-actuated piston tip exhibited a resonance at approximately 630 Hz; several oscillations are evident in the piston-tip trajectory. The gently-accelerated servo-controlled piston takes approximately 2 ms to reach the same jet speed as the spring-based actuator, during which time approximately 1-2 μL of drug is expelled. During the motion of the spring-actuated piston, the total displacement signal in the 500-700 Hz frequency band was 56 μm RMS; during servo-controlled motion, the displacement signal in this band was reduced to 2.8 μm RMS. The mean equivalent sound pressure level (determined over eight injections) generated by the Injex spring injector was 71.4 ± 2.1 dB; our device created a mean sound pressure of 59.6 ± 0.8 dB. The peak sound pressure from the Injex was 95.2 ± 1.5 dB; the peak pressure from our device was 77.0 ± 0.8 dB.

The injections into acrylamide (Fig. 7a) show that in 10% gels, erosion depth was linearly related (R^2=0.99) to jet speed. For 20% gels, the relationship between jet speed and erosion depth was non-linear, and the erosion depth achieved for a given jet speed was more variable. Our results show a CV of 0.035 for 10% gel, and 0.18 for 20% gel. By modulating the time at high speed (T_{jet}) while holding the jet speed and follow-through speed constant, we achieved injection depths ranging from 4 mm to 10 mm (Fig 7b). The CV for these injections ranged from an average value of 0.042 for T_{jet}= 2 ms to an average value of 0.028 for $T_{je\,t}$ > 10 ms.

Repeated ejections into vials of a subset of the ampoule contents (Fig. 8a) demonstrate that our jet injection system ejects a mean volume of drug that equates to 99.18 ± 0.04 % (σ ± se) of the target volume with a CV (quantified across 24 ejections) of typically better than 0.01.

The injections into tissue (Fig. 8b) show delivery of typically > 80% of the fluid to the target tissue. In rabbit tissue, we were able to deliver, on average, more than 90% of a 100 μL volume to depths of 3 mm (100 m/s) and 15 mm (200 m/s). The thinner, more compliant tissues of mouse and guinea-pig allowed us to deliver 81 % and 60% respectively of a 20 μL volume of fluid to a depth of 2-3 mm. Once injected, the injectate spread along

local cleavage planes in the tissue (Fig 8c,d) in a highly specimen-specific manner.

4 Discussion

Most jet-injection systems comprise a fluid-filled ampoule and a piston that is accelerated by the rapid release of potential energy to produce a step-like increase in jet pressure upon activation of the device. There is limited opportunity to control pressure, or to regulate the depth or volume of injectate delivered by such devices. Moreover, they behave as underdamped resonant systems, reflecting the energy storage method, the mass of the drive mechanism and fluid, and the viscous losses associated with jet formation. As a result, most commercial systems exhibit resonance in jet pressure and piston motion (Fig. 7, see also Fig. 4(a) in [25] and Fig. 2 in [29]). In this paper, we describe a jet injection system that utilizes a linear Lorentz-force actuator in which electronic closed-loop control is used to regulate piston motion and the drug volume delivered. This capability allows us to avoid the resonant frequency of the system, gently accelerate the piston, and thereby retain tight control over the motion of the piston and drug.

Our controllable jet injection system allows us to deliver user-specified drug volumes of up to 250 μL from the Injex ampoule with a high level of repeatability and precision. The use of feedback control of piston position allows jet velocity to be regulated throughout the injection cycle, and the ampoule to be rapidly reloaded. Also, using this system, it is possible to inject the total ampoule volume by means of multiple, smaller doses at several sites [20]. These are major advances over piezoelectric jet-injection systems, which offer the possibility of closed-loop control, but are presently limited to injection volumes of the order of 1-10 μL [16]. Finally, our system is quieter than comparable commercial systems (11.8 dB and 18.2 dB reductions in equivalent sound pressure and peak sound pressure, respectively, compared to the Injex spring jet injection system). We hypothesize that this advance will offer advantages in patient compliance when administering injections.

In acrylamide, it was possible to select the depth of injection with a high level of repeatability. The depth of the erosion hole in acrylamide is determined during the high-velocity phase of delivery and can be altered by varying either jet speed or the duration of this phase. Upon cessation of the erosion phase, the injectate begins to disperse in a manner that is highly dependent upon the structure of the acrylamide. In gels of 10 % to 20 %

concentration, cracking occurs at the end of the erosion hole, resulting in the dispersion of a disc-like volume of fluid (Fig. 4a). This process was less predictable at higher gel concentrations.

The injections of fluid into animal tissues using this system were less precise than those into acrylamide, reflecting the layered, anisotropic and inhomogeneous structure of the tissue specimens. A fraction of the injectate is likely expelled from the delivery site during the erosion phase, while some may also leak away post-injection, as a consequence of the inability of the tissue to absorb the full dose. However, in most cases more than 80% of the drug delivered was to the target region (see Fig 8b) - a significant advance over other controllable jet injection systems, which deliver as little as 10% to the specified site [16]. Others have demonstrated that some drug can be lost during the phase of hole-erosion into acrylamide [see supplementary materials of reference 16]. However, by maintaining our ampoule orifice in apposition with the tissue, limiting the time that high jet speed is maintained, and by delivering the bulk of the drug volume at reduced velocity, we have successfully increased the percentage of drug delivered into tissue over that previously demonstrated. Post-delivery leakage of drug from the delivery site was most noticeable for shallow injections into mouse and guinea pig specimens. Further research is required to determine whether reducing the follow-through velocity would increase the proportion of injectate retained in the tissue, but our device certainly offers this capability.

A possible limitation of the control scheme is the need to implement a feed-forward model to account for the non-linear pressure-velocity relationship of the injection system. However, this calibration need only be performed once for a given combination of target tissue and drug compound. The relationship between injection depth and jet velocity has been investigated in a variety of tissue specimens *in vitro*. These studies indicate that injection depth is affected by tissue structure and composite tissue properties including the epidermis, dermis and fat layer. Further work is necessary to characterize this relationship fully in appropriate *in vivo* animal models. Future versions of this device will incorporate the capability of rapidly measuring tissue mechanical properties via system identification techniques [30] potentially allowing injection parameters to be determined prior to delivery.

5 Conclusions

Our real-time feedback-controlled approach to needle free jet injection has allowed us to demonstrate highly-

repeatable independent control over injection depth and delivered dose to a range of different tissues and tissue-analogs. Control of injection depth is achieved by modulating the peak jet speed, and the time for which peak jet speed is maintained. Control of injection volume is achieved by real-time feedback control of piston position as it describes a band-limited injection trajectory. The ability to smoothly accelerate and decelerate the injection system allows us to deliver a subset of our total available drug volume in a number of smaller controlled injections. These advances are enabled by real-time feedback control during the time-course of delivery, a significant advance over our previous open-loop devices.

The performance of this device demonstrates the potential of using linear Lorentz-force motors in highly-controllable, high-volume portable jet injectors for a range of applications in animal and human drug delivery. To this end, an inexpensive miniature embedded-controller and digital power amplifier is currently being developed for future integration into the handle of this device. This development will enable the creation and deployment of highly-controllable, yet low-cost and portable devices for jet delivery of liquid drug.

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