A Device for Controlled Jet Injection of Large Volumes of Liquid

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***Abstract*— We present a needle–free jet injection device controllably actuated by a voice coil and capable of injecting up to 1.3 mL. This device is used to perform jet injections of ~900 µL into porcine tissue. This is the first time that delivery of such a large volume has been reported using an electronically controllable device. The controllability of this device is demonstrated with a series of ejections where the desired volume is ejected to within 1 % during an injection at a predetermined jet velocity.**

I. Introduction

Jet injection is a drug delivery technique in which a liquid drug is formed into a thin, high-speed jet which is capable of penetrating the outer layers of skin and being delivered to the underlying tissue [1], [2]. The key benefit of this technique is that liquid drug injection can be achieved without the use of a needle, thereby avoiding issues like needle phobia and accidental needle stick injury [1].

Commercially-available jet injection systems typically rely on the uncontrolled expansion of springs or compressed gases [3], [4]. In devices intended for livestock these systems are capable of delivering volumes up to 5 mL, but to uncontrolled depths. More recently, jet injection devices capable of providing sufficient bandwidth to control the injection depth have been developed. These devices have employed voice coils [2], [5], mechanically amplified piezoelectric actuators [6], or pulsed lasers [7] to drive the injection. These controllable devices have been used to deliver volumes of up to 300 µL in the case of voice coils and up to 1 µL with piezoelectric and laser based devices.

For a voice coil actuated system the issue limiting this deliverable volume is the fundamental scaling relationship between the injectable volume (V) and the motor mass (M). As previously established [8], given a fixed electrical power input, M and V are related by:

$$M \propto V^{\frac{6}{5}}. \quad (1)$$

Previously [9] we presented a novel ‘compound ampoule’ (CA) mechanism which overcomes this motor mass scaling issue by breaking the injection into two phases. As shown in Fig. 1 the CA works through initially actuating a smaller inner piston before engaging a larger outer piston which, under a constant force input, generates a phase of high pressure followed by a phase of lower pressure.

This CA assumes that the highest pressure and jet velocity is required only while the jet initially is penetrating through the skin, while the majority of the delivery can be performed at a lower jet velocity. The results presented in [9] reveal that although the CA device functioned as designed, the pressure and jet velocity achieved in the second phase of delivery did not provide near-complete injection of the target volume. This finding highlighted the need for a greater understanding of the relationship between the jet velocity and final penetration of the jet. To what extent can the jet velocity be reduced following skin penetration without sacrificing the completeness of delivery?

An understanding of the relationship between jet speed and fluid delivery could be achieved through experimentation with a high power, controllable, large volume injector. A high power actuator can enable delivery of large volumes, while the controllability of the actuator can be used to create the two phase injection of the CA using a single piston. In this work we construct such an injection device, actuated by a voice coil motor driving a single piston and ampoule, providing a maximum injectable volume of 1.3 mL. We demonstrate the device’s controllability and its ability to successfully deliver a large volume (~900 µL) of liquid into porcine tissue.

II. Methods & Materials

A prototype large volume controllably-actuated injection device was constructed as shown in Fig. 2. The voice coil actuator (BEI Kimco, LA25-42-000A) had a stroke of

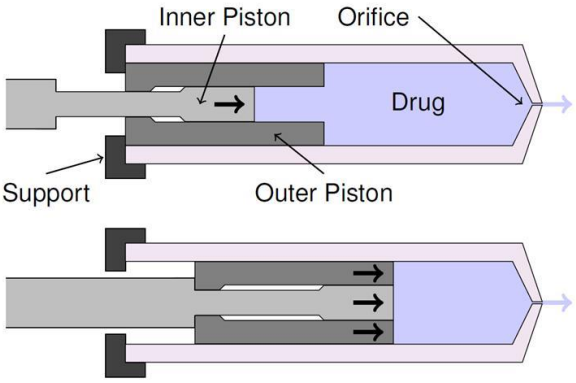

Fig. 1. A schematic diagram of the compound ampoule (as presented in [9]). A force applied from the left results in the smaller piston first being actuated before engaging the outer piston, resulting in a phase of high pressure followed by a phase of lower pressure for the bulk of the delivery.

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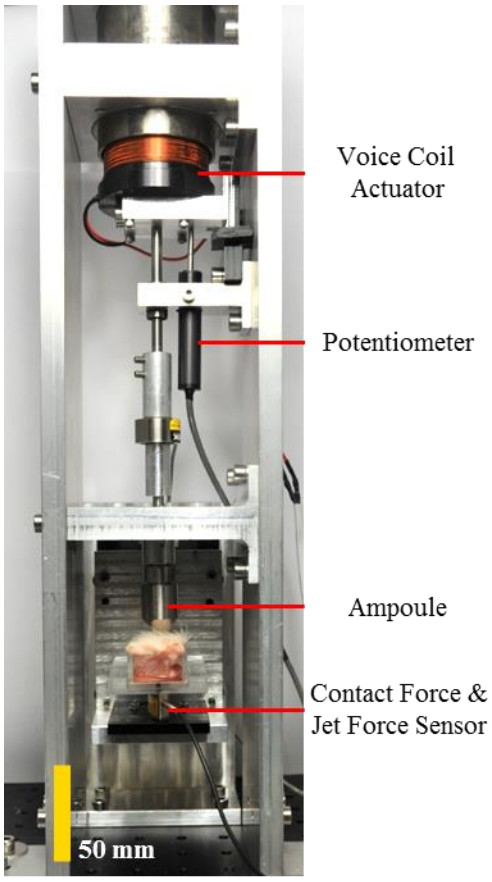

Fig. 2. The high power, large volume, controllable injection device. The voice coil actuator can be seen at the top of the image with the ampoule below pressed against a sample of porcine tissue.

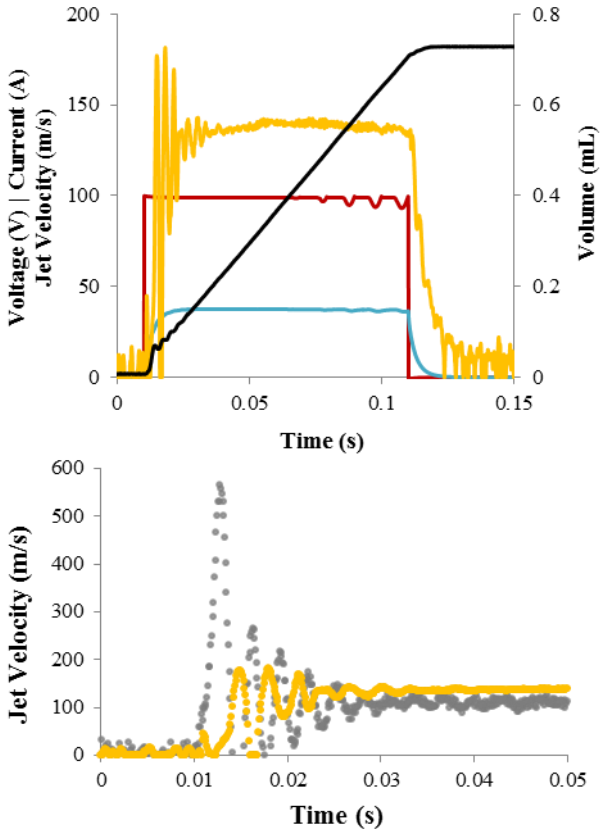

Fig. 3. **Top**: The resultant jet velocity and volume traces from a 100 V step input (red) with current (blue), ejected volume (black) and jet velocity (yellow). The jet velocity is based on a jet force measurement. **Bottom**: The volumetric (grey) and jet force (yellow) measurements of jet velocity in the first 50 ms of the injection.

25 mm, moving mass of 540 g, force constant of 21.35 N/A, and DC resistance of 2.4 Ω. It was rigidly connected to a single piston which moved within a 1.3 mL cylindrical ampoule with an inner diameter of 8.34 mm. The jet was emitted from the ampoule through an orifice 280 µm in diameter (O'Keefe Controls ZMNS-11-M3.5-SS-BN). A potentiometer (Omega LP-803-1) provided a measurement of coil position, from which we calculated the volume of fluid ejected from the ampoule.

The voice coil actuator was controlled by a field-programmable real-time controller [5] (NI cRIO-9024, using LabVIEW2011, National Instruments). This system provided a sufficiently high bandwidth to perform position feedback control over the time-course of an injection (~100 ms). The drive signal for the actuator was generated within the controller and amplified by two power amplifiers (AE Techron 7224) connected in parallel.

The mechanical function of the system is demonstrated in Fig. 3 by its response to a simple voltage step input of 100 V. The jet velocity was measured by two methods: *volumetric*, in which the jet velocity is determined from the measured motion of the coil; and a *jet force* measurement [10] where jet velocity is computed from the change in momentum of the jet as it impinges on a force sensor.

Fig. 3 shows these two measures of jet velocity at the beginning of the step input, demonstrating the difference between the peak and steady state jet velocities during such a test. The jet force measurement can be considered the more useful measure during these early stages of injection as it is not influenced by the compliance within the system, as is the volumetric measurement. Following this initial period ($t \geq 30$ ms) the volumetric measurement reliably provides the mean flow across the jet. The delay observed between the volumetric and jet force based measurements can be attributed mainly to the response time of the force sensor and its associated signal conditioning. The time of flight between the injector and this sensor explains ~0.1 ms of this ~2 ms delay. As we wish to compare our results to those existing in the literature (particularly [5]), all references to jet velocity in the remainder of this paper refer to the volumetric measurement.

III. Controllability

The real time control strategy of the voice coil actuator matches that presented in [5]. This system relies on two components: a feed-forward model which predicts the required voltage from the desired jet velocity, and a linear proportional controller. Due to the highly nonlinear characteristics of the system, a proportional-integral-

Table 1. The summarized results of the 20 controllability injections

Jet Velocity (m/s)	Volume (µL)	Volume Delivered (µL) (mean ± standard deviation)
110	600	598.1± 1.1
	1000	991.6 ± 1.9
80	600	602.6 ± 2.4
	1000	998.8 ± 0.8

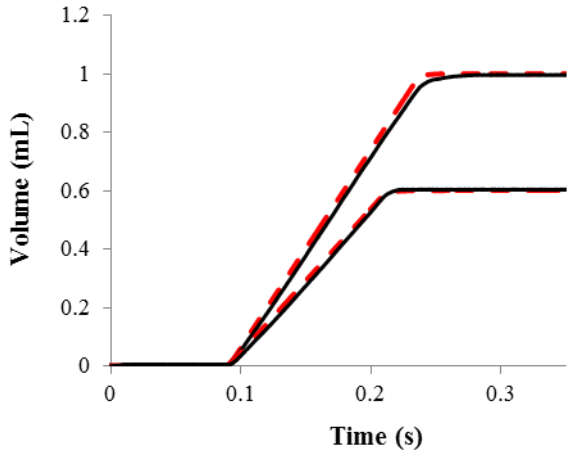

Fig. 4. Two examples (110 m/s, 1000 µL and 80 m/s, 600 µL) of the ejected volume (black) following the generated set-point (red).

derivative feedback controller alone is insufficient. The feed-forward model is developed from a series of injections where the voice coil is given a step input and the resulting jet velocity is measured. The linear proportional control provides the system with the ability to respond to disturbances, or to changes to the plant, which might otherwise result in slight differences between the desired and measured paths.

The controllability of the injection system was evaluated through performing a series of injections into air. A desired jet velocity and total volume were selected and used to generate a position set-point profile for the actuator to follow. The measured displacement of the actuator was then used to estimate the actual volume ejected and provide an indication of how closely the motor's travel matched the set-point. This experiment was performed at two jet velocities (80 m/s and 110 m/s) and two total volumes (600 µL and 1000 µL). Five injections were performed at each combination of jet velocity and volume resulting in a total of 20 injections.

Table 1 shows the summarized results of these 20 injections. The mean ejected volume is within 1 % of the target volume in all four cases. The standard deviation is largest in the 80 m/s, 600 µL case where it is still only 2.4 µL, demonstrating the repeatability of these injections.

The ability of the injector to follow the set-point, and therefore deliver the desired jet velocity, is shown in Fig. 4. This figure shows data from two injections (one from a 110 m/s, 1000 µL injection and another from an 80 m/s, 600 µL injection) where the measured volume is almost indistinguishable from the set-point.

IV. Tissue Injection

To investigate the ability of this injector to successfully deliver large volumes of fluid into tissue, a series of injections were performed into post mortem porcine tissue. The tissue was harvested, post mortem, from the chest of pigs aged 9 weeks to 12 weeks in accordance with the University of Auckland Code of Ethical Conduct for the Use of Animals for Teaching and Research. A total of 16 injections were performed at nominal jet velocities ranging from 80 m/s to 120 m/s. These jet velocities were generated by varying the magnitude of a step voltage applied to the voice coil actuator. The maximum jet velocity was limited by the capability of the power amplifiers. The contact force applied by the injector to each 50 mm × 25 mm tissue sample was approximately 1 N at the time of injection. All injections involved the attempted delivery of between 850 µL and 900 µL of fluid. The volume delivered to the tissue was measured by weighing the tissue before and after the injection. Any fluid remaining on the surface of the tissue following the injection was removed prior to weighing with a piece of tissue paper. The injected fluid contained dye (1.8 % Brilliant Blue FCF, Queen New Zealand Pty. Ltd.) so that the dispersion of the fluid within the tissue could be visualized.

Fig. 5 shows the proportion of fluid delivered (as a percentage of fluid ejected from the device) during this series of injections. This delivery percentage is presented as a function of the nominal volumetric jet velocity. This measure of jet velocity was of particular interest as it represents the velocity toward the end of the injection, which was the limiting factor in our previous large-volume injection attempts [9].

The results presented in Fig. 5 demonstrate that this device can consistently deliver large volumes of fluid (~900 µL) into tissue, making it the first controllably actuated device to do so. Consistent delivery was achieved at nominal volumetric jet velocities of at least 115 m/s; the proportion of fluid delivered to the tissue was much more variable at jet velocities less than 115 m/s and became low when the jet velocity was less than ~100 m/s. Over the 5 injections at 115 m/s or greater an average of 97.7 % of the fluid was delivered to the tissue. This is an improvement on results previously reported for controllable injectors. For example, the porcine tissue injections reported in [5] were delivered at similar jet velocities (125 m/s to 150 m/s), but the mean proportion of drug absorbed by the tissue was 74 % for 100 µL injections.

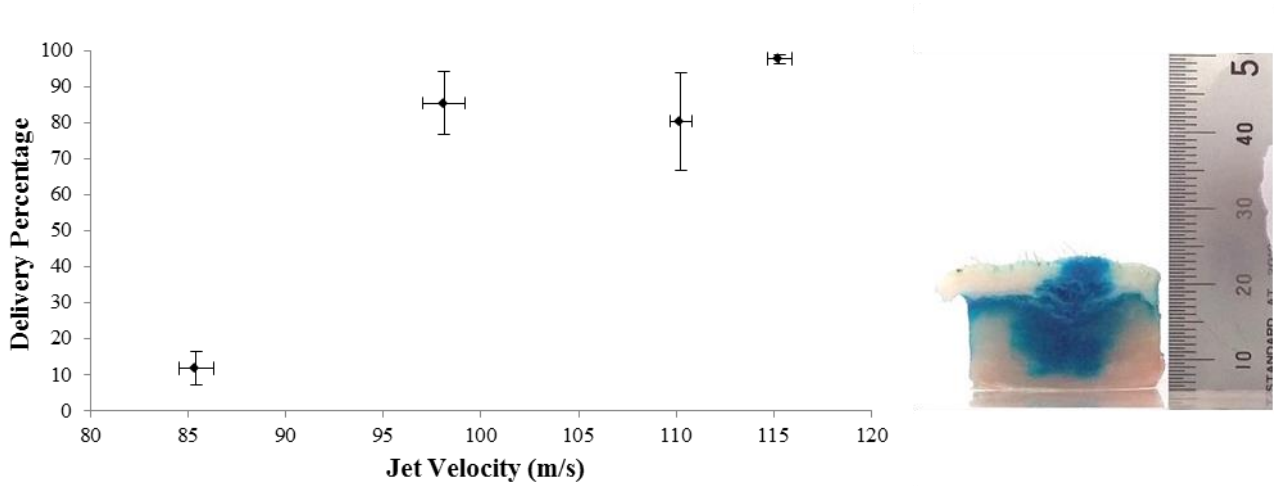

Fig. 5. **Left**: The results from the injection tests into post mortem porcine tissue. The volume of fluid delivered as a percentage of fluid ejected from the orifice is plotted against the nominal volumetric jet velocity. The error bars represent one standard deviation either side of the mean (n= 3 to 5). **Right**: An injected sample which has been sliced through the injection site to observe the dispersion of the injected fluid.

An example of an injected sample, which was frozen then sliced through the injection site, is provided in Fig. 5. The fluid can be observed to have been delivered mostly to the muscle layer, with some present in the subcutaneous fat. This distribution is typical of what was observed throughout these large volume injections.

V. Conclusion & Future Work

We have constructed a controllable jet injection device with a maximum volume of 1.3 mL per injection. This voice coil actuated device has been controlled to produce a jet injection at a velocity of up to 120 m/s through a 280 µm orifice, and eject a volume of ~1 mL with a relative repeatability of better than 0.2 %. We have demonstrated the devices ability to successfully deliver volumes of up to 900 µL into tissue with a delivery rate of ~97 %, a first for a controllably actuated device. With the use of a new custom-built amplifier, we plan to fully extend this volume to the limit of the current device — 1.3 mL.

The bench-top device developed here can now be used to conduct experiments to explore the effects of changing jet velocity over the course of an injection. In particular, we can establish what jet velocity is required during the latter part of an injection (the 2nd phase), and use this information to inform the design of a new compound ampoule (CA) device. An appropriately designed CA would allow the use of a much smaller voice coil actuator, resulting in a hand held injection device which would be much more appropriate for a clinical environment.

The controllability of this device can extend beyond the injection of a desired volume at only one or two phases of jet velocity. In principle, the voice coil actuator could be made to follow a wide range of delivery velocity profiles. This could include mimicking the jet velocity profiles produced by spring or gas actuated devices, presenting a unique way to compare the benefits and drawbacks of such profiles.

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