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Jet Injection of Viscous Fluids

Rhys Matthew James Williams

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

in Bioengineering

The University of Auckland, 2016
Abstract

In the work presented in this thesis, I develop a controllable jet injector capable of delivering viscous fluids through the surface of the skin and into the tissues underneath. Jet injectors use a high-speed jet of a drug (up to 200 m·s⁻¹) to pierce through the skin and then force fluid through the resultant hole to disperse drug either within the dermis, sub-cutaneous fat or underlying muscle. As my work built upon that of previous researchers, the first step of my project was the development of an electromechanical model of the jet injector that was in use at the time. The model captured elements of the device’s mechanical compliance that had previously not been accounted for and also included a viscous loss term in its fluid formulation. Using this model as a guide, I designed and built a jet injector that used a commercial moving coil actuator to provide the required force as part of a stiff injector rig, including a custom stainless steel fluid ampoule and piston. This injector had the additional benefit of a removable orifice insert. I tested the injector to determine its performance and the effect of viscosity and orifice diameter on its behaviour. These tests suggested that a 200 µm orifice, as used in the original ampoule, performed the best across a range of fluids with different viscosities. The results formed the basis for the feed-forward model that controls the injector. I then created a simulation of the flow within both the new and the original ampoules using computational fluid dynamics to investigate the causes of loss. The results suggest that a smooth, short geometric approach to the orifice diameter reduces loss within ampoules as it reduces both turbulence and viscous drag. I followed this investigation by injecting into gels and pig skin to determine the effect of viscosity on dispersion of a fluid underneath the surface of the skin. I found that viscosity had no significant effect on the dispersion as the variability in skin properties impacted the dispersion to a much larger degree.
Acknowledgements

The four and a half years I have spent on my PhD initially seem to be a lot of time to spend on one project and people are often surprised when I tell them. However, when I think of the person who first committed to the project back in 2011, I realise that not only have I learnt a lot about researching over the period, the freedom of pursuing a PhD has allowed me to develop personally. It has enabled me to think about what I should focus on, and how to be more effective at what I am passionate about. I am as passionate about my project as I was on day one, which even I find hard to comprehend. Therefore, I have no regrets about my decision to commit to this project, as it has benefited me in ways I could not have ever expected.

Associate Professor Andrew Taberner has been my guide through the whole process, with weekly meetings and the odd impromptu meeting at my desk when he was enthused by a new idea (definitely a highlight). His enthusiasm often revitalised my interest and his passion for making something novel and useful is, in my view, what researching in engineering is all about. He has also consistently been supportive and understanding, critical to my success in this degree. I consider myself very lucky that a project I cared about was led by someone who understood the ups and downs of my pursuit of the degree and was always willing to talk.

My co-supervisor, Professor Poul Nielsen, was my mentor for the science behind the ideas I was pursuing. Many meetings I would be getting side-tracked in my work and Poul would interject with a question so on point that I was forced to look at the problem in a whole new way. He kept me grounded throughout my PhD, encouraging me to pursue science and to be rigorous throughout my work. I have learnt a huge amount about how to approach research from him and hope to keep his principles in mind when I pursue further scientific goals.

Dr. Bryan Ruddy, who started at the ABI as a post-doctoral researcher after my PhD had entered its 2nd year, became an important contributor to my work, always willing to help me work out a concept with a whiteboard session. His questions during meetings challenged me to anticipate criticism and respond appropriately. He guided my experiments to ensure that they provided useful data I could trust and
helped me to analyse them in a way that was rigorous. Finally, he provided extensive feedback on all my thesis chapters, encouraging me to structure them in a way that enabled the reader to fully comprehend the results and my conclusions, an arduous job that is greatly appreciated.

Dr. Richard Clarke and Dr. David Budgett served on my advisory panel and provided important guidance early in the PhD, as I submitted my thesis proposal to the panel for consideration. There is no doubt that their help saved me strife later in the degree. The other two members of the panel were Dr. Cathy Hogan and Professor Ian Hunter, at the Massachusetts Institute of Technology. Both hosted me for three months in 2011, during the first year of my PhD and were excellent substitutes for my supervisors during that period. They helped define my project early on and our continuing collaboration on research papers and jet injector work has been very valuable. The base for the injector project is MIT and the opportunity to pursue the work on such an important project in New Zealand is something special.

The Auckland Bioengineering Institute (ABI) is a great environment to pursue a PhD. My period as postgraduate representative at the ABI involved attending the principal investigator (PI) meeting. My experience of this meeting made it very clear that the PI’s are a group of highly motivated researchers and this encouraged me to persist with my own research. It was also clear that they care greatly about their students and focus on creating not only a well-resourced institute but one with a social culture that is inclusive and welcoming, important for graduate students early in their careers.

My fellow students at the ABI have been a constant source of support and help with research. The general culture of approachability means that I was able to use equipment and learn things much quicker than otherwise. I am thankful to everyone who helped me, even if just in a conversation about a concept I had not fully grasped. The bioinstrumentation group has morphed over time as people have come and gone. What has not changed is the fact that it is full of hard-working students who are willing to help you pursue your goals and I’d like the thank them all. A special thanks to Matthew Parker, Paul Roberts, Tom Lintern, Mark Finch, and Callum Johnston for their help early on in my PhD and their friendship, important especially when I first started out at the Institute. Also, I would like to give a big thank you to both Stephen Olding and Peter Blythe, the two workshop managers at the ABI during my PhD. Both machined important parts of my project and provided design advice that was necessary to get my devices to work like I intended. Finally, I’d like to acknowledge the support of James McKeage, Sam Richardson and Kieran Brennan who have only known me as I have been frantically trying to finish my PhD, but were important in helping me achieve that goal.
My friends and family provided a huge amount of support during the ups and downs of my PhD. I was lucky enough to have a close friend right next to me every day at work. I can’t express how grateful I am to Nikini for his never-ending optimism and the emotional support I received from him. The ‘Fluffy Crew’ on Level 1, Nikini along with Sophia and Dharshini, gave me much needed comic relief and companionship on Friday afternoons and became close friends as a result. Close friends outside the ABI were also a great support, continually willing to chat and allow me to relax outside work. In particular, I’d like to thank Harry Aitken, Ethan Worley, Suneil Narsai, Chris Okey, Larry May, Amrish Ram, Mike Dey, Kel Rayens, Evan Blumgart, Devan Jackson, Tian Du Toit, and Lance Wynyard. I am very proud of my friends and you are all important to me. I hope that we continue to be close into the future. I’d also like to specially thank Yves Plusjé for his help as I neared the end of my PhD. With the stress of writing settling in, Yves helped immensely both with grammatical editing and emotional support right through to the end and helped carry me across the finish line.

Finally, I’d like to thank my family. To my sisters; Briar, Phillipa, Caroline and Victoria. At various points throughout my PhD I have stayed at your houses, and you have always been there to provide support and mentor me as I have progressed. I treasure our family time together and am very grateful for having such wonderful siblings. I am also very lucky to be a part of your families and enjoy very much being an uncle to Greer, Sam, Cate, Lucy, Olivia and Conner. To mum and dad, Catherine and Morris Williams, you have always been there for me and consistently put the effort in to understand where I was at. You help me selflessly even when I do not have the courage to ask. I am very thankful and appreciate you both every day.

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# Table of Contents

Abstract .................................................................................................................................................. iii

Acknowledgements ................................................................................................................................... v

Table of Contents .................................................................................................................................. ix

List of Figures ......................................................................................................................................... xv

List of Tables .......................................................................................................................................... xxi

Nomenclature ........................................................................................................................................... xxiii

1 Motivation and Outline ...................................................................................................................... 1
   1.1 Motivation ....................................................................................................................................... 1
   1.2 Outline of Thesis ............................................................................................................................ 3

2 Background and Literature Review .................................................................................................. 5
   2.1 Jet Injection in the Context of Transdermal Delivery ................................................................. 5
   2.2 Jet Injection: Benefits and Drawbacks .......................................................................................... 9
   2.3 Jet Injection Applications .............................................................................................................. 12
      2.3.1 Vaccines ............................................................................................................................... 12
      2.3.2 DNA Transfer ....................................................................................................................... 13
      2.3.3 Hormones ............................................................................................................................ 15
      2.3.4 Other ..................................................................................................................................... 16
   2.4 Skin Models .................................................................................................................................... 17
      2.4.1 Relevant Mechanical Properties of Skin ............................................................................... 17
      2.4.2 Testing and Physical Models of Skin .................................................................................... 18
      2.4.3 Requirements for a Jet to Pierce the Skin ......................................................................... 20
      2.4.4 Models of Penetration and Dispersion ............................................................................. 21
2.5 Current Work

2.5.1 MIT/ABI Research

2.5.2 Control System used at ABI and MIT

2.5.3 Other Research Groups

2.6 Jet Injector Modelling

2.7 Future Developments

2.8 Delivering Viscous Fluids Transdermally

2.8.1 Monoclonal Antibodies

2.8.2 In Situ Forming Drug Delivery Systems

2.9 Progression to Creating a Model

3 Modelling of Jet Injectors

3.1 The Following Chapter

3.2 Abstract from Paper

3.3 Introduction

3.4 Model Formulation and Parameterization

3.4.1 Jet Injector System Design

3.4.2 Model Formulation

3.4.3 Parameter Estimation

3.5 Validation

3.5.1 Piston Tip Measurements

3.5.2 Jet Force Measurement

3.6 Design Predictions

3.7 Discussion

3.8 Conclusions

3.9 The Effect of Stiffening System Components

3.9.1 Fabrication and Testing

3.9.2 Results and Discussion

3.10 Model Predictions for Viscous Fluids
5.2.2 Mesh Independence ................................................................. 95
5.2.3 Turbulence Variation ............................................................. 96
5.3 Results from Computational Model of Commercial Ampoule ......................... 97
  5.3.1 Jet Speed Profiles ................................................................. 97
  5.3.2 Comparison with Experimental Results ........................................... 98
  5.3.3 Qualitative Results ................................................................. 99
  5.3.4 Shear Rate ........................................................................ 99
5.4 Investigation of the Simulation Settings with Glycerol ...................................... 101
  5.4.1 Process of Investigation ............................................................ 101
  5.4.2 Results from Range of Simulations with Glycerol ............................... 102
  5.4.3 Effect of Viscous Heat ................................................................ 103
  5.4.4 Preliminary Review of Commercial Ampoule Results .......................... 103
5.5 Stainless Steel Ampoule Investigation .......................................................... 105
  5.5.1 Structure and Settings of Computational Model .................................... 105
  5.5.2 Mesh Independence .................................................................. 107
  5.5.3 Turbulence Variation .................................................................. 107
5.6 Results from Computational Model of Stainless Steel Ampoule ....................... 109
  5.6.1 Jet Speed Profiles .................................................................... 109
  5.6.2 Comparison with Experimental Results ............................................ 109
  5.6.3 Comparison with Results from Commercial Ampoule Simulation .......... 110
  5.6.4 Qualitative Results .................................................................... 111
  5.6.5 Shear Rate .............................................................................. 113
5.7 Discussion ..................................................................................... 114
  5.7.1 Discussion of Simulation Methods for Both Ampoules ......................... 114
  5.7.2 Jet Speed Profiles for Commercial Ampoule ....................................... 115
  5.7.3 Extension to Stainless Steel Ampoule ............................................ 116
  5.7.4 Guidance for Ampoule Design .................................................... 118
5.8 Conclusions and Future Work .................................................................. 119
6 Dispersion of Viscous Fluids Underneath Skin ................................................................. 121
   6.1 Introduction .................................................................................................................. 121
   6.2 Injection into Acrylamide Gels .................................................................................. 125
      6.2.1 Methods ............................................................................................................. 125
      6.2.2 Results ............................................................................................................. 126
      6.2.3 Preliminary Discussion ...................................................................................... 127
   6.3 Injection into Porcine Skin ........................................................................................ 130
      6.3.1 Methods ............................................................................................................. 130
      6.3.2 Results ............................................................................................................. 134
   6.4 Discussion .................................................................................................................. 140
   6.5 Conclusions .............................................................................................................. 143
7 Conclusions ..................................................................................................................... 145
   7.1 Review of Outcomes .................................................................................................. 145
   7.2 Novel Contributions .................................................................................................. 148
      7.2.1 Electromechanical Model ............................................................................... 148
      7.2.2 Control System ............................................................................................... 148
      7.2.3 Viscous Fluid Jet Injector Construction and Testing ........................................ 148
      7.2.4 Computational Fluid Dynamics Modelling of Ampoule Geometry ............... 149
      7.2.5 Fluid Dispersion Testing Across Viscosities ..................................................... 149
      7.2.6 Overall Review ............................................................................................... 150
   7.3 Future Work ................................................................................................................ 151
A Appendix: Data from Dispersion Studies ..................................................................... 153
   A.1 Gel Test Data (next page) ....................................................................................... 153
   A.2 Porcine Skin Test Raw Data .................................................................................... 155
   A.3 ANOVA Results for Porcine Skin Tests .................................................................. 156
Bibliography .......................................................................................................................... 157
List of Figures

Figure 1 - Diagram showing layers of skin and the location of the stratum corneum........................................6

Figure 2 - Scanning electron microscope images of microneedles used in the study by Henry et al. [29]. A shows a 20 x 20 array of microneedles, and B is a close up of one microneedle........................................7

Figure 3 – A series of commercial disposable cartridge jet injectors (DCJIs). (A) LectraJet HS motorized DCJI which uses a motor to compress a spring. (B) LectraJet M3, a manual version of the HS model. (C) Pharmajet Stratis DCJI, a device that works with traditional drug vials and delivers into the subcutaneous and intramuscular layers under the skin. (D) Medi-Jector Vision DCJI, used to deliver insulin into the sub-cutaneous fat. (E) Sumavel DosePro, used to deliver a migraine treatment into the subcutaneous fat. (F) J-Tip, an injector powered by compressed nitrogen gas. (G) Injex, a compressed-spring device used to deliver insulin. I use the ampoule of this device in my early modelling and testing. (H) Imule syringe for needle-free influenza vaccine delivery. (I) Biojector 2000 by Bioject Medical Technologies delivers to sub-cutaneous fat and intramuscular layers with force provided by compressed carbon dioxide. (J) ZetaJet spring-powered injector uses different cartridges for subcutaneous, intramuscular, and intradermal injection. (K) Iject injector uses a glass dose chamber as an ampoule. Reprinted from [17] with permission from Elsevier..................................................................................................................11

Figure 4 - Reproduction of Figure 1 with the antigen-presenting cells (APCs) identified, including the Langerhans cells of the dermis. The different layers of the dermis are identified. Layers where APCs are present are the best targets for vaccines...........................................................................................................................................................................12

Figure 5 - Reproduction of figure from [154] published under license showing injecting of naked DNA into mouse skin sample with three layers identified. A is a top view of the injection, B indicates the movement of the injectate after injection near the dermis, C shows an injection that went deeper into the subcutaneous and muscular layers, and D is an image of a control injection without staining, focusing on the dermal layer.................................................................................................................................................................14

Figure 6 - Diagram showing the two-phase nature of jet injection. The phases have been associated with the penetration and dispersion mechanic that they are supposed to cause. .................................................................................................................................18

Figure 7 - Example of jet injection test into polyacrylamide gel. Brilliant Blue FCF was used to colour the injected fluid...........................................................................................................................................................................20

Figure 8 - Jet injector system (LJI) as used in my research group and documented by Taberner et al. [9]. ..................................................................................................................................................................................24

Figure 9 - Diagram of piezoelectric system used by Stachowiak et al. [36]. The piezoelectric stack actuator in the centre expands, forcing the piston forward and the fluid out the orifice.................................................................................................26

Figure 10 - Diagram of needle-free injector system.................................................................................................................................37

Figure 11 - Block diagram of JI electromechanical system........................................................................................................................................................................38

Figure 12 – A: The current response to a 7.25 V voltage step (black dots), in comparison to the predicted current response to the same voltage step of a 1/(Ls+R) transfer function (green line) and using the impulse response function (blue dotted line). B: The results of force constant tests over the
stroke range of the JI (cross), and a fitted 2nd order polynomial with $R^2 = 0.9815$ (line). C: Fit of piecewise linear piston compliance (tip compliance - green dashed line, shaft compliance - blue dotted line) to measured compression data (black line). D: The fit of the friction coefficient multiplied by the area of tip contact to the loss attributed to friction (cross) across the range of pressures with $R^2 = 0.9940$. 

Figure 13 - Plot of coefficient of discharge ($K_p$) over the range of viscosities tested. A model fit is represented by the black line with $R^2 = 0.727$. 

Figure 14 - The results of three piston-tracking experiments conducted during pulse tests of 120 V (A), 200 V (B), and 260 V (C). The solid line is the model prediction, and the dotted line represents the measured position from the tracking software. The fluid used was water. 

Figure 15 - Comparison of measured jet speed calculated from jet impact upon force plate (dotted black line) and model predictions (grey line). The current is presented as a dashed black line. 

Figure 16 - Steady state jet speed (blue circles), maximum jet speed (black squares), rise time to first peak of position profile (green plus signs), period of coil position oscillations (purple crosses) when model parameters are modified. These parameters are piston spring constant ($A$), friction coefficient ($B$), ampoule bulk modulus ($C$), and viscosity ($D$). 

Figure 17 - The model estimates (dotted line) and actual measurements (solid line) for a variety of different compliance element configurations. A: the results for the original piston matched with the stiff ampoule. B: the result for a stiff piston and ampoule test. C: the result for a stiff piston and original ampoule test. Each measured result is the average of ten tests. 

Figure 18 - The model estimates (dotted line) and actual measurements (solid line) of coil position for a variety of different viscous fluids. A: the results for a solution of 0.002 Pa·s viscosity. B: those for a solution of 0.012 Pa·s viscosity. C: those for a solution of 0.042 Pa·s viscosity. D: those for a solution of 0.109 Pa·s viscosity. 

Figure 19 - Contour graph of 3-D polynomial indicating jet speed attained at certain voltages over a range of viscosities. The dotted black line indicates the section of the fit used in feed-forward control for the 0.0209 Pa·s fluid. 

Figure 20 - A: The rheometer-measured viscosity of a fluid plotted against the injector estimated viscosity. B: A comparison of the desired jet velocity to the achieved velocity with the 0.0209 Pa·s viscosity fluid in the ampoule. The voltage applied in this test was determined using the injector estimated viscosity. 

Figure 21 - Drawing of stiff piston with thread and O-rings labelled. 

Figure 22 - Photograph of stiff ampoule and inserted piston with important sections marked, and diagram of internal threads and O-ring seal. The slight skew of the front end where it screws into the shaft had no significant effect on the performance of the ampoule. 

Figure 23 - O-Keefe Controls Ltd provided diagram of orifice insert, and photo of 200 µm orifice insert. 

Figure 24 - Viscous fluid jet injector (VFJI) with the component parts labelled. 

Figure 25 - Control system and amplifiers. The three interacting parts of the control system are labelled. 

Figure 26 - Coil position results for four different fluids (viscosity indicated) when a 30 ms voltage pulse is applied to the coil. Each test was repeated five times. The similarity of the traces is indicative of the consistency of the injector’s behaviour. 

Figure 27 - Energy analysis of jet injection. The blue line in A indicates the change in energy associated with the current that passed through the coil during the injection to produce the injection force. The
purple line is the coil energy dissipated as heat. The black line is the gain or loss in kinetic energy that the coil experienced during the injection (10 pt. average), and the red line is the kinetic energy of the emitting jet. B presents the same results, zoomed in on the coil and jet energies.

Figure 28 - High speed camera images of jet emitted from the VFJI orifice. A: The jet when at peak jet speed (135 m·s⁻¹). B: The jet during the follow-through phase (50 m·s⁻¹).

Figure 29 - Cross-sectional geometry of commercial ampoule near the orifice. The flow of the fluid is from left to right. The profile was based off a set of micro-CT images. The process to obtain the images is outlined in Section 5.2.1.

Figure 30 - Graph of jet speeds developed when a steady-state force is applied to a range of viscous fluids composed of glycerol and water. The JI is the LJI modelled in Chapter 2, while VFJI is the injector described in this chapter.

Figure 31 - A: The jet speeds achieved during voltage pulse tests across all viscosities, plotted against the steady-state force. B: The discharge coefficient at four of these viscosities plotted against the force applied in steady state to the injector.

Figure 32 - Relationship between steady-state force and both jet speed (1), and discharge coefficient (2) with different orifice diameters using a range of viscous fluids (A: 0.001 Pa·s, B: 0.012 Pa·s, C: 0.108 Pa·s, D: 0.635 Pa·s). The orifice diameters measured 100 µm (blue cross), 150 µm (orange cross), 200 µm (black cross), and 310 µm (green cross).

Figure 33 - Relationship between steady-state force and both jet speed (1), and discharge coefficient (2) using different viscous fluids over a range of orifice diameters as indicated (A: 100 µm, B: 150 µm, C: 200 µm, D: 310 µm), a representation of the data from Figure 32. The fluids tested had viscosities of 0.001 Pa·s (blue plus), 0.012 Pa·s (orange plus), 0.109 Pa·s (black plus), and 0.635 Pa·s (green plus).

Figure 34 - Jet power achieved in steady-state with different viscous fluids across four tested orifice diameters. A: the results with the fluid with a viscosity of 0.001 Pa·s. B: the results with a fluid of 0.012 Pa·s viscosity. C: the results with a fluid of 0.109 Pa·s viscosity. D: the results with a fluid of 0.635 Pa·s viscosity.

Figure 35 - Plot of discharge coefficient (Dc) versus Reynold’s number. The blue crosses (x) are the results with an orifice of 100 µm in diameter, the red diamonds (♦) are the results with an orifice diameter of 200 µm and the green circles (o) are the results with an orifice diameter of 310 µm.

Figure 36 - Illustration of application of finite volume method (FVM) to a simple fluid flow problem. The control volumes (dashed orange lines) are visualized around the central nodes (orange dots) of the mesh. These control volumes are also defined around all other nodes.

Figure 37 - Diagram indicating area of device where viscous energy loss occurs.

Figure 38 - Flow diagram of ANSYS Workbench environment.

Figure 39 - Micro-CT reconstruction of the inside of the commercial ampoule. The orifice and direction of flow are indicated.

Figure 40 - Fluid mesh for commercial ampoule. The legend indicates the boundary conditions applied in FLUENT with all other surfaces treated as walls.

Figure 41 - Screenshot of inflation layer outline (thick blue dotted line) within ANSYS meshing along curve of commercial ampoule wall. The red box shows where along the profile the inflation layer is shown.

Figure 42 - Jet speed profiles at the orifice of the commercial ampoule resultant from simulations with applied pressure of 10 MPa (indicated viscosity is that measured at room temperature).
Figure 61–Bar graph of the mean radius that captures 63% of the radial distribution in x and y across five different viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).

Figure 62–Bar graph of the mean depth that had 63% of the injected fluid above across five viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).

Figure 63–Bar graph of the mean percentage of fluid injected into the skin across five different viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).

Figure 64 - Examples of dispersion patterns for the five different fluids with varying viscosities. A: 4.75 mPa·s, B: 22.4 mPa·s, C: 22.8 mPa·s, D: 47.1 mPa·s, and E: 101 mPa·s. The colour indicates the normalized concentration according to the colour bar.

Figure 65 - Examples of the dispersion patterns for each of the five tests with one viscosity (22.7 mPa·s). The colour indicates the normalized concentration according to the colour bar.
List of Tables

Table 1 - Mechanical properties of skin.................................................................17

Table 2 - The values used in the simulations to represent the jet injector system. Ranges are given where fluid properties change.............................................................44

Table 3 - Results of consistency tests. The average and standard deviation (SD) for volume and jet speed are shown for 4 fluids (n = 5). Different voltages were used for each viscosity to try achieve an average jet speed between 130 m·s⁻¹ and 140 m·s⁻¹..........................................................71

Table 4 - Cross-correlation results for position traces with different fluids (n = 5)........................................72

Table 5 - Total energy that passes through the three measurements of energy within the injector system......................................................................................................74

Table 6 - Results of mesh independence investigation with water as the fluid in the ampoule. RMS jet speed difference indicates the deviation observed as mesh parameters were changed..................................................96

Table 7 - RMS velocity differences in jet speed profiles at orifice between simulations with 5 % turbulence and 10 % turbulence compared to the simulation with 1 % turbulence. The mean jet speed is also indicated. The turbulence is applied at the pressure boundary condition.................................................................96

Table 8 - Mean jet speed results for the range of simulations explored in section 5.4.1....................................103

Table 9 - Details of mesh convergence study with water as the fluid in the ampoule. RMS velocity difference in jet speed profile is shown as compared to the simulation with the most elements.............107

Table 10 - RMS velocity differences in jet speed profiles at the orifice between simulations with 5 % and 10 % turbulence and that with 1 % turbulence for the stainless steel ampoule. The turbulence is applied at the pressure boundary condition. Two fluids were tested in the simulation; water and glycerol......108

Table 11 - Mean and standard deviation of jet measurements for gel tests (n = 10)........................................126

Table 12 - Mean and standard deviation for each test set (n = 10) and p-values representing evidence against the hypothesis that viscosity has no effect on a dispersion measurement in gels........................................126

Table 13 - Order of testing into pig skin over the five days of testing..............................................................131

Table 14 - Mean and standard deviation for tissue measurements, and the p-value that represents the evidence that there is no effect of temperature on the result of the measurement (n = 5)............135

Table 15 - Raw data from gel test experiments..............................................................................................154
Nomenclature

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>ABI</td>
<td>Auckland Bioengineering Institute at the University of Auckland</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen-presenting Cell</td>
</tr>
<tr>
<td>AWG</td>
<td>American Wire Gauge</td>
</tr>
<tr>
<td>back-EMF</td>
<td>back Electromotive Force</td>
</tr>
<tr>
<td>CMOS</td>
<td>Complementary Metal-oxide Semiconductor</td>
</tr>
<tr>
<td>CFD</td>
<td>Computational Fluid Dynamics</td>
</tr>
<tr>
<td>DC</td>
<td>Direct Current</td>
</tr>
<tr>
<td>DCJI</td>
<td>Disposable Cartridge Jet Injector</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DXF</td>
<td>AutoCAD Drawing Exchange Format</td>
</tr>
<tr>
<td>FPGA</td>
<td>Field-programmable Gate Array</td>
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<td>Finite Volume Method</td>
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<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IEEE</td>
<td>Institute of Electrical and Electronic Engineers</td>
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<tr>
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<td>Jet Injector</td>
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<tr>
<td>LC</td>
<td>Langerhans Cell</td>
</tr>
<tr>
<td>LJI</td>
<td>Original Lab Jet Injector</td>
</tr>
<tr>
<td>LR</td>
<td>Inductor-Resistor</td>
</tr>
<tr>
<td>micro-CT</td>
<td>X-ray Microtomography</td>
</tr>
<tr>
<td>MIT</td>
<td>Massachusetts Institute of Technology</td>
</tr>
<tr>
<td>MUJI</td>
<td>Multi-use Jet Injector</td>
</tr>
<tr>
<td>PID</td>
<td>Proportional-Integral-Derivative</td>
</tr>
<tr>
<td>RAM</td>
<td>Random Access Memory</td>
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Re  Reynolds's Number (normally at the orifice)
RMS  Root Mean Square (quadratic mean)
SC  Stratum Corneum
SST  Shear-stress Transport
STL  Stereo Lithography
VFJI  Viscous Fluid Jet Injector
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### Certification by Co-Authors

The undersigned hereby certify that:
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- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

**Thesis:** Section 3.10 Viscous Estimation


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*Last updated: 25 March 2013*
1 Motivation and Outline

1.1 Motivation

The focus of my work is transdermal delivery of viscous fluids using a jet injector (JI) powered by a linear moving coil actuator. JIs are devices that form a liquid jet that pierces through the surface of skin and delivers a drug to the tissue underneath. JIs enable the delivery of a liquid drug without the risk of a needle-stick injury and with levels of pain either equivalent to or less than that experienced during an injection with a needle [1]–[3]. Recently, linear moving coil actuators have been used to power the formation of this jet within an ampoule [4], [5]. A piston seals the drug within the ampoule and the actuator forces the piston forward, pushing the drug at speeds up to 150 m·s⁻¹ through an orifice with a diameter in the order of 200 µm. Until now, these devices have only been demonstrated to deliver relatively inviscid fluids, with the drugs exhibiting flow behaviour similar to that of water.

However, many of the new drugs that are under development and are coming out on the market have high viscosity, due to their active proteins and their high concentration [6]. Viscous fluids are significantly more difficult to inject, whether by needle and syringe or by needle-free techniques, because of their high resistance to movement [7], [8]. However, linear moving coil actuators have the potential to provide the sustained and controlled forces that might be required for needle-free jet delivery of viscous fluids. I intended to determine the requirements for a viscous fluid jet injector powered by a controllable linear moving-coil actuator. Additionally, I wanted to investigate the capabilities and characteristics of such a device.

In order to accomplish this, I modelled the behaviour of a jet injector previously developed by our group [9]. The model was validated against experimental data, and the behaviour of the injector was simulated computationally as design and material parameters were varied systematically. Using information from the model, I designed and assembled a device that was capable of viscous fluid injection and carried out tests to quantify its repeatability, and to determine how effective it was at forming a high-speed jet. I tested a range of orifice diameters to determine which was best suited for
viscous fluid jet injection. Using a computational fluid mechanics solver, I discovered where viscous loss was occurring in the injection system, which provided insight into how to design an ampoule for viscous fluids. Finally, I carried out injections into post-mortem pig skin to determine whether a viscous jet behaves similarly to a water-like jet and whether further modification would be required to deliver viscous drugs in viscosities of up to 0.6 Pa·s beneath the surface of the skin. From these investigations I have revealed the challenges that viscous fluids present when being jet injected, how to design an injector to meet those challenges, and how well the injector performs once the challenges are met.
1.2 Outline of Thesis

There were two primary aims of the work that I pursued. The first was to determine the device characteristics required for achieving controlled viscous-fluid jet injection. The other was to discover the impact of viscosity on jet formation, penetration and injection pattern. I hypothesised that viscous jet injection would require significantly more power and a much larger motor, and that viscosity would significantly impede jet formation, reduce the likelihood of penetration and reduce the extent of the fluid dispersion pattern. The chapters of the thesis are outlined below:

Chapter 2, the next chapter, begins by examining the existing literature to provide background information relevant to viscous fluid injection. The process of jet injection itself is detailed, providing the necessary knowledge for the modelling presented in the following chapter. The benefits and drawbacks of JIs and their applications are explored, indicating the current state of the technology and its uses. The use of gels to mimic skin is outlined, in anticipation of their use in the research of Chapter 6. I then look at the modelling work that has been published in this field, expected future developments, and the reasons for developing a viscous fluid jet injector.

The modelling of the original jet injector (termed the lab jet injector, or LJI) was the first step of my progression towards viscous fluid injection. Chapter 3 presents my work in this area, and is largely based upon the scripts of two publications [10], [11]. The model formulation, validation, and results are presented, together with discussion of the improvements made upon previous models in the areas of rise-time of current, the compliant response of device components, and the effect of viscosity on jet speed. The chapter also reports on the development of a control system for the injector that accounts for viscosity.

The model helped me to decide what engineering improvements could be made to our injector technology to improve how the jet injector delivered viscous drugs. These improvements are presented in Chapter 4 and consisted of reducing the compliance of various components of the system and the use of a more powerful motor as part of a stiffer rig. This chapter contains a thorough experimental analysis of the response of the new injector (the viscous fluid jet injector, or VFJI) to a wide range of pulse tests of different amplitudes with ampoules of different orifice diameters containing fluids of a range of viscosities - the first data set of its kind. The range of orifice diameters was between 100 µm and 380 µm. After testing, I continued to use a 200 µm orifice diameter as it was best suited to the range of fluids I was targeting, mainly due to its low viscous loss within this range. Conveniently, the results with this orifice allowed easy comparison with previous test results using the original lab jet injector (LJI)
(which has a 190 µm orifice). I tested the repeatability of its position profile during a pulse test and response of the new motor rig to the control system input.

The speed of the jet is dependent not only on the orifice diameter, but also on the way in which the diameter decreases as the flow approaches the orifice. This ‘approach to orifice’ profile appears to be very important in determining the jet speed achieved when delivering viscous fluids. I present a computational fluid dynamics model of the approach in Chapter 5 for both the original commercial ampoule and the stiff ampoule. I compare the speed developed in the real device and the simulation to validate the model, and then use the results to suggest further improvements to ampoule design that I expect will improve performance across a range of viscosities. The simulation environment enabled me to investigate phenomena within the ampoule that had not previously been examined, such as the viscous heating that occurs when injecting viscous fluids.

I then pursued an investigation of the effect of viscosity on the dispersion pattern of a jet in human skin models. The results of this investigation are presented in Chapter 6. I first conducted a pilot study on polyacrylamide gels to test whether viscous fluids behaved differently from water in a simple gel model of skin. These tests proved inconclusive. Since the background literature often prefers pig skin as a model for human skin, I then conducted an injection study into post-mortem pig tissue, using micro-CT with iodine contrast to determine the dispersion pattern. I quantified the repeatability of the new injector, showing reduced variation between tests, and that my model-based control term ensured that the desired jet speed was achieved despite any variation in viscosity. Never before had the effect of viscosity on the dispersion pattern observed after jet injection into skin been investigated while controlling for jet speed.

Chapter 7 reveals the main conclusions that I have drawn as a result of the work presented in this thesis. The end result of my work is an injector capable of injecting a wide range of viscous fluids repeatably and controllably into skin. During the course of this development, new knowledge about the behaviour of voice-coil powered jet injectors has been uncovered, informing the design of JIs for viscous and inviscid fluids. The results will continue to guide the development of jet injectors of this type, thus enabling the development of jet injectors for a wide range of drugs.

The necessary background that provides context to the thesis is provided in the following chapter. It starts with an overview of the field of jet injection, and ends by covering the viscous drugs that are currently available and in development.
2 Background and Literature Review

I carried out a thorough literature review, looking at the wider field of transdermal delivery, the different drugs which lend themselves towards the transdermal route, and the detailed modelling of the interaction between jet injection and skin. I investigated the current state of jet injector technology, a basis for my work in the field, and profiled the viscous drugs which a viscous-fluid jet injector could be used to deliver.

2.1 Jet Injection in the Context of Transdermal Delivery

Transdermal drug delivery by needle and syringe currently dominates the provision of pharmaceuticals by methods other than oral administration [12], [13]. The development of needle and syringe technology in 1853 enabled quick administration of medications which could not survive the conditions of the stomach or would cause damage to the liver after ingestion [12]. The needle method of delivery remains widely used, but is hampered by significant drawbacks that reduce its effectiveness and discourage patient compliance. These include the pain encountered during the skin penetration and delivery process, the possibility of needle-stick injuries to patients and healthcare professionals, and the training required to administer drugs by this method [14]. Needle phobia is reported in up to 10% of patients and is a major contributor to non-compliance with injection procedures, especially in developing countries [15], [16].

In response to the issues associated with drug delivery by needle and syringe, research groups have investigated new methods of transdermal drug delivery with the intention of replacing the needle and syringe in particular applications. The methods detailed in the academic journals are passive absorption, ablation, iontophoresis, electroporation, sonophoresis, microneedles, powder jet injection, and liquid jet injection [6], [13], [17]–[19]. All active methods involve either the degradation or the piercing of the stratum corneum (SC), the apical surface layer of the skin (Figure 1). The SC is made of dead cells that protect inner layers of the skin from harm [20]. It has a mechanical breaking stress of up to 20 MPa and is resistant to the passage of molecules into the epidermal tissue underneath [21].
The simplest method of transdermal and intradermal delivery is via passive absorption. The skin will absorb a small amount of a drug through an intact stratum corneum. The rate of absorption can be increased with abrasion or optical ablation [20] of the upper part of the epidermis over an area of skin, if followed by a patch containing the drug [22] or the application of a topical cream [23]. Both of these methods are limited by the speed at which they can transfer drug fluid into or across the skin and into the bloodstream. Patches for passive transfer of drugs into the skin can only deliver 50 mg of drug per day [24].

Electrical fields can provide some assistance. Iontophoresis is the application of an electric field along the skin surface, with the intent to repel charged pharmaceuticals on the surface of the skin across the stratum corneum and into the epidermis. Unfortunately, this method is not as effective as it seems because most of the drug travels along the skin surface to the electrode of opposing charge [24]. Nonetheless, some reports indicate that it can increase the absorption of analgesics by an order of magnitude when compared to passive absorption (~500 mg of drug per day) [25]. Like iontophoresis, electroporation involves applying pulses of electricity to the skin in order open cracks in the stratum corneum and increase the skin surface permeability. A drug on the surface of the skin subsequently travels into the epidermis and dermis in greater quantities than simple passive absorption. As a relatively new technology, electroporation has demonstrated a higher transfer speed into dermal tissue than the more commonly encountered process of iontophoresis [3]. It requires further development and investigation before being widely applied.

Beyond electric fields, both sonic and mechanical piercing has been used to improve volume transfer rates. The process of sonophoresis uses ultrasound waves on the surface of the skin to increase its permeability. Once again, even with the assistance of ultrasound, the volume transfer rate is modest.
nowhere near enough to replace needle delivery [26]–[28]. The volume transfer rate of more invasive methods is significantly higher. For example, microneedle patches have demonstrated that they increase permeability by up to four orders of magnitude [29]. Each patch consists of a set of small needles that pierce through the stratum corneum to a depth no more than that of the epidermis. As the epidermis has no nerve endings, the application of the patch is painless. The needle patch is sometimes followed by another patch of the pharmaceutical, allowing the drug to pass through the newly created holes and into the epidermal tissue [13], [30]. A more brute force approach than microneedles is powder jet injection. This process uses a blast behind a solid drug compound, which forces the drug onto the stratum corneum, eroding the surface and transporting the drug into the epidermis. Though it has been proven effective at delivering particular drugs with the same level of efficiency as a needle and syringe, it requires a solid formulation of a drug to be developed before it can be used to deliver that drug [13] and has only been effective at delivering into the epidermis [31].

Liquid jet injection, the method of transdermal delivery explored in this thesis, uses a jet of drug fluid with a diameter that typically ranges between 76 μm and 260 μm travelling at speeds up to 200 ms\(^{-1}\). The formed jet can pierce through the stratum corneum as it applies pressure of around 20 MPa to the skin's apical surface. The jet diameter is much smaller than the outer diameter of the typical hypodermic needle used for intramuscular injection (~810 μm) [12]. The fluid jet is usually the result of a piston in a drug chamber (ampoule) being propelled forward against a liquid drug, forcing the drug through a small orifice, which has a slightly greater diameter than the jet, located at the end of the

![Figure 2 - Scanning electron microscope images of microneedles used in the study by Henry et al. [29]. A shows a 20 x 20 array of microneedles, and B is a close up of one microneedle.](image)
chamber [13]. The energy to drive the piston can be obtained from one or more sources, as seen both in commercial jet injectors and those reported in the literature.

These jet injector methods overcome the limits of other methods as they are not restricted by the speed of diffusion which, depending on the drug, can be very slow, even with the help of electric fields or microneedles. There are also molecular weight cut-offs for many drug compounds with the result that effective delivery of drugs above the cut-off weight requires physical breakdown of membranes [32]. Breaking down the stratum corneum removes this limitation and allows delivery regardless of molecular weight.

Commercial jet injectors usually use either springs or compressed gases, such as nitrogen, carbon dioxide, or air, to provide the energy to push the piston forward [20]. In addition, jet injectors in development and reported in academic journals have used Lorentz-force and piezoelectric motors [9], [33]. The Auckland Bioengineering Institute (ABI) jet injection research group (of which I am a member), together with its Massachusetts Institute of Technology (MIT) collaborators, has developed a controllable Lorentz-force motor as its source of power for injection. Our team hopes to gain immediate, high-bandwidth control over the progression of the jet underneath the skin's surface.
2.2 Jet Injection: Benefits and Drawbacks

Commercial jet injectors, powered by compressed springs or compressed gas, rely on end-users to change properties such as spring compression to achieve the correct penetration depth. These same end users have little information about the properties of the skin that they are injecting into, and these properties are highly variable [12]. No strong correlation has been observed between any skin thickness and demographic measures such as age and ethnicity [34]. The variability in skin is especially evident when different anatomical locations are compared [35]. A greater level of control over jet characteristics, such as diameter and speed profile, has been suggested [36] as one way to improve the drug delivery by jet injectors. In particular, it is proposed that control will decrease the pain experienced by the subject and allow targeting of the drug to the layer underneath the skin where it is most effective. The increased consistency between injections as a result of control will allow a certain depth of injection to be achieved with less variation than when using springs or compressed gas [13], [15], [36], [37]. Current injectors on the market are used in a limited number of applications (such as insulin injection) and have not yet achieved a market share that reflects the potential of the technology [12].

Needle stick injuries in the United States number 300,000 a year and occur in 5% of injections worldwide [14]. The prevention of these injuries is a major benefit of needleless transdermal injection which could lead to a significant reduction in the number of infections of contagious diseases [15]. These benefits led to the decision to use multi-use jet injectors (MUJIs) in the 1970’s for immunization against polio. However, researchers observed that the use of MUJIs resulted in a high risk of Hepatitis B (HBV) transfer between patients [12]. Just 10 pL of blood transfer is required to infect another patient with HBV, and MUJIs did not provide the level of isolation required to ensure that this did not occur [38]. Even when a replaceable cap was used, the transfer exceeded 10 pL, as blood passed into the ampoule itself [38]. A transition to the disposable cartridge jet injectors (DCJIs) currently on the market was seen as a simple means to address the problem of fluid transfer. DCJI use eliminates fluid or surface transfer of blood between patients and, coupled with the needle-free nature of these devices, minimises the chance of any transmission of pathogens between different patients and the health professionals treating them [3], [14], [39]. While DCJIs are more expensive per injection, an inclusion of the decreased health costs per injection resulting from their very low transmission rate decreases their real cost below needles. Giudice et al. calculated the cost for each method and found that each needle and syringe injection cost $26.77 each, MUJI injections cost $1 each, and DCJI injections cost $0.37 each on average [3].
The pain and local bruising reported with MUJIs were of greater intensity than those experienced with needles. As a result, significant non-compliance was observed in the population of the developing countries where they were used. The devices did not demonstrate dynamic control over the jet and, without control catering the injections to the skin being injected into, large variations in the dispersion pattern of the drug between injections resulted [12]. A mixed reception to the more recent DCJIs (Figure 3) is evident in scientific studies where the level of pain experienced is analysed and local bruising are examined [2], [3], [35], [40]–[49]. A patient survey on the use of the MediJector Vision found patients registered 63% less pain than with needles [49] while those in a survey on the Genotropin ZipTip [46], J-Tip [47], and HSI-500 [38] systems reported significantly more pain than needle-based injection. Users of the Vitajet II U 40 [2], Injex [41], and Biojector [50] systems reported that the level of pain was no greater or less than sub-cutaneous injection by needle. Some groups hypothesize that the increased pain and local bruising of DCJIs are due to the uncontrolled nature of the injection and the depth to which the jet penetrates [9], [36]. Nerve endings exist in the dermis and, given the speed of the jet, interaction of the jet with these structures can lead to significant pain [51].

The primary local effect observed across all studies was bruising, often of greater intensity than that experienced with needle injection, as well as induration and redness of the skin [12], [35], [42], [49].
Figure 3 – A series of commercial disposable cartridge jet injectors (DCJJs). (A) LectraJet HS motorized DCJI which uses a motor to compress a spring. (B) LectraJet M3, a manual version of the HS model. (C) PharmaJet Stratis DCJI, a device that works with traditional drug vials and delivers into the sub-cutaneous and intramuscular layers under the skin. (D) Medijector Vision DCJI, used to deliver insulin into the sub-cutaneous fat. (E) Sumavel DosePro, used to deliver a migraine treatment into the sub-cutaneous fat. (F) J-Tip, an injector powered by compressed nitrogen gas. (G) Injex, a compressed-spring device used to deliver insulin. I use the ampoule of this device in my early modelling and testing. (H) Imule syringe for needle-free influenza vaccine delivery. (I) Biojector 2000 by Bioject Medical Technologies delivers to sub-cutaneous fat and intramuscular layers with force provided by compressed carbon dioxide. (J) ZetaJet spring-powered injector uses different cartridges for sub-cutaneous, intramuscular, and intradermal injection. (K) Iject injector uses a glass dose chamber as an ampoule. Reprinted from [17] with permission from Elsevier.
2.3 Jet Injection Applications

2.3.1 Vaccines

Jet injection is sometimes used to deliver vaccines into the epidermis (Figure 4), the layer of skin immediately below and including the stratum corneum [30], [37]. The epidermis is targeted due to the presence of Langerhans cells (LCs) in the layer, which form 1% of the volume and 20% of the surface area [35]. LCs act as antigen-presenting cells (APCs) that process antigen fragments from viruses they encounter, and present these fragments to naïve T cells. The presentation process activates an immune response culminating in the production of antibodies that are effective against the virus introduced [37], [52]. Vaccines present low-harm versions of viruses so that the antibodies are produced without the harmful effects of the disease [37]. The epidermis can be targeted with the needle and syringe method, but the training required to achieve epidermal localization is arduous. Therefore, the uptake and use of needle epidermal delivery has been minimal [3].

Jet injectors induce an immune response equal to or greater than that of intradermal, epidermal, or intramuscular injections by needle and syringe [14], [35]. This equates to higher seroconversion rates, a measure detailing the level of expression of an antibody in a subject's blood. The higher rates have been attributed to the high pressure of the jet in the skin, as it leads to a greater dispersion in the tissue in comparison to the dispersion observed after needle injection. A wider distribution of the vaccine increases its level of contact with APCs such as Langerhans cells [3]. However, some research suggests that an inflammation response is required in order for cutaneous vaccination to occur as injection alone cannot recruit the T-cells of the immune system [53]. Therefore, more information is required with

![Figure 4](image-url) - Reproduction of Figure 1 with the antigen-presenting cells (APCs) identified, including the Langerhans cells of the dermis. The different layers of the dermis are identified. Layers where APCs are present are the best targets for vaccines.
regards to the inflammation caused by jet injection in order to assess its effectiveness. Additionally, reports suggest that the high pressure causes the penetration of the dermal tissue underlying the epidermis where nerve endings are located. A greater level of localization of the vaccine in the epidermis will reduce the pain associated with jet injection of vaccines and likely increase seroconversion rates [14].

Successful delivery of vaccines with jet injectors has been reported in academic journals for the provision of immunity against Hepatitis A [40], measles, mumps, rubella [41], HIV-1 (in mice) [50], and poliovirus [54]. Outside academia, the injectors have been used for the prevention of many other diseases [3], [14]. In the application to mice of the HIV-1 vaccine, it was reported that the needle-free injector device Biojector provided more consistent results and lower intragroup variations than intramuscular delivery [50]. The application of the measles, mumps, and rubella vaccine by the Injex jet injector indicated no significant differences in immunogenicity compared to needle and syringe delivery. While, pain scores were not significantly different, local reactions were reported to be of greater severity after delivery using the jet injector [41]. Delivery of a Hepatitis A vaccine with a Biojector jet injector resulted in a significant increase in immunogenicity [40]. Reports suggest that the increased immunogenicity with jet injectors that sometimes occurs is dependent upon the vaccine that is being applied, and the jet injector that is used. Even if the devices repeatedly demonstrated greater immunogenicity, local bruising, and pain remain major issues affecting the uptake of jet injector technology [14].

Based on these observations, the ideal jet injector for vaccine delivery would be able to deliver a drug to the epidermis or dermal layer without penetrating through to the subcutaneous fat, so that the drug is targeted properly. This would require a high degree of control over jet depth over the whole range of skin mechanical properties. The mechanical system of the jet injector should be stiff, so as to not exhibit oscillations in jet speed that may penetrate further than desired.

### 2.3.2 DNA Transfer

The delivery of deoxyribonucleic acid (DNA) directly into cells in the human body leads to the expression of the introduced DNA that can improve body function and treat certain diseases such as cancer [55]. Histology of a DNA injection into skin is given in Figure 5 which from which the skins layers can be clearly identified. Increasingly, jet injection is being used to inject naked DNA into cells on the skin of which the measured level of gene transfer after early reports is encouraging. For instance, in one study by Walther et al., jet injection of 50 µg of a DNA plasmid increased gene expression 322 fold after 24 hours without excessive presence of the diffused DNA in other organs [56], [57]. Naked DNA does
not enter cells efficiently, due to its size and hydrophilic nature, but the high pressure stream of fluid central to jet injection can form pores on the membranes of target cells allowing the entry of DNA into a cell. Jet injection provides an alternative to viral vectors for DNA transfer which are difficult to produce and can elicit immune responses against themselves reducing future applicability [58].

Jet injection causes gene expression up to 50 times greater than needled injection of naked DNA when the pressure of the jet is between 280 kPa and 300 kPa [59]. For example, the application of a 50 µg jet of DNA to skin metastases of breast cancer and melanoma led to gene expression. The level of expression was equivalent to that recorded when 1 mg of DNA was applied with other non-viral gene transfer methods. Six out of the seven patients in this study tolerated the jet injection well [56]. DNA injected with jet injection hits a peak of concentration after 5 minutes in the target cells and after 30 minutes in the nucleus. Jet injections caused a greater proportion of open circle plasmids relative to closed circle plasmids than recorded after needle delivery. The authors hypothesised that the collision

![Figure 5](image.png)

*Figure 5 - Reproduction of figure from [154] published under license showing injecting of naked DNA into mouse skin sample with three layers identified. A is a top view of the injection, B indicates the movement of the injectate after injection near the dermis, C shows an injection that went deeper into the subcutaneous and muscular layers, and D is an image of a control injection without staining, focusing on the dermal layer.*
of the DNA on the skin opened the plasmids [57].

A significant concern with DNA injection is that the injected DNA could travel to other parts of the body and have adverse effects on body function. DNA in the bloodstream peaks five minutes after jet injection, and DNA in organs peaks after 20 minutes. The recorded magnitude of the DNA in organs was on the nanogram scale when 50 µg of DNA was injected. Exposure of organs to such a small concentration of DNA is considered to have an insignificant effect on their function, limiting the effect of the DNA injection to the injection site. A large difference between concentration in blood and in the internal organs was observed and attributed to the speed of blood flow through organs as it reduced the chance of DNA transfer into the organs [57].

A jet injector for DNA transfer needs to be able to pierce through the surface layer of the skin and stop penetrating shortly afterwards. As with the vaccine delivery, the control of the jet injector should therefore be highly responsive to within a millisecond and stiff so as to not oscillate above the desired jet speed.

### 2.3.3 Hormones

Commercial jet injectors are currently used for insulin injection by diabetics in some parts of the world [49]. Uptake is reduced by the lack of standardized ampoule between jet injectors, as well as the local bruising and pain associated with jet injection itself [3]. For example, the use of a MediJector Vision to deliver insulin led to 85% of users recommending the needle-free device over needle injection. However, all subjects recorded a failed injection during the 26 weeks they used the device [49]. A ZipTip system enticed only 20% of users in one study due to its higher incidence of pain, soreness, and bleeding when compared to needle injection [46]. Devices intended for insulin delivery can be extended to deliver other hormones. The use of a needle-free injection system (J-Tip) for alprostadil injection to treat erectile dysfunction found that the pain produced was much greater than the pain experienced when using the needle and syringe method. The efficacy of the drug delivery with the jet injector was significantly less than that recorded after needle delivery, and all patients preferred the needle method when given a choice [47]. It is clear that, across all comparative hormone injection studies in the academic journals, the low patient compliance when using a needle-free injector is a major concern [48], [49]. Non-compliance is best addressed by decreasing the intensity of the pain and local bruising caused by needle-free injectors. Ensuring that they are effectively delivering to the required skin or muscular layer will further reinforce the case for their widespread use [49].

Further to these tests, polymeric particles have been explored as a potential way to increase the efficiency of jet injection [60]. A study of drug delivery using a Vitajet 3 commercial jet injector (Bioject
Medical Technologies Inc.) indicated that the use of polymeric particles, composed of polylactic-glycolic acid, increased the percentage of the fluid delivered to the dermis where the drug was being targeted. These particles have the benefit of controlled release, increasing the period between injections for patients on regular injection schedules.

Unlike in the previous two applications, jet injectors for hormone delivery are normally targeted to the subcutaneous or muscular layers underneath the skin's surface. Therefore, the direct control and stiffness of the mechanical components is not as important. However, the volume of these injectors is required to be around 300 µL and be highly repeatable so that consistent results are obtained. This is particularly important in the case of insulin delivery as proper therapy requires knowledge about the volume delivered into the bloodstream [61].

2.3.4 Other

Outside of the categories previously discussed, two more applications for needle-free injection have been reported. Firstly, a DCJI was used to deliver immunisations in pigs in order to reduce pork carcass defects formed after needle injections. The use of the jet injector ensured no needles are left in the pork after slaughter, reducing the cost of needle detection for the plant that processed the carcasses [62]. The other application, reported in two papers, is the use of a DCJI to deliver an anaesthetic (lidocaine). In the papers, the DCJI successfully anaesthetised the area concerned before a no scalpel vasectomy and a thyroid biopsy [1], [63]. The jet injector characteristics required for these applications are similar to the vaccine and hormone requirements respectively.
2.4 Skin Models

2.4.1 Relevant Mechanical Properties of Skin

To give context to the work presented below and throughout the thesis, I present the currently known mechanical properties of skin. These properties define the bounds of what is possible in drug delivery by jet injection and inform the development of models, whether physical or theoretical.

The table below indicates those properties which are known and unknown, their ranges and the source of the information.

<table>
<thead>
<tr>
<th>Mechanical Property</th>
<th>Value or Range of Values</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breaking stress of stratum corneum (SC)</td>
<td>22.5 MPa-3.2 MPa (as relative humidity increases from 0-100 %)</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>17 MPa - 1.85 MPa (as temperature increases from 25 °C to 60 °C) (neonate pig skin)</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>9 MPa - 295 MPa (different sites around body)</td>
<td>[66]</td>
</tr>
<tr>
<td>Maximum passive diffusion rate across surface</td>
<td>50 mg/day. For glycerol, 61 µM/m²/s (dependent on molecular size)</td>
<td>[24], [32]</td>
</tr>
<tr>
<td>Young’s modulus of dermis</td>
<td>420 kPa - 850 kPa, torsion test</td>
<td>[67], [68]</td>
</tr>
<tr>
<td></td>
<td>4.5 kPa - 8 kPa, indentation test</td>
<td></td>
</tr>
<tr>
<td>Poisson's ratio of dermis</td>
<td>Approximately 0.48</td>
<td>[69]</td>
</tr>
<tr>
<td>Young’s modulus of subcutaneous fat</td>
<td>Non-linear, 1 kPa at low strain rates (0.002 s⁻¹) and 3 MPa at high strain rates (1000 s⁻¹)</td>
<td>[70]</td>
</tr>
<tr>
<td>Poisson's ratio of subcutaneous fat and muscle</td>
<td>0.490 - 0.499</td>
<td>[71]</td>
</tr>
<tr>
<td>Young’s modulus of muscle</td>
<td>32 kPa – 96 kPa</td>
<td>[68]</td>
</tr>
<tr>
<td>Damping of skin</td>
<td>0.08 – 0.12 N·s·m⁻¹ (visco-elastic model)</td>
<td>[72]</td>
</tr>
<tr>
<td>Passive diffusion rate in dermis, fat and muscle</td>
<td>Highly variable, depends on lipophilicity, molecular weight, pH. Much faster than across SC.</td>
<td>[73]</td>
</tr>
</tbody>
</table>

**Unknowns:**

1. Inhomogeneity,
2. Limit of absorption,
3. Change in properties during jet injection,
4. Breaking stress between layers,
5. Maximum passive diffusion rate in dermis, fat and muscle.

Table 1 - Mechanical properties of skin.
2.4.2 Testing and Physical Models of Skin

Previous analyses of the fluid jet interaction with skin have indicated that jet injection is a two-stage process [74]. The first stage of injection is a high-pressure piercing of the stratum corneum. The magnitude of this pressure is typically between 10 and 20 MPa. The speed of the jet for the first stage needs to be above 100 ms\(^{-1}\) for a standard jet orifice between 100 µm and 300 µm. A hole is formed in the dermis and reaches a peak depth as the backflow against the jet reduces fluid speed to zero at the end of the hole. Once this phenomenon (termed stagnation) has occurred, it is succeeded by the follow-through stage as the drug starts to disperse throughout the porous medium of the dermis. This speed of the jet is required to be from 30 ms\(^{-1}\) to 50 ms\(^{-1}\) during this period in order to continue the delivery of the fluid underneath the skin surface. The follow-through period can continue as long as the volumetric flow rate of the jet is less than the diffusive flow rate of the dermis, which decreases over time. Once the full volume has been delivered, the fluid pressure drops, and the tissue around the hole relaxes, reducing backflow and ending the injection process [9], [36].

The movement of the drug fluid post-injection was analysed by Wagner et al. using an isolated porcine forelimb [75]. The forelimb was chosen because the hair density, skin thickness, and morphological and functional characteristics are similar to human skin. An Injex system was used to deliver 0.3 mL of

![Figure 6 - Diagram showing the two-phase nature of jet injection. The phases have been associated with the penetration and dispersion mechanic that they are supposed to cause.](image)
Liquemin. The venous blood flow was sampled and histology indicated that the fluids did not pass into bone, into the walls of blood vessels, or into nerve fibres. The fluid dispersion pattern after injection was bulb-shaped with an injection hole travelling between 3 mm and 9 mm into the skin and then diffusing out from the end of this hole. The drug was observed to reach maximum accumulation in the blood between 3 and 4 hours after injection.

Investigation by Baxter and Mitragotri verified that the width of the hole in the skin is in the order of the diameter of the jet and smaller than a hypodermic needle [21]. The critical stress of skin was approximated using the Bernoulli equation to be around 15 MPa. The jet itself exhibits a turbulent flow with Reynold's number between 7,600 and 40,000. Due to the pressure loss that occurs in the flow as it focuses in on the orifice, the Bernoulli equation can only approximate the jet speed of the fluid from pressure measurements. The flow of the jet is free flowing until it pierces through the stratum corneum. Until the pressure of the jet is greater than the breaking stress of the stratum corneum, causing penetration, all flow is splashed back towards the face of the injection device. After penetration, the jet erodes the dermal tissue. Any flow that cannot progress into the newly created space flows back against the jet and slows down the velocity of the jet. A small amount of dispersion into the surrounding tissue occurs. When the jet is slow enough so that further erosion doesn't take place, ideally all fluid is absorbed by dispersion in the dermal tissue. Any fluid unable to be absorbed passes out through the top of the hole onto the surface of the skin.

The depth of the hole through which an injection occurs often determines the tissue into which the drug disperses. Targeting to the correct layer underneath the skin surface increases the effectiveness of drug delivery [21]. For example, targeting the muscle rather than sub-cutaneous fat during insulin injection saw a 50 % greater absorption of soluble insulin in one study [76]. Depth is independent of the critical shear stress of the stratum corneum and decreases as the standoff distance of the injector increases. The mechanical properties of the skin, the jet diameter, and jet speed are correlated with injection depth, with studies indicating that both greater jet speed and greater jet diameter increase depth of the penetration hole. Finally, depth has been shown to be a positive nonlinear function of volume and to linearly increase with time [21], [77]. These influences can be combined into one parameter, the jet power. This value accounts for a majority of the variation in hole depth, with most of the remaining variation being dependent on the skin properties [77]. The stiffness of skin can be used to establish a base level for these skin properties and can be broadly correlated with breaking stress, with 31 % mean error [21].
Polyacrylamide gels are often used to model the skin in physical tests (Figure 7), primarily because they enable visualization of the jet and fluid dispersion in the skin model [74]. While polyacrylamide gels can represent the critical local stress required for an injection, the progress of the jet through polyacrylamide is significantly different from the progress of a jet through human skin [78]. In gels, the jet pierces through by erosion of the gel at around 18.2 m·s⁻¹, and once the jet cannot progress any further, a stagnation pressure develops. When this pressure is high enough to form a crack, the gel splits, and fluid disperses radially around the end of the formed hole in a crack plane. The depth growth and extent of the jet hole is highly dependent on Young's modulus in polyacrylamide gels, where a tenfold increase in Young's modulus leads to a tenfold decrease in hole depth.

2.4.3 Requirements for a Jet to Pierce the Skin

The mechanical breaking stress range given in Table 1 indicates the required pressure on the surface of the skin that will break through the stratum corneum. This metric suggests that the pressure of the flow, determined by \( \frac{1}{2} \rho v^2 \) (\( \rho \) as the density of the fluid, and \( v \) as the velocity) under a Bernoulli model, will determine whether a jet pierces through the skin. Therefore, the capability of a jet is determined mostly by its speed but also, to a lesser extent, by its density. This is important to consider when using fluids like glycerol that exhibit higher densities than water. Jet power has also been suggested as a determinant of the capability of a jet [77]. The equation for this is \( \frac{1}{8} \pi \rho D_o^2 v^2 \) (\( D_o \) as the diameter of the jet), though it has mainly been used to determine jet penetration and dispersion rather than the ability to pierce the skin. Some authors [79], [80] have also suggested that the momentum of a particle \( \frac{\pi}{4} \rho D_o^2 v^2 \) is a good determinant of its penetrative capability. This formulation increases the influence that the density would have on the ability of the jet to pierce the skin. However, given the amount of
evidence that connects the mechanical breaking stress to the pressure applied directly to this jet [21], I believe that the jet speed is the most important factor to consider.

### 2.4.4 Models of Penetration and Dispersion

Shergold et al. have investigated the way in which the jet pierces the skin and modelled this action as a sharp-tipped punch penetration [79]. This approach relies upon treating human skin as an incompressible, hyper-elastic, and isotropic solid with a one term Ogden strain energy function [81], properties reflective of those of gel, but not necessarily those of skin samples. Shergold et al. predict that the hole in skin is a planar mode I crack of greater width at depth than on the surface. This one term Ogden strain energy function approximated the concave stress-strain curve for skin and is validated by tests using an Intraject™ compressed nitrogen jet injector. According to the model, as the jet progresses through the skin, the crack propagates ahead of the jet, and, as the fluid fills the space, the crack expands. When this expansion is large in proportion to the diameter of the jet, stored strain energy in the skin is the dominant contributor to pressure in the crack. Conversely, when the expansion is significantly less than the diameter of the jet, the dominant term influencing pressure is the work of crack formation. The pressure reaches a peak when the expansion is between these extremes. The model described by Shergold et al. corresponded well with measurements in silicone rubber, but the distribution of fluid in skin samples was not well-represented.

The work by Shergold et al. was expanded by Comley and Fleck [70]. They tested the effect of the piercing of adipose tissue by needles on the structure of the tissue and the distribution of injection fluid in the tissue. The adipose tissue they used is equivalent to the sub-cutaneous fat layer under the skin. They found that the distribution was of greater extent than predicted, and attributed this to the formation of micro-cracks around the main ring crack of the injection at the bottom of the needle. The micro-cracks increase the permeability of the tissue and allow the fluid to spread further in the fat. Therefore, the permeability of the tissue being injected into, and the effect of micro-cracks on this value, will be an important part of understanding the process of jet injection into tissue.

Chang [82], a member of the allied MIT injection group, modelled the penetration of fluid across the surface of the skin with the help of a high-speed x-ray machine. Her model of penetration focussed on the dispersion in the dermis as the jet penetrated and was then extracted by the injector for analysis. The model was based on Darcy's law, which describes fluid flow through a porous medium. It's application was mainly to the extraction period as low Reynold's numbers were required for the assumptions of Darcy's law to be valid. Of relevance to my work was the fact that diffusion was considered insignificant in comparison to the hydraulic conductivity of the flow in the dermis, and that
this conductivity was increased as the tissue swelled with the introduction of the jet fluid. Chang considered this process the likely mechanic of penetration through the skin as the jet increases the permeability of skin during an injection. Additionally, the x-ray images revealed that the fluid penetrates through areas of weakness within the collagen network. These areas appear as dendrites within the dermis of high injection fluid concentration. An analogy can be drawn with hydraulic fracturing as the injection of fluid increases the permeability of the matrix. This work built upon that of Comley and Fleck [70] and expanded its application.
2.5 Current Work

2.5.1 MIT/ABI Research

Concerns about the pain, local bruising, and lack of control of DCJIs have led to the development of new jet injectors with direct control of the displacement profile of the piston in the ampoule. Control of this element enables a variety of different injection profiles to be applied, allowing an injection profile to cater to the intended target [9]. While skin is highly variable in its mechanical properties, the mechanical breaking stress of the stratum corneum can be consistently overcome with pressures above 20 MPa, and the location of the injection site provides guidance as to what is expected beneath the surface [79]. Controlled injection achieves more consistent dispersion depth underneath the skin, encouraging its use [9].

An early motor-based jet injector was developed by Hemond et al. at the MIT Bioinstrumentation Lab [83]. The main motivation for the development of the device was the high bandwidth required for the control of jet injection (>1 kHz). This is well beyond the ability of purely mechanical actuators such as springs or valves. A commercial moving coil motor (BEI Kimco Magnetics, model LA25-42-000A), coupled with a piston in an injection cylinder, was used to power the device. Capable of auto-loading, the injector used a set of valves and ports to form a fluid bolus in front of the commercially sourced piston. The fluid was forced through a 100 µm orifice by the piston, creating a high-speed jet. The control system used was written in C#, and the output was amplified by a linear DC-coupled power amplifier (AE Techron, model LVC-5050). The pressure response of the system was characteristic of a second-order system with pure delay. The system’s behaviour was repeatable enough to allow the derivation of voltage profiles based upon desired pressure profiles in the injection cylinder. Testing of the device suggested that injection was inherently a two-phase process where a high-speed erosion phase is followed by a low-speed dispersion phase.

Depth of injection was identified as both a function of the peak pressure of the jet [84] and of the time the jet is at high speed [33]. The gel tests conducted by Hemond et al. revealed injection depth varies approximately linearly with pressure, and delivery volume varied linearly with length of time spent in the follow-through low speed phase [83]. In porcine tissue tests, the depth increased with pressure nonlinearly in contrast with the linear relation in acrylamide gels, exposing the effects of the inhomogeneous and anisotropic nature of skin [78].

Taberner et al. subsequently created a smaller linear moving coil jet injector where the force from the motor is applied to the piston of the commercially available Injex™ ampoule system [9]. These motors
use a coil wrapped around a permanent magnet in a magnetic circuit. The motor exhibited a force constant of 10.8 N/A ± 0.5 N/A. It is controlled by a compactRIO system (National Instruments) that performed trajectory updates every millisecond and used a spline engine to calculate a run of set points from the trajectory at a rate of 64 kHz. An amplifier (AE Techron LVC5050), capable of achieving an output of 4 kW, provided the required power for successful injections.

The device was tested for its consistency of volume delivered into vials and achieved a mean volume that was 99.18 % ± 0.04 % of the target volume [9]. However, similar tests into skin samples encountered skin resistance which reduced the percentage volume delivered. Hole depth was linearly related to calculated jet speed. Injections into skin reported volume delivered as 81 % of ejected volume in rabbit skin and around 60 % of ejected volume in rodent skin.

2.5.2 Control System used at ABI and MIT

In the context of jet injection, by control system I mean the system within the device that forces the piston to follow a particular trajectory of coil position. As a result of this system, the device produces a desired jet speed profile over time. The control system used by Taberner et al. [9] relied upon a
nonlinear feed-forward model during injection, while a displacement feedback controller counteracted noise and disturbances to the system [9]. The feed-forward model was calibrated with five constant velocity jet injections into the target tissue. A third-order polynomial was fit to the results and used for all injections involving the same injector and target tissue. The Bernoulli equation, which does not take into account frictional losses in the fluid [85], was used to calculate the constant jet speed. However, as long as the process was identical between calibrations, there was little error introduced when trying to achieve a jet speed. Taberner et al. used the control system to create trajectory profiles that enforced a two-stage mode of injection. A high-speed (150 ms$^{-1}$ to 200 ms$^{-1}$) initial phase, reached within 1 ms to 2 ms, was followed by a low-speed (50 ms$^{-1}$) follow-through phase. The initial phase focused on creating a hole to the desired depth beneath the skin’s surface, and the follow-through phase increased the volume delivered through the hole by dispersion. The trajectory was low-pass filtered to 50 Hz so as to not excite the mechanical resonances of the ampoule system. The recorded position trace was much smoother than a normal Injex™ injection as a result.

The parameters of the control system used by Taberner et al. [9] are the PID (proportional-integral-derivative) gains and the coefficients of the third order feed-forward model (a polynomial). Due to the mass of the coil and the high speeds required by the injection process, simple feedback control with PID gains was unable to match the desired trajectory effectively. With such a basic system, a delay would be experienced when the motor attempts to reach the required speed and is unable to because the system is slow to react. Such a delay would make the system very sensitive to the integral gain (the I in PID) and if this is set too high, the system would go unstable. Additionally, a high proportional gain would cause oscillations in the response that would decrease the consistency of injection results. Such a system is also very sensitive to any backward movement as the resistance against the piston is much higher in the forward direction because of the water passing through the orifice than in the backward direction where air easily enters the ampoule. The feed-forward model was introduced to reduce the delay as it added more voltage based upon the desired speed using the four polynomial coefficients that define it. Such a system is very sensitive to these values. Therefore, it was necessary to base the values upon multiple measurements with the same injector that was to be injecting. This system performed well for Taberner et al. [9] however the feed-forward model remains a loosely defined parameter set that is not understood in its entirety. In fact, the whole control system is empirically based, as PID gains are also set during a tuning process. It is possible that a control system based upon a computational model of the device could provide more insight on the meaning of the control parameters, and thereby achieve more stable and consistent control.
2.5.3 Other Research Groups

There are a number of other development groups active in this field. Stachowiak et al. have focused on developing a piezoelectric motor-based jet injector [33], [36]. In their device, a lead zirconium titanate piezoelectric actuator is used, rated for 17.4 µm expansion at 150 V (Figure 9). While the volume can be mechanically amplified, the base device is limited to fluid delivery of volumes of less than 10 µL. A side-effect of amplification is an increase in the natural frequency of the system, which was found to have little effect on the operation of the jet injection device, and, in fact, improve its stability. The piezoelectric device was indicated to have a bimodal distribution, and skin tests revealed an average volume delivered of 10% of ejected volume over all tests. This percentage is well below that achieved by Taberner et al. who have achieved above 95% delivery [9].

A moving coil jet injector has been developed by Chen et al. similar to that developed by Taberner et al. Chen et al. focused on the application of this device to animal vaccination, and powered their device using a discharging capacitor supplemented by a controllable direct current (DC) [4]. A force transducer was placed under the orifice at a distance of around ten millimetres. A measurement of pressure was deduced from the force recorded to determine if the jet met the requirement of 15 MPa of pressure necessary to pierce through the stratum corneum. They showed the average pressure in the first 5 ms was around 20 MPa demonstrating the ability of the device to pierce the skin. For their control system, they used a pressure transducer to feed the DC voltage applied back to the capacitor. An H bridge enabled the movement back and forth of the coil and piston.

Figure 9 - Diagram of piezoelectric system used by Stachowiak et al. [36]. The piezoelectric stack actuator in the centre expands, forcing the piston forward and the fluid out the orifice.
2.6 Jet Injector Modelling

Outside jet injection, linear motor control is normally achieved by a proportional, integral, and derivative control system (PID) where gains to the position, integral, and derivative error are applied in order to calculate the applied voltage and conform the movement to a certain profile [9]. Jet injectors require control of position beyond the ability of a simple PID which is limited by the speed at which the system runs. The response of the system can be predicted by a mathematical model before the application of the voltage in order to calculate the voltage profile that will achieve the desired trajectory. Error occurs in the models due to the variation in basic mechanical and electromagnetic properties of each injector system. Three of the JI development groups who report to literature, Stachowiak et al, Taberner et al., and Schramm and Mitragotri, have used mathematical modelling of their devices to inform the control system how to behave.

Both Stachowiak et al. and Taberner et al. based their models upon that of Baker and Sanders [85]. Baker and Sanders’ model relied upon the Bernoulli equation to calculate the energy balance along a streamline in the ampoule, and derived a differential pressure equation. A series of force balance differential equations on the piston, the main mechanical element of the model, formed a set of equations that could be solved in a closed loop. The model in reverse can calculated the required voltage profile for a desired jet speed profile.

For their modelling, Stachowiak et al. initially used basic voltage ramping to try to achieve a desired jet speed profile based on dimensional analysis [33], [36]. However, this method only worked when the ampoule of the jet injector was empty. Fluid compressibility caused latency in pressure development decreasing the response time of the whole system to voltage ramping. A change to using a Runge-Kutta based closed-loop simulation of the injector, based upon Baker and Sanders’ model, achieved successful control of injection velocity profiles. The simulation was set to have a maximum time step of 1 μs and a relative error tolerance of $\varepsilon = 10^{-6}$.

Schramm and Mitragotri modelled the formation of the jet and the effect of jet properties on the profile of the injection in the skin [86]. The jet was identified as turbulent, and they identified a set of experimentally defined jet speed adjustment constants that vary the jet speed from that calculated by the Bernoulli equation. These constants lower the jet speed to levels that agree with experimental data from various sources. Unfortunately, a whole new set of experiments is required for each device in order to determine the jet speed adjustment constants.
2.7 Future Developments

Stachowiak et al. suggest that a nonlinear spring may improve the delivery of drugs using spring-based needle-free injectors. Nonlinearity would enable the transition from a high speed initial phase and a low-speed follow-through phase in a passive system [36]. Approaching the problem in this way is still restrictive as the nature of the nonlinearity would not be adjustable to the requirements of delivery to different skin layers, and the parameters could not be changed to accommodate different skin types and injection sites.

Several shallow injections might reduce the pain associated with needle-free injections. These injections could be concentrated on the epidermis, which has no nerve endings [33]. Piezoelectric actuators would be well suited as the source of power for these injections due to their controllability and short stroke length.

Shergold and Fleck have suggested that an orthotropic elastic solid is a more accurate representation of skin than the isotropic silicone rubber model used in their study [81]. Adopting this description of the skin might enable better estimation of drug movement in the skin. The results from experiments on animal and human skin may also match the model better, enabling more accurate prediction of movements. The porcine forelimb has been suggested as the ideal animal model for analysis of fluid delivery in skin [75].

The most commonly identified improvement is better control over the jet created by the jet injector [12], [87]. Control is being pursued through the use of moving coil motors [9] and piezoelectric motors [33], as variation of the applied voltage will change the form of the jet. This approach is beneficial as motor control system theory is able to be applied to the formation of the fluid jet. The fluid mechanics of the jet are complicated because the flow is turbulent, and the pressure drop is not easily calculated. The ability to make control of a motor translate to control of a water jet formed by a motor is the critical challenge for the developers of controllable jet injectors.
2.8 Delivering Viscous Fluids Transdermally

2.8.1 Monoclonal Antibodies

A rapidly developing area of research is the application of antibody treatment for cancers and inflammatory diseases. Most drugs used in these treatments are monoclonal antibodies, which attach to a cell and either induce an immune response, to eliminate the cell, or inhibit the cell's function, to reduce the effects of a pathology [88]. Due to the self-association of the proteins in monoclonal antibody formulations, the viscosities of these drugs can be quite high and exhibit a wide range of viscosities as the components and concentrations change [89]. One monoclonal antibody tested by Liu et al. [89], when at a relatively high concentration of 16 % (w/w), had a viscosity of 120 mPa·s, a level similar to motor oil. This highlights an essential trade off in drug formulation. Formulations with higher concentrations of the active protein often have higher viscosities, but require less administered volume to be effective. Formulation constraints could be relaxed if injection was achieved easily across a wide range of viscosities. Given that 25 % of drugs under development are monoclonal antibodies [89], jet injection must be able to deliver viscous antibody formulations in order to be considered an effective method of transdermal drug delivery, particularly to demonstrate versatility similar to needled injection. Additionally, jet injection must deliver these compounds without significant denaturation due to shear, as observed during the production process [90]. More guidance is required as to the degree of shear that is experienced during jet injection and the percentage of drug that is denatured. Early results [91] suggest that only a small percentage is affected, but little is known about the cause of the denaturation.

2.8.2 In Situ Forming Drug Delivery Systems

Normally when injection is mentioned, the perception is that the drug is injected directly or indirectly into the bloodstream to spread throughout the body and work to improve the body's function. The time scale for this is normally seen as a matter of minutes, rather than hours. Recently, however, interest has developed in injectable polymers that form gels under the skin and function as a drug depot for controlled release [92]. For instance, if a normal insulin injection for a diabetic is replaced with the injection of a gel, the period before another injection is required will be longer as the gel continues to release insulin into the surrounding tissue and into the bloodstream. Often these gels are hard to inject with a needle as their viscosities range between 0.1 Pa·s to 100 Pa·s [93].

The gels come in four main forms: thermoplastic pastes, in situ cross-linked systems, in situ polymer precipitates, and organogels. Thermoplastic pastes are injected at temperatures between 25 °C and
65°C and cool to form a semi-solid. The viscosity of the paste can be high enough such that injection by a standard hypodermic needle is too hard to be used clinically, requiring new formulations with less viscous polymers to be developed [92]. The heat can cause damage to the surrounding tissues, but the benefit is that, once administered, the temperature at the injection site allows them to set in place.

The in situ cross-linked systems require a reaction underneath the skin surface to form into the solid gels that release the drug [92]. Thermosets are moulded underneath the surface and then set when heat is applied. Photo-cross-linked gels use a laser to start the polymerisation process, and alginates form a solid when they come in contact with ions such as calcium, encountered in most soft tissue. The injectability of these systems is greater than thermoplastic pastes, as the crosslinking that makes them viscous occurs underneath the skin surface, reducing the need to force the viscous fluid through the needle.

However, the gels can be formed before injection. A methyl cellulose gel has been shown to effectively release lidocaine in a rat model, with a viscosity before injection of around 4 Pa·s [94]. Similarly, a hydrogel formed out of polyethylene oxide and α-cyclodextrin has demonstrated injectability [93]. The gel is thixotropic, where at high shear its viscosity is greatly reduced. Measured results show a reduction from 1000 Pa·s to 10 Pa·s with a gel made from polyethylene oxide of 35,000 kg/mol molecular weight. This property is highly desirable as it reduces the viscosity when low viscosity is most desired, during the injection of the gel, and increases it when the gel is required to set and slowly release the drug.

Similarly, in situ polymer precipitates use a solvent to carry the components of a polymer through the surface of the skin, usually in a fluid with low viscosity [92]. Once the fluid is underneath the surface, the solvent is removed from the solution, normally through contact with the surrounding tissue, allowing the polymer to form into a drug-releasing hydrogel. Once again, the viscosity of the injectable is reduced.

Organogels face greater problems when being injected due to viscosity. Made of amphiphilic lipids, they are waxes at room temperature, requiring heating or the addition of vegetable oils in order to be injected. Luckily, adding oil also lengthens the release duration, improving their performance. However, the viscosity is often reduced just enough to enable injection as the volume must be kept within 2 mL, resulting in a viscous drug.

A needle-free injection device may make viscous gels easier to inject, as the restriction of wall friction effects that make some gels hard to inject is replaced with the necessity to force the gel through a tiny orifice. Little is known of the effect of viscosity on the delivery of a drug or gel with a jet injection device,
and it may be the case that the jet injection method encounters less resistance than needled techniques. A focus of this thesis is determining the effect that viscosity has on needle-free jet fluid delivery, potentially revealing it as a technology that expands the range of drugs that can be delivered transdermally.
2.9 Progression to Creating a Model

The literature review I carried out in the early stages of my PhD established the range of viscosities that I was aiming to inject, between 0.001 Pa·s and 1 Pa·s. I built upon the work of the ABI/MIT research group, setting up my own moving-coil actuator jet injector in order to gain familiarity with the device.

I considered that a good first step to understanding the function of the jet injector would be to model its electromechanical behaviour, with a view to getting an idea of the jet speed profile versus time at the orifice. I believed the modelling would help me understand the different components which may need to be modified to inject viscous fluids, and the model itself would serve as a helpful assistant in improving the performance of the jet injector. The model, its testing, and its applications are outlined in the following chapter, mainly extracted from conference and journal papers submitted during my PhD. The model development was part of collaboration between the ABI and MIT, a result of an exchange program between the two institutions.
3 Modelling of Jet Injectors

3.1 The Following Chapter

In this chapter, I present two published papers that detail both an electromechanical model and a method to estimate the viscosity of a fluid using the jet injector itself. Coupled with this work is the result from some improvements I made to the jet injector. This injector was given to me when I started my PhD and is similar to that detailed in the work of Taberner et al. [9].

The following includes substantial content from the article:

Analysis of Moving-Coil Jet Injectors for Viscous Fluids [10]

as submitted to IEEE Transactions of Biomedical Engineering for consideration on the 21st May 2015 and accepted for publication on the 18th September 2015.

The work is written in first person plural to reflect its collaborative nature. The bibliography has been incorporated into that of the thesis.
3.2 Abstract from Paper

Objective: A jet injector (JI) is a device that can be used to deliver liquid drugs through the skin using a fluid jet, without the use of a needle. Most jet injectors are designed and used for the delivery of inviscid liquids, and are not optimized for the delivery of viscous drug compounds. To better understand the requirements for delivering viscous drugs, we have developed a mathematical model of the electromechanics of a moving-coil actuated jet injector as it delivers viscous fluids. Methods: The model builds upon previous work by incorporating the non-linear electrical properties of the motor, compliant elements of the mechanical piston and ampoule system, and the effect of viscosity on injector characteristics. The model has been validated by monitoring the movement of the piston tip and measurements of the jet force. Results: The results of the model indicate that jet speed is diminished with increasing fluid viscosity, but overshoot and ringing in the jet speed is unaffected. However, a stiffer ampoule and piston will allow for better control of the jet speed profile during an injection, and reduce ringing. Conclusion: We identified that the piston friction coefficient, the compliance of the injector components, and the viscous properties of the fluid are important determinants of performance when jet injecting viscous fluids. Significance: By expanding upon previous jet injector models, this work has provided informative simulations of jet injector characteristics and performance. The model can be used to guide the design of future jet injectors for viscous fluids.
3.3 Introduction

Drugs designed to be absorbed in the tissue underneath the skin are typically delivered by needle and syringe. This method causes pain and is prone to needle-stick injuries for medical professionals [37]. A jet injector (JI) is a device that forms a fluid jet that can pierce through the skin and deliver drugs to dermal, sub-cutaneous, and muscular tissue in humans and animals [12]. The delivery is achieved without the risk of needle-stick injuries, and with reduced or equivalent levels of pain compared to the needle and syringe method [1]–[3]. In these systems, force is applied to a piston that increases the pressure in a fluid-filled ampoule; the pressure forces the fluid to form a jet that ejects from a small orifice at the opposite end of the ampoule. The force can be applied by a variety of different means including compressed gas [57], springs [21], [51], piezoelectric actuators [33], and Lorentz-force actuators [9].

Current JI technology is unable to deliver highly viscous fluids, such as glycerol, as effectively as low viscosity solutions [95]. Many modern drug formulations, such as monoclonal antibodies, are created in high concentrations and exhibit high viscosity (between 0.01 Pa·s and 0.1 Pa·s) [89]. These formulations are used to treat inflammatory and allergic diseases, cancer, and asthma, and may be more beneficially delivered by controllable jet injection [89], [96]. In the following work, we use glycerol to increase the viscosity of the tested fluids. Glycerol was chosen as it is a Newtonian fluid and, therefore, is a conservative estimate of shear-thinning monoclonal antibodies [97]. It is also relatively easy to measure the viscosity of glycerol (a cone-plate rheometer is sufficient). Other fluids, especially viscous drugs such as monoclonal antibodies, can form films that make measuring their viscosity difficult [98], making measurements with glycerol more accurate. In order to develop devices for jet-delivery of viscous fluids like these, we require a more complete understanding of the process of pressurizing the mechanical system that forms a viscous jet that is able to pierce through the skin.

To this end, we report on a detailed mathematical model of a jet injector device that uses a moving-coil actuator (sometimes referred to as a voice-coil or Lorentz-force actuator) as the source of force. Such motors allow a much greater degree of control over the device's behaviour than other force generating devices. A control system with the motor allows the production of a wider range of jet profiles compared to those achievable when using a spring or compressed gas device [9].

Previous models [85], [99] of such devices have focussed upon the delivery of fluids similar to water in density and viscosity and have not accounted for the influence of viscosity on jet formation. Some (e.g. [85]) have not modelled how voltage applied to a moving-coil motor produces a force that pressurizes the drug, and while others (e.g. [99], [100]) have only applied first-order modelling of the response of
Chen et al. [100] model pressure loss due to fluid viscosity using a Darcy friction factor determined from the Moody chart, commonly used for fully-developed flows in constant diameter pipes. However, flows in jet injection are far from fully-developed and pass through large diameter changes. Our model incorporates knowledge about the motor’s electrical and mechanical behaviour, the impulse response function of current to an applied voltage, and an empirically defined relationship that anticipates pressure losses in the fluid for a given orifice. In addition, we include in our model the nonlinear, volume-dependent elastic properties of the piston tip and ampoule.

The model is used to investigate the behaviour of a moving-coil actuated jet injector when the mechanical properties of the device and the fluid are modified, and thereby to derive the parameters that are most conducive to jet delivery of viscous fluids.
3.4 Model Formulation and Parameterization

3.4.1 Jet Injector System Design

The jet injector (Figure 10) consists of a moving-coil actuator coupled to a disposable plastic piston (with rubber tip) and ampoule. A 6-layer coil surrounds an NdFeB magnet of 25.4 mm outer diameter. The coil is formed from 0.361 mm (27 AWG) copper wire wound onto a bobbin of 27 mm outer diameter. A potentiometer (ALPS RDC1032) is attached to the coil to measure its position. The piston is made of a polycarbonate shaft with a rubber piston tip that seals the fluid in the ampoule; the total length of the piston is 50 mm. The polycarbonate ampoule has an inner diameter of 3.57 mm and a 190 µm orifice at the far end where the jet emits.

During characterisation experiments the actuator's position, voltage, current, and force were measured and/or controlled by a data acquisition and control system (cRIO 9022, National Instruments) with a loop rate of 20 kHz. Tests presented in this text were run in open loop with the voltage generated by the controller at a rate of 20 kHz. All software was written in LabVIEW 2011 (National Instruments). A pair of series-bridged power amplifiers (AE Techron 7224) amplified signals to the coil.

3.4.2 Model Formulation

Electrical Model:

The elements of the injector form a coupled electromechanical and fluidic system that can be described by the block diagram of Figure 11. In this model, the voltage across the coil \( V \) drives an electrical...
current in the coil. The current in the coil \((I_c)\) is estimated using the empirically-measured impulse response function of the coil. A finite impulse response filter on the input voltage uses the impulse response function to calculate the current on a point-by-point basis in each simulation time step. The force produced by the coil \((F_c)\) is calculated using \(K_c\) as the force constant of the motor (Figure 11). The force constant is allowed to vary with coil position.

The coil displacement \((x_c)\) is estimated through a nonlinear mechanical model. The velocity of the coil induces a back-electromotive force (back-EMF) in the coil; the back-EMF is the source of a difference between the applied voltage \((V_A)\) and the voltage across the coil.

**Mechanical Model:**

The piston has a rubber tip that deforms to seal against the fluid when force is applied to the piston. The model combines the compliance of the tip and the piston shaft by ascribing a non-linear stiffness \(k_p\) to the piston (Figure 12C). The coil’s acceleration is described by

\[
\ddot{x}_c = \frac{F_c + k_p(x_p - x_c)}{m_c},
\]

where \(F_c\) is the force applied by the motor, \(x_c\) is the displacement of the coil, \(x_p\) is the displacement of the end of the piston tip and \(m_c\) is the mass of the coil. The piston tip acceleration is described by

\[
\ddot{x}_p = \frac{-k_p(x_p - x_c) - F_{FR} - P A_p}{m_c},
\]

where \(F_{FR}\) is the friction force, \(P\) is the pressure of the fluid in the ampoule, and \(A_p\) is the area of the piston. The mass of the piston is ignored, as it is much less than the coil mass.

Sliding friction arises at the interface between the rubber piston tip and the walls of the ampoule and is
proportional to the pressure in the rubber piston tip, which is assumed to be identical to the pressure in
the fluid. Therefore, the friction \( F_{FR} \) is calculated using

\[
F_{FR} = \mu A_c P, \tag{3-3}
\]

where \( A_c \) is the contact area of the piston tip against the ampoule wall and \( \mu \) is the friction coefficient [101]. A constant level of static friction is present until the coil starts moving.

At the pressures encountered in jet injection, the compliance of the fluid itself, measured by its bulk modulus, becomes significant. In addition, the ampoule tends to expand under the influence of the high pressure, contributing additional compliance. The ampoule compliance is proportional to the length (and thus the volume) of the fluid column, and can therefore be lumped with the fluid compliance by way of an effective ampoule-fluid bulk modulus \( K_{AF} \).

A differential equation for the change in pressure over time can be determined via a mass balance [85]. To account for the effective bulk modulus, this equation was slightly modified to

\[
\dot{P} = \frac{(k_{AF}+P) x_P - \frac{K_{AF} A_O}{A_p} \dot{u}_O}{x_P}, \tag{3-4}
\]

where \( A_O \) is the area of the orifice, and \( u_O \) is jet speed. The pressure that results from this equation was applied against the piston as indicated in (3-2). The pressure loss due to viscous fluid interactions is captured by

\[
P_{loss} = \frac{K_D}{2} \rho u_O^2, \tag{3-5}
\]

where \( K_D \) the discharge coefficient, is empirically determined and \( \rho \) is the density of the fluid. \( P_{loss} \) is subtracted from pressure when calculating jet speed. Its formula can be combined with Bernoulli’s equation and rearranged to incorporate viscous loss in equation (3-4) [102],

\[
u_O = \sqrt{\frac{2P}{\rho (1+K_D)}}, \tag{3-6}
\]

The model was implemented in LabVIEW 2011 (National Instruments) using the Runge-Kutta-45 method in the Control and Simulation Module. This solved the model in 0.6 s.
3.4.3 Parameter Estimation

Coil Impulse Response:
A low-noise linear amplifier (KEPCO BOP 50-4D) and the CompactRIO previously mentioned were used to evaluate the coil impedance impulse response function. Gaussian white noise of ten volts peak amplitude was applied to the coil. The sample rate of the input and output was 100 kHz. The coil was locked in position at 5 mm from full retraction. The measured voltage and current were used to calculate the impulse response function using stochastic system identification. 500 points of the impulse response function were used. The impulse response function method produced model results that fit measured current values significantly better than a simple first-order series-circuit model of the inductance (4.8 mH) and resistance (9.4 Ω) of the coil (Figure 12A).

Force Production over Stroke:
A coupling mechanism was manufactured to connect the coil to a load cell. The force was measured at constant current over the stroke of the motor and a 2\textsuperscript{nd}-order polynomial of force constant was fit to the results. The average force constant over the stroke length of the injector, between 2.5 mm and 30 mm from the fully retracted position (Figure 12B) was 8.78 N·A\textsuperscript{-1} and exhibited a standard deviation of 1.58 N·A\textsuperscript{-1}. The maximum force constant measured was 10.2 N·A\textsuperscript{-1}, and the minimum was 5.05 N·A\textsuperscript{-1}.

Piston Compliance:
The compliance of the piston was measured using an electromechanical test instrument (Instron 5866). Epoxy was drawn into the ampoule up to the 0.05 mL mark and allowed to cure; the cured epoxy prevented the ampoule from compressing under load. Compression length was monitored and recorded up to a compressive force of 120 N. The non-linearity of piston compliance was modelled with a piecewise linear function that captured both the rubber piston tip compliance and the compliance of the polycarbonate shaft. This approach was preferred over the direct use of the experimental results as it allowed the effect of the two compliant elements to be modelled separately. The piecewise linear function shown in Figure 12C determines the value of $k_P$. When the piston tip is compressing (up to 0.4 mm), a spring constant of 20 kN·m\textsuperscript{-1} is used and, once the tip compressed, a spring constant of 200 kN·m\textsuperscript{-1}, representative of the stiffness of the piston shaft alone, is used. The fit exhibited in Figure 12C demonstrated root mean square (RMS) error of 0.86 N over the first 0.5 mm of deformation.

Friction:
Static friction was given by the force required to initiate piston motion. Sliding friction ($F_{fr}$) was measured by applying a voltage to the motor (with attached water-filled ampoule) for a period of
20 ms, and determining the steady-state force during the last 5 ms of the test. Eighteen tests were undertaken using a piston and ampoule with the applied voltage ranging from 20 V to 250 V. The sliding friction was determined by subtracting from $F_{FR}$ the force required to eject water through the orifice (given by the solution of Equation 4). This method assumes that water is inviscid and that all losses when ejecting water can be attributed to sliding friction. The area of contact ($A_c$) between the piston tip and ampoule was measured during the compression test at a force of 170 N, a value similar to the force applied to the piston during an injection. The fit of the friction model (equation 3-3) to the measurements of force less the Bernoulli loss (Figure 12D) exhibited an RMS error of 3.35 N. This value is 4% of the average friction value. The static friction was a small percentage of the total friction (Table 2).

**Ampoule and Fluid Compliance:**

The effective bulk modulus of the ampoule and its contained fluid was determined by applying a force of 200 N to the fluid, corresponding to a fluid pressure of 20 MPa. The piston compression was subtracted from the coil displacement, and the remaining displacement attributed to ampoule and fluid compliance. This displacement was converted into an increase in volume of the ampoule. The pulse tests were repeated over a range of starting positions from 25 mm to 10 mm from the end of the ampoule. The equation

$$K_{AF} = V_F \frac{dP_F}{dV_F}$$

(3-7)

where $V_F$ is the volume of fluid in the ampoule, allowed the effective ampoule and fluid bulk modulus to be calculated after each test. The average value of the combined fluid and ampoule bulk modulus was calculated to be 649 MPa with a standard deviation of 12.8 MPa across six tests.
Figure 12 – A: The current response to a 7.25 V voltage step (black dots), in comparison to the predicted current response to the same voltage step of a $1/(Ls+R)$ transfer function (green line) and using the impulse response function (blue dotted line). B: The results of force constant tests over the stroke range of the JI (cross), and a fitted 2nd order polynomial with $R^2 = 0.9815$ (line). C: Fit of piecewise linear piston compliance (tip compliance - green dashed line, shaft compliance - blue dotted line) to measured compression data (black line). D: The fit of the friction coefficient multiplied by the area of tip contact to the loss attributed to friction (cross) across the range of pressures with $R^2 = 0.9940$. 
Pressure Loss across Orifice:

Solutions of glycerol (30%, 60%, 75%, and 85% glycerol by volume) and water were used to form a series of fluids with different viscosities, and subjected to pulse tests of 20 ms duration ranging between 60 V and 260 V. The viscosity of each glycerol-water solution was evaluated using a rheometer (TA Instruments AR1000) at the MIT Hatsopolous Microfluids Laboratory. The viscosity of the solutions was 0.0022 Pa·s (30% glycerol), 0.0125 Pa·s (60% glycerol), 0.0423 Pa·s (75% glycerol), and 0.1090 Pa·s (85% glycerol). The pressure on the fluid was determined by subtracting the friction force from the coil force (estimated from the current and the force constant of the motor at the average position over the last 5 ms of the test (see Figure 12B)), and dividing by the area of the piston. The steady state coil speed was calculated from the last 5 ms of position data; this speed was converted into an average jet speed using the area ratio between the piston and the orifice. The difference between the pressure actually developed during the test and the value calculated from the jet speed using the Bernoulli equation is the pressure drop over the orifice structure. Equation (3-5) was used to evaluate the $K_D$ value for the test. The value determined for the discharge coefficient ranged from 0 (for water) to 0.35 (for 85% glycerol). The nature of the relationship between viscosity and discharge coefficient has been represented by a variety of power, logarithmic and polynomial laws operating on the Reynolds number of the fluid [103]–[105]. For our data, shown in Figure 13, the relationship is represented by a log-linear model with viscosity normalized to water as the dependent variable ($n = 8$). The equation of the model fit is

$$K_D = 7.27 \times 10^{-2} \ln \left( \frac{\mu}{\mu_W} \right) + 3.88 \times 10^{-3},$$

(3-8)

where $\mu$ is the viscosity of the fluid, and $\mu_W$ is the viscosity of water (0.001 Pa·s). The standard error of the log coefficient is $1.49 \times 10^{-3}$, and the standard error of the constant is $1.06 \times 10^{-2}$. 


### Empirical Parameter Values

<table>
<thead>
<tr>
<th>Name of Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coil Mass</td>
<td>0.050 kg</td>
</tr>
<tr>
<td>Piston Diameter</td>
<td>3.57 mm</td>
</tr>
<tr>
<td>Piston Spring Constant</td>
<td>201 kN·m⁻¹</td>
</tr>
<tr>
<td>Maximum Rubber Tip Deformation</td>
<td>0.400 mm</td>
</tr>
<tr>
<td>Effective Tip Spring Constant</td>
<td>20.0 kN·m⁻¹</td>
</tr>
<tr>
<td>Area of Tip Contact</td>
<td>5.60E⁻⁵ m²</td>
</tr>
<tr>
<td>Combined Bulk Modulus</td>
<td>6.49E+8 Pa</td>
</tr>
<tr>
<td>Fluid Density</td>
<td>1000 kg·m⁻³–1260 kg·m⁻³</td>
</tr>
<tr>
<td>Sliding Friction Coefficient</td>
<td>0.240</td>
</tr>
<tr>
<td>Static Friction</td>
<td>1.50 N</td>
</tr>
<tr>
<td>Viscosity</td>
<td>0.001 Pa·s–0.100 Pa·s</td>
</tr>
<tr>
<td>Discharge Coefficient</td>
<td>0.000–0.350</td>
</tr>
</tbody>
</table>

Table 2 - The values used in the simulations to represent the jet injector system. Ranges are given where fluid properties change.

![Figure 13 - Plot of coefficient of discharge (K_D) over the range of viscosities tested. A model fit is represented by the black line with R² = 0.727.](image-url)
3.5 Validation

The model uses knowledge about the elements of the system to predict the piston tip displacement profile over time. Direct measurements of piston tip position can thus verify that the model is correctly incorporating the effects of system parameters. The model also predicts the jet speed as a function of time, which can be compared to estimates of jet speed inferred from the force of the jet as it impacts on a load cell.

3.5.1 Piston Tip Measurements

A Phantom v9 CMOS high-speed camera was used to measure the piston tip position during pulse tests of voltage amplitude between 120 V and 250 V, and 20 ms duration. The voltage was pre-filtered using a 2\textsuperscript{nd} Order Butterworth low-pass filter with a cut-off frequency of 125 Hz. Video was captured at 10,000 fps, and the tip was followed in one dimension using the program Tracker (Douglas Brown,

![Graphs A, B, C]

Figure 14 - The results of three piston-tracking experiments conducted during pulse tests of 120 V (A), 200 V (B), and 260 V (C). The solid line is the model prediction, and the dotted line represents the measured position from the tracking software. The fluid used was water.
Cabrillo College). The results shown in Figure 14 exhibit RMS error of 0.09 mm, 0.23 mm, and 0.38 mm for 120 V, 200 V, and 250 V pulse tests respectively. The error was calculated over 25 ms from the initiation time of the pulse test to include the relaxation of compliant elements.

3.5.2 Jet Force Measurement

A 225 V filtered pulse was applied for 20 ms while a contact force sensor (FUTEK LSB200, resonant frequency of 3000 Hz) was placed perpendicular to the jet, 1.4 mm from the orifice. The decrease in speed (and pressure) as the jet travelled the standoff distance was expected to be minimal. The jet force was measured with a 20 kHz sample rate, converted into a pressure $P$ by assuming the jet had the same area as the orifice, and then into a measurement of jet speed using

$$u_o = \frac{2P}{\rho}$$

(3-9)

The measured jet speed matches the model prediction with an RMS error of 18.0 m·s$^{-1}$ over the 30 ms following pulse initiation (Figure 15). Most of the error is due to the difference in the amplitude of oscillations between the results. The modelled jet speed overshoots by 44 %, whereas the estimated actual jet speed overshoots by only 26 %. The frequency of these oscillations has been correctly predicted although the level of damping is greater in the measured jet speed profile.

![Figure 15 - Comparison of measured jet speed calculated from jet impact upon force plate (dotted black line) and model predictions (grey line). The current is presented as a dashed black line.](image-url)
3.6 Design Predictions

The model can be used to predict the effect of changing parameters that characterize the behaviour of the device. The model was run with a range of piston spring constants, friction coefficients, ampoule bulk moduli, and viscosities to establish the behaviour changes that are attributable to these particular parameters. For each run, the input was a 20 ms pulse of 200 V, with all parameters other than the one being tested set according to Table 2. The default fluid was water, for which the viscosity was set to 0.001 Pa·s, the discharge coefficient was set to zero, and the fluid density was 1000 kg·m⁻³.

Figure 16 indicates how changing parameters affect the behaviour of the device. Increasing the piston spring constant has little effect on the jet speed (Figure 16A), but the coil rise time and oscillation period both decrease. Increasing coil friction (Figure 16B) reduces the steady state and maximum jet speeds, and slightly decreases the rise-time, but not the period, of coil position oscillations. When the bulk modulus of the ampoule is increased (Figure 16C), decreased oscillatory behaviour is evident in the jet speed and the coil position, corresponding to a reduction in overshoot. The period of coil position oscillation and the rise time decreases with increasing bulk modulus. As viscosity increases (Figure 16D), the steady state jet speed and maximum jet speed both decrease, and the overshoot slightly increases. The decrease in coil rise time evident when friction was increased is not seen when viscosity is increased.
Figure 16 - Steady state jet speed (blue circles), maximum jet speed (black squares), rise time to first peak of position profile (green plus signs), period of coil position oscillations (purple crosses) when model parameters are modified. These parameters are piston spring constant (A), friction coefficient (B), ampoule bulk modulus (C), and viscosity (D).
3.7 Discussion

The use of stochastic techniques to estimate the impulse response function allowed for the rise time of the modelled current to match measured current. As a result, the frequency of oscillations in modelled coil and piston tip position was well-aligned, providing a more accurate prediction of JI behaviour.

Sliding friction in the injector system occurs between the rubber piston tip and the inside surface of the polycarbonate ampoule. A review of the literature indicates that we should expect the friction coefficient between these surfaces to be between 0.15 and 0.25 [106]–[108]. The friction model presented fits well (Figure 12D), and the estimated friction coefficient is in the expected range (Table 2) when all losses with water are attributed to friction. We conclude that this attribution is valid in the context of the model.

The discharge coefficient results show a reasonable level of standard error for the fit coefficients. The error is indicative of the nature of the fluids as variable in the magnitude of their internal impedance. It is clear that the effect of increased viscosity is significant; in the pulse tests, jet speed reduces from 143 ms\(^{-1}\) to 109 ms\(^{-1}\) as viscosity is increased from 0.001 Pa\(\cdot\)s to 0.1 Pa\(\cdot\)s (Figure 16D). However, it is important to keep in mind that density has increased from 1000 kg\(\cdot\)m\(^{-3}\) to 1221 kg\(\cdot\)m\(^{-3}\), which would account for a drop to 127 m\(\cdot\)s\(^{-1}\). Nonetheless, previous published tests by other authors [86] indicate that this reduction in jet speed would lead to greatly reduced probability of successful delivery, even with the increase in density. It is likely that more power or modifications to the current device will be required to effectively deliver fluids with 0.1 Pa\(\cdot\)s viscosity and above. The current portable device is capable of jet injections of fluids with up to 0.1 Pa\(\cdot\)s viscosity, though it is restricted by the size of the attached amplifiers. We are pursuing the development of portable amplifiers as well as portable jet injectors that exhibit a higher force constant to extend the ability of the device to new applications.

Piston tip measurements can better predict the jet speed profile as the effect of piston compliance is removed (Figure 14). The model predicts much smoother profiles than the measured profiles, but the discrepancy can be attributed to the noise of up to 0.3 mm present in the high-speed camera images. The results indicate that the oscillations evident in coil position are not coupled through to the piston tip position. We conclude that when a compliant piston is used, the coil position cannot be relied upon to provide an acceptable estimate of jet speed during the dynamic phase of jet injection.

The jet force measurements (Figure 15) show a reasonable fit between the force plate measurement and model predictions. The oscillation amplitude and the damping of the oscillations is less accurately predicted than the steady-state jet speed and the rise to that jet speed, likely due to the variability in the
response of the compliant elements in the system. Alternatively, the force transducer used may not have had the necessary frequency response required to pick up the magnitude of the oscillations in the jet speed.

The model can be used to inform design decisions for future development of jet injectors. As the device used in the experiments is primarily used for fluids with viscosities near to that of water, the model can be used to identify areas of improvement for future viscous-drug devices. The effect of piston compliance on the developed jet speed is negligible; this is despite significant variation in the amplitude of fluctuations for the coil position. Hence, a stiffer piston allows the potentiometer to better estimate the fluid volume and jet velocity, and exhibits tighter coupling between coil speed and jet speed.

Variation of the input parameters revealed the dominant second-order nature of the system. An important parameter to reduce when trying to control the jet speed is the overshoot, and it is clear that the compliance of the ampoule plays a major role in its determination. A stiffer ampoule will produce a steady-state jet speed much earlier than with the original compliant set-up. It is easier to achieve control of injection depth when the jet speed is tightly controlled, as a relationship between jet speed and injection depth can be identified [21], [36]. Therefore, a stiffer ampoule will help with producing a smoother, more effective jet for delivery.

If the sliding friction coefficient is reduced, the jet speed increases with no change in the input energy from the coil. We anticipate that much would be gained from pursuing an investigation into how to reduce the sliding friction coefficient as friction accounts for a loss of 50% of the force generated in the coil. Reducing this loss would increase the efficiency of the system, allowing higher speed jets to be formed more easily, regardless of viscosity.

The modelling will guide the future development and use of the device. The first improvement that we pursue will be stiffening the ampoule and piston to improve the control and shape of the jet speed profile over time. Secondly, we will take advantage of the controllability of our system to rate-limit the application of force to the coil and thus avoid exciting excessive jet-speed overshoot. After this, an investigation of the effect of orifice diameter and the geometry of the ampoule on the discharge coefficient will guide us in choosing the best shape through which to force the fluid.
3.8 Conclusions

The jet injector electromechanical model presented in this article expands upon previous knowledge by better characterizing the electrical system, expanding the modelling of compliance to include the ampoule, and taking account of the loss due to the viscosity of the injected fluid. Throughout the characterization of the JI presented in this paper, we focused on identifying the elements of the system that most affect its performance when jet-injecting viscous fluids. We identified these as the friction coefficient, the compliance of the JI components, and the properties of the fluid being injected. The model provides a better prediction of the jet speed profile over time than that provided by a direct conversion of coil speed to jet speed. The insight that the model provides into jet development will be used to develop methods that improve the reliability of jet injection, focusing on delivering fluid to a particular layer underneath the skin surface with a targeted jet.
The following work is related and in addition to that of the paper presented above.

3.9 The Effect of Stiffening System Components

3.9.1 Fabrication and Testing

The compliant elements of the piston and ampoule affect the position of the coil and the piston tip during the period of an injection. In order to validate the model’s predictions of the impact of this compliance, we fabricated a much stiffer piston and ampoule set from stainless steel, the details of which are elaborated upon in Chapter 4. The stainless steel piston used O-rings to form a seal instead of a rubber piston tip, further reducing the compliance of the element. All other dimensions were the same as the polycarbonate/rubber piston. The stiff components were used in pulse tests of the injector system of 20 ms duration and 180 V amplitude. The model parameters for piston stiffness, piston tip compliance, and effective bulk modulus of the ampoule were determined for the new elements. The predictions of the model were then compared to the measurements using the steel piston and ampoule.

3.9.2 Results and Discussion

The results of compliance element testing, presented in Figure 17, show the impact of removing the piston tip compliance and increasing the piston shaft stiffness to 500 kN/m. The results for the polycarbonate/rubber piston matched with the stiff ampoule (Figure 17A) present an RMS error of 0.15 mm, which over a travel of 9 mm is a good fit. Figure 17B and Figure 17C show an offset in the final position which develops within the first 2 ms of the pulse test when the stiff piston is used and exhibits RMS errors for the model of 0.87 mm when the stiff ampoule is used and 0.59 mm when the original ampoule is used. Figure 17C shows that the change in the oscillation frequency can be predicted by the model when the original piston and ampoule are used, and the model has an RMS error of 0.12 mm.

The modification of the stiffness of the piston provided some insight into how the model deals with changes to device compliance. The effect of stiffening the ampoule (Figure 17A) on the oscillation frequency was predicted effectively though the degree of compliance was overestimated. The effect of stiffening the piston (Figure 17C) was observed to be a change in oscillation frequency that was predicted by the model; however, an offset in the coil position profile was apparent. This same offset is apparent in the stiff piston and stiff ampoule results. We believe that the offset can be attributed to the positioning of the rubber O-ring in the grooves on the new stainless steel piston. During testing, we surmise that the O-ring compresses and moves into a position closer to the coil; this movement is registered as the coil moving forward, introducing the offset. We also suspect that the O-rings introduce
an oscillation frequency by modifying mechanics at the seal, as suggested by [109]. This effect is not predicted by the model because it is based upon the dynamics of a rubber piston tip.

Figure 17 - The model estimates (dotted line) and actual measurements (solid line) for a variety of different compliance element configurations. A: the results for the original piston matched with the stiff ampoule. B: the result for a stiff piston and ampoule test. C: the result for a stiff piston and original ampoule test. Each measured result is the average of ten tests.
3.10 Model Predictions for Viscous Fluids

3.10.1 Testing with Viscous Fluids

With the discharge coefficient modelling the steady-state impact of viscosity, we looked into the transient effect of viscosity on the behaviour of the injector. Four solutions of glycerol (30 \%, 60 \%, 75 \%, and 85 \% by volume in water) were mixed and drawn into the ampoule. A 200 V, 20 ms voltage pulse was applied to the injector. The coil position trace was compared to the model prediction using the particular viscosity of the fluid to evaluate how well \( K_D \) captured the effect of viscosity over the period of the coil’s movement.

3.10.2 Results and Discussion

The results presented in Figure 18 indicate model RMS errors of 0.15 mm, 0.13 mm, 0.14 mm, and 0.21 mm for fluids with 0.002 Pa·s, 0.012 Pa·s, 0.042 Pa·s, 0.109 Pa·s viscosity respectively. The rise to the first peak is well followed for all solutions except the fluid with 0.109 Pa·s viscosity. There is more damping in measured coil position than modelled coil position, and a delay in the oscillations of the coil between the two traces is apparent.

As viscosity is increased, the change in steady state speed is the most apparent effect on the dynamics of injection. The results in Figure 18 indicate that the model captures this change to a high degree of accuracy validating the relationship of equation (3-8). Variations in the phase of piston oscillations can be explained by the large impact of small piston spring constant differences on the dynamics of the coil.
Figure 18 - The model estimates (dotted line) and actual measurements (solid line) of coil position for a variety of different viscous fluids. A: the results for a solution of 0.002 Pa·s viscosity. B: those for a solution of 0.012 Pa·s viscosity. C: those for a solution of 0.042 Pa·s viscosity. D: those for a solution of 0.109 Pa·s viscosity.
3.11 Viscous Estimation

The following section includes substantial content from the 2 page abstract:

**Adjustment of Needle-free Jet Injector Control to Account for Viscous Loss** [11]


The 2-page abstract was available to Controlled Release Society members.

The bibliography has been incorporated into that of the thesis.

3.11.1 Motivation

With the effect of viscosity on the injector's behaviour characterised, the model could provide guidance on what to expect when a viscous fluid is loaded into the ampoule. However, the viscosity of a fluid might not always be known a priori. By evaluating the behaviour of injector when the fluid was ejected in a simple test, the viscosity of the fluid could be estimated, enabling better injection performance. We pursued this method to make the injector more adaptable and to make use of the model's knowledge in a novel way.

3.11.2 Methods

I added viscosity as an input to the feed-forward model. Pulse tests, similar to those that informed the feed-forward model previously, were repeated with solutions of 0 %, 30 %, 60 %, 75 %, 85 %, 95 %, and 100 % glycerol. The relationship between voltage, viscosity, and steady-state coil speed formed a 3-D polynomial. I could interpolate the 3-D polynomial to determine the required voltage to make a fluid with a certain viscosity go at a prescribed speed. This function was the new feed-forward model of the controller. The base ten logarithm of viscosity was used as the input parameter to the polynomial as its use allowed the polynomial to more accurately relate viscosity to the steady-state coil speed and voltage.

By extending the feed-forward model to include viscosity, I had created a device that could measure the viscosity of a fluid. If an unknown fluid is encountered, it can be loaded in the ampoule and a pulse test will reveal a steady-state coil speed. Feeding this steady-state speed and the voltage step amplitude into the 3-D polynomial noted above gives an estimate of the fluid's viscosity. The method assumed that the fluid was Newtonian and that the reduction in coil speed experienced with glycerol during the creation of the polynomial is exclusively attributable to its viscosity. For non-Newtonian fluids, the method can still be used if the fluid is tested at a speed around that which it will be injected as the shear rate will be...
the same. After testing, the estimate can be set as the viscosity into the feed-forward model to inject the fluid with unknown viscosity successfully.

To test the ability of the device to inject an unknown fluid, I conducted a blind study where a colleague mixed a series of fluids of random glycerol concentration. I used a pulse test, as described previously to estimate their viscosity. With one of the fluids for which I had an estimate of viscosity, I tried to achieve a range of steady-state coil speeds, comparing the achieved coil speed with that which was desired.

### 3.11.3 Results

The fit to the results of the pulse experiments is shown in the contour plot of Figure 19. The plot shows a clear increase in the voltage required to achieve any given jet speed as viscosity increases. The polynomial was fit to the results of 67 experiments; the RMS error of the fit was 3.844 m·s⁻¹. Relative to the range of jet speed, this fit can be considered sufficiently valid for prediction.

The results of the viscosity measurements using the modelled jet injector (Figure 20A) indicate that the test can be relied upon to estimate the viscosity with a mean error of 15%. The viscosity estimate for the 0.0209 Pa·s fluid was used to form a 3rd order polynomial (Figure 19). The polynomial acts as the feed-forward model. The results of using the feed-forward model to estimate and set the applied voltage (Figure 20B) show that the derived polynomial can assist in achieving a desired jet speed with a mean error of 10.9%. The remaining error can be removed with the use of feed-back control methods [9].

![Figure 19 - Contour graph of 3-D polynomial indicating jet speed attained at certain voltages over a range of viscosities. The dotted black line indicates the section of the fit used in feed-forward control for the 0.0209 Pa·s fluid.](image-url)
Figure 20 – A: The rheometer-measured viscosity of a fluid plotted against the injector estimated viscosity. B: A comparison of the desired jet velocity to the achieved velocity with the 0.0209 Pa·s viscosity fluid in the ampoule. The voltage applied in this test was determined using the injector estimated viscosity.
3.12 Concluding Remarks

At the conclusion of the work in this chapter, I had the basis for a feed-forward model for a jet injector for viscous fluids, a greater awareness of the effect of viscosity on the behaviour of a moving-coil jet injector, and an electromechanical model implemented in LabVIEW that provided guidance on how to improve the injector. The extent to which the electronics had been modelled, the incorporation of piston and ampoule compliance, and the modelling of the effect of viscosity were novel contributions to the field of jet injection that gave the final model its utility. I concluded during my time constructing and testing the model that I had to move to a stiffer ampoule and piston than the commercial ampoule (produced by Injex) in order to investigate the effect of orifice design on jet injection of viscous fluids. I have presented some of the results of a stiff ampoule design in section 3.9. Not only would I be able to change the geometry as the flow approached the orifice as a result, I had the opportunity to modify the orifice diameter, potentially revealing that viscous fluids were easier to inject when force through a larger or smaller orifice.

Most importantly, the investigations presented here provided a solid basis for understanding of jet injectors, as I could now anticipate the effects of design changes on injection performance. Throughout the period over which I produced the work presented in the following chapters, I would often consult the model, comparing my expectations of the injector’s behaviour with the model’s predictions. The most useful output was the jet speed profile as it predicted the speed of the jet, a good determinant of the jet’s ability to pierce the skin’s surface and the depth of the injection [21]. If fluids of significantly different properties were to be used, the same model could have predicted the profiles over time for other parameters that have been correlated with penetration, such as jet power or momentum [77], [80]. Thereby, the model would be taking into account the effect of these fluid property changes. Finally, the profile also predicted the stability of the jet speed and the duration the jet was applied, indicative of how well the control system of the injector was performing, as ideally it would control the jet speed profile rather than the coil speed profile. The model saved me time because it could take the output of a jet injection record and produce the expected jet speed profile in seconds. In the future, I expect that coil trajectories will be designed with consultation of the model, allowing users to extract better performance out of their injector hardware.

From here I set out to design and build my own injector, capable of forming powerful viscous jets. The model was used throughout this design process and helped me build the control system for the new injector. I used the injector to look at the effect of orifice diameter on the jet across a wide range of speeds, something that I was unable to investigate with the model alone. This investigation allowed me
to comprehend the effect of viscosity to a greater extent than that explored during the modelling process
4 Design of Jet Injector for Viscous Fluids

4.1 Introduction

As discussed in the introduction to this thesis, I wanted to build a viscous fluid jet injector to increase the range of drugs that can be delivered by jet injection and adapt the technology to many of the new drugs being currently formulated. I built the model presented in Chapter 3 to guide the design of a new viscous fluid jet injector (VFJI), as this model provides information on the effect of viscosity as well as how to increase the efficiency and controllability of jet injectors. The new device needed to be able to inject fluids with viscosities up to 1 Pa·s at speeds up to 200 m·s⁻¹. To be effective, it also had to exhibit enough control over the speed of the jet so that the jet speed achieved by the device was repeatable, with close linkage between coil speed and jet speed.

The available literature describes a wide range of jet injectors using a variety of different power sources. The ABI jet injection research group, and its MIT collaborators, have developed a moving coil jet injector over a number of years. This injector will be referred to as the lab jet injector (LJI) [5], [9]. Previous testing of this device has determined that the motor can only achieve a jet speed of 160 m·s⁻¹ with glycerol through an orifice of 190 µm diameter. Literature shows that this speed would not reliably penetrate human skin. In comparison, Stachowiak et al. found that the maximum jet speed that they could achieve with water using their piezoelectric motor was 160 m·s⁻¹[33], [36]. Schramm-Baxter and Mitragotri reported jet speeds of 200 m·s⁻¹ with water, but used uncontrolled spring-based needle-free injectors [21]. As I had observed up to a 25 m·s⁻¹ decrease in jet speed when glycerol was ejected into air, I needed more electrical power than any reported technology to achieve my objective.

I saw scope for the modification of more than the power of the device delivering the jet. Baxter et al. [21] had demonstrated that modifying orifice diameter can give greater control over hole depth and drug dispersion underneath the skin, according to their predictive model. However, there were no reports in the literature that described the effect of viscosity at different orifice diameters. I wanted to investigate this further to inform the choice of an orifice diameter for the VFJI.
Additionally, I hypothesised that a change to the geometry through which the jet is formed would lead to a reduction in viscous loss during injection, thereby reducing the power requirement of the VFJI. I thus wanted to design a system in which the injection orifice could readily be exchanged for one with different dimensions. My modelling of the LJI had indicated that the compliance of the system hindered effective jet injection. These compliant elements decoupled the estimated jet speed, based upon coil position measurements, from the actual jet speed of the fluid emitting from the orifice. I wanted to reduce the compliance so that the estimate of jet speed from coil position was more accurate, providing more accurate information to the control system and the end-user. Finally, I wanted to reduce the rise time to steady-state coil speed so that after a burst of voltage was applied to the new device, it settled to steady-state coil speed more rapidly than the previous LJI did. In combination with knowledge of the breaking stress of the stratum corneum, I believed that the increased control and repeatability of jet speed with the new VFJI would ensure penetration of the surface of the skin during the jet injection of viscous fluids.

The control system and user interface in the LJI did not adjust its operation when the viscosity of the fluid in the ampoule changed, and did not use any of the knowledge gained from the modelling presented in Chapter 3. Partially as a result of this, the LJI controller did not reach the desired maximum jet speed when trying to follow a trajectory during the attempted delivery of viscous fluids. I aimed to develop a device with a stable and consistent control system that accounted for viscosity and provided feedback on the impact of viscosity on its performance.

In this chapter, I outline the process I undertook to develop an injector that was able to inject viscous fluids, the VFJI. Throughout the process, I viewed the system as a set of interdependent subsystems. The different subsystems include the control system, the amplifiers, the motor, the piston and the ampoule. All of these are involved in the process of forming a jet capable of piercing the skin. Each subsystem was modified to ensure that the new device would perform more consistently and expose the fluid to a greater pressure than the previous LJI. I present the results of testing the new injector, that characterise the impact of the new changes — their benefits, and their drawbacks.
4.2 Stiff Ampoule and Piston

During the testing and modelling of the LJI, the compliance of the polycarbonate commercial ampoule and piston affected the results of the injection tests. Any attempt to verify that a jet speed had been reached during the transient phase was obscured by the compression of the piston and the expansion of the ampoule and fluid. I sought to replace these components with stiffer versions so that the effect of compliance was reduced.

I designed a stiff piston (Figure 21) with help from Stephen Olding, the ABI workshop manager. The new piston was made from stainless steel with two O-ring grooves, two and four millimetres from the end. The front end was designed to be a flat surface in front of the fluid. With this modification, the primary source of friction was expected to be between the rubber O-ring and the wall. The O-rings were set to be the standard -002 size, made of nitrile rubber and obtained from Seal House Ltd. The O-rings were expected to compress during operation, introducing some compliance. The magnitude of this was predicted to be around 0.1 mm, a reduction from the 0.4 mm observed during LJI operation.

The new piston fit inside a new stainless steel ampoule designed by Bryan Ruddy (Figure 22), with the help of Stephen Olding, who machined it. The new ampoule had a main body that could screw into the existing ampoule mount on the LJI. The front part of the stainless steel ampoule screwed onto the shaft. I obtained a range of stainless steel orifices (O’Keefe Controls Inc.) that fit in an M3.5 thread inside the front end of the ampoule (Figure 23). Their orifice diameters ranged from 100 µm to 430 µm, with the typical difference between each size being 30 µm. I chose these orifices because of the wide range available with the same attachment point, the stiffness of their stainless steel construction, and their stated orifice diameter accuracy of ± 13 µm, enough to significantly separate the range that I ordered. The interface between the shaft and the front end was sealed with a nitrile rubber O-ring. This O-ring had an inner diameter of 3.5 mm and cross-sectional diameter of 1 mm. The thread on the screw-in orifice was sealed with Teflon thread-seal tape. The result was a stiff ampoule where the orifice diameter could be modified, and the only fluid exit path was through the orifice.

![Figure 21 - Drawing of stiff piston with thread and O-rings labelled.](image-url)

M2.5 Thread

Nitrile O-rings

10 mm
Figure 22 - Photograph of stiff ampoule and inserted piston with important sections marked, and diagram of internal threads and O-ring seal. The slight skew of the front end where it screws into the shaft had no significant effect on the performance of the ampoule.
Figure 23 - O-Keefe Controls Ltd provided diagram of orifice insert, and photo of 200 µm orifice insert.
4.3 New Motor and Housing

Viscous fluids require more energy to form a jet capable of piercing through the skin. The VFJI had to use a motor that could provide force up to 400 N onto the back of the piston, a value much higher than the previous LJI.

I designed housing for a new motor (Figure 24). The supports that held the motor, the bearing, and the ampoule were machined in-house. First, I chose a motor to power the new injector. I selected a linear motor (LA25-42-000A, BEI Kimco Magnetics), that had previously been used in the lab and had exhibited repeatability and durability in previous tests on another jet injection rig. The motor was capable of forces over 400 N when used in combination with the amplifiers previously part of the LJI set-up, a level of force far exceeding the maximum force output of the previous LJI motor. The ability to produce a much greater force gave me headroom to achieve the speeds I was aiming for with viscous fluids. The force constant of the motor was 21.35 N/A (compared to the original injector’s ~10 N/A), and it had an internal resistance of 2.4 Ω. I used the same bridged amplifiers as in the model tests (7224, AE Techron), given that these provide enough power to the new motor for 400 N of force. The new motor had a higher mass than the one used in the LJI, making the new motor difficult to use in a hand-held injector. However, I decided that the goal of producing a 200 m·s\(^{-1}\) fluid jet of glycerol took precedence here. I used a 12 mm thick stainless steel plate with tapped M6 holes at 12.5 mm centres to form a base for the rig. I chose this plate as it provided a rigid base and it was simple to make parts that attached to the plate.

![Figure 24](image)

Figure 24 – Viscous fluid jet injector (VFJI) with the component parts labelled.
Based on a previous design [110], I designed a holder for the new motor. A stainless steel precision rod was passed through the centre of the motor and through two ball bearings, one on either end. The holder contained these ball bearings within an aluminium block that rigidly held the motor in place. The central axis of the rig was 50 mm from the mounting plate’s surface. At the end of the coil, two blocks of aluminium clasped the precision rod and fastened it to the end of the coil through a set of screws, transferring the force of the coil onto the precision rod. In the direction of this force, the rod passed through the bearing and met an adapter. The adapter clasped the rod with setscrews and had, at its other end, a tapped M3 thread into which the piston screwed. The stainless steel ampoule and piston were introduced to the central axis of the rig. The ampoule was screwed into a U-shaped aluminium bracket that also held the bearing, aligning all components. The system was then able to develop a jet as voltage was applied to the coil, and the coil forced the fluid in the ampoule out the orifice.

A linear potentiometer (Omega Engineering LP803-01) was held in the same U-shaped bracket as the bearing and the ampoule. It faced back towards the coil, and a magnet fastened it to the front of the aluminium blocks that attached the coil to the precision rod (as pictured in Figure 24). The potentiometer was calibrated so that it followed the trajectory of the coil, providing feedback on the progression of the injection during delivery.

I tested the performance of the new system with a series of pulse tests. I applied 19 voltages, equally spaced between 6 V and 60 V (increment of 3 V), to the injector for 25 ms, in a random order. For these, I used the orifice insert with orifice diameter closest to that of the commercial ampoule, being 200 µm. I loaded 7 different fluids into the ampoule for each set of tests, randomly changed between the options. The fluids had glycerol concentrations of 0 % (water), 30 %, 60 %, 75 %, and 85 % fraction by volume with water. I measured the voltage, current, and coil position over the 25 ms period of the pulse, enabling steady-state variables, such as jet speed, to be extracted from the resultant data set. From these results, I calculated the discharge coefficient, a measure of energy loss due to sliding friction and viscous pressure loss. The equation that I used for this coefficient ($C_d$) was:

$$C_d = \frac{\frac{u_O}{\sqrt{\frac{2p}{\rho}}}}$$  

where:

- $u_O$ is the measured jet speed at steady state,
- $p$ is the pressure applied to the fluid, and
- $\rho$ is the density of the fluid.
This is equivalent to that used by Ning et al. [111] but redefined in terms of mean jet speed rather than mass flow rate.

The orifice diameter was easily changed with the VFJI, a significant advantage over the LJI. In order to investigate the effect of orifice diameter on the behaviour of the injector, I replaced the orifice insert several times with inserts of different diameters and ran the same tests as described above. I conducted tests using orifice diameters of 100 µm, 150 µm, and 310 µm, as well as the original 200 µm. I chose this range because 100 µm was the smallest orifice through which glycerol could be drawn without sometimes introducing an air bubble, and 310 µm was the largest orifice where the piston travel throughout the set of pulse tests was within the limits of the ampoule.
4.4 Changes to Control System

I redeveloped the control system for the new injector (Figure 25), building upon what I had used for the LJI. Using the LabVIEW environment, I built a system based on the National Instruments CompactRIO 9022 real-time controller, which is effectively a separate computer dedicated to control the injector. The controller was installed into a NI cRIO-9112 field programmable gate array (FPGA) chassis, a processor with a 40 MHz clock, and the ability to run compiled FPGA code on a Xilinx Virtex-5 FPGA processor. I configured the FPGA to run at 20 MHz. The chassis interfaced with C-Series modules, these being specialised input-output units that can receive and transmit digital and analogue signals.

I recorded the voltage applied across the coil of the motor with a NI 9222 C-series module, a 500,000 sample per second analogue input module that plugged into the FPGA chassis. I also monitored the amplifier's current monitor output, proportional to the current through the coil, with the same module. The system sent the control output to the amplifiers via a NI 9263 C-series module, a 100 kS·s\(^{-1}\) analogue output module also plugged into the FPGA chassis. The amplifiers then applied the amplified voltage across the coil. The two C-series modules worked together and applied 2.3 V across the potentiometer (the maximum before the reading saturated) and measured the position-based voltage. I calibrated the measurement by moving the coil to five positions along its stroke, measuring the coil position with callipers and relating the potentiometer voltage to the position of the coil. The FPGA code
calculated and recorded the position of the coil based upon the calibration.

Consistent with the previous work of my research group [9], I used a combination of feedback and feed-forward in my control system. To start with, I set the measured position as the control input to a proportional-integral (PI) feedback control system, which determined the control output based upon the error between the measured and desired position (proportional control), and the integral of this position error. However, the speed of control required by the application meant that the PI system could not keep up with the desired trajectory of the coil, which was derived from the desired jet speed profile over time. To overcome this limitation, the control system was set to supplement the feedback with a feed-forward control effort, based upon a model that related applied voltage to steady-state coil speed, similar to previous control systems used with injectors at MIT and the ABI [9]. A series of 18 voltage pulse tests were performed, applying between 6 V and 60 V for 20 ms, with the coil speed being calculated over the last two milliseconds of the pulse. The results from these tests informed the model. The feed-forward system used the previously acquired model during an injection to calculate the required voltage for the desired coil speed at the current time and added this value to the control output (divided by the amplification value). The result was a reduction in the error between the desired trajectory and the recorded position trace as the injector reached a desired speed in less time.

I added safeguards to the system to improve its safety during testing. I included upper and lower position limits that cut power when tripped, ensuring that the coil was not damaged by hitting either end at a high speed. Following this, error limits were included and active during jet injections with the VFJI. These worked by reducing the control output to zero if the measured position was not following the set trajectory within 1 mm. If any safeguard was tripped, the code had to be re-run to reactivate the control output.
4.5 Injector System Performance

4.5.1 Consistency of Injection

I conducted a series of tests where a voltage pulse was applied for 25 ms to the coil several times, and the resultant position traces were recorded. Four fluids were used in the tests; water, 60 % and 85 % glycerol fraction by volume with water, and glycerol itself, covering the viscosity range I have studied throughout this chapter. I set the magnitude of the voltage pulse differently for each viscosity, to a magnitude that I estimated would produce steady-state jets speeds between 130 m·s\(^{-1}\) and 140 m·s\(^{-1}\). I repeated the test five times with each fluid.

The position traces from these tests in Figure 26 show the consistency of the results. They reveal a consistent overshoot in the water results, which is not evident in the data from the other fluids tested. Table 3 presents the average and standard deviation for the volume ejected and the steady-state jet speed, the latter measured between 22.5 ms and 25 ms after pulse initiation.

<table>
<thead>
<tr>
<th>Fluid Viscosity (Pa·s)</th>
<th>Average Volume (µL)</th>
<th>SD Volume (µL)</th>
<th>Average Jet Speed (m·s(^{-1}))</th>
<th>SD Jet Speed (m·s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>130.78</td>
<td>0.79</td>
<td>128.00</td>
<td>0.53</td>
</tr>
<tr>
<td>0.012</td>
<td>131.76</td>
<td>0.27</td>
<td>135.22</td>
<td>0.16</td>
</tr>
<tr>
<td>0.109</td>
<td>140.24</td>
<td>0.29</td>
<td>142.07</td>
<td>0.28</td>
</tr>
<tr>
<td>0.635</td>
<td>137.27</td>
<td>0.47</td>
<td>143.81</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Table 3 - Results of consistency tests. The average and standard deviation (SD) for volume and jet speed are shown for 4 fluids (n = 5). Different voltages were used for each viscosity to try achieve an average jet speed between 130 m·s\(^{-1}\) and 140 m·s\(^{-1}\).

To measure the degree of similarity between the different tests, I calculated the maximum cross-correlation magnitude for all comparisons within each data set over a 50 ms period starting from the initiation of the pulse test. 50 ms was long enough to allow the coil to come to a stop after the 25 ms pulse. I identified the minimum point within the results to identify the least similar traces and quantified the degree of difference. The results are presented in Table 4.

The results of the consistency tests show that the VFJI can be relied upon to behave in a certain way when a voltage pulse is applied. With the previous version of the jet injector, the degradation of the piston and ampoule meant that they had to be replaced after every five to ten tests [9]. The process of degradation was gradual causing the behaviour of the injector to be variable. The orifice diameter and the compliance of each piston and ampoule pair also varied, making it hard to determine what the jet speed profile over time would be, as mentioned in Chapter 2. With the VFJI, I changed the piston O-rings
every six tests to ensure any possible degradation did not affect the injector’s operation. The effect of the change of O-ring was not identifiable, suggesting that, with my replacement schedule, the O-rings had little effect on the behaviour of the injector. I expect that in the future, more knowledge about the O-ring’s degradation would allow for a less arduous replacement schedule to be used. The consistency of jet speed development, shown in Table 3, improved the performance of the feed-forward model in the control system. Previously, I have mentioned that the effect of viscosity is less with the VFJI than with the LJI. The consistency of the jet speed achieved with the VFJI allows the model to compensate for viscosity, even if the required change of voltage is less.

<table>
<thead>
<tr>
<th>Fluid Viscosity (Pa·s)</th>
<th>Least similar comparison</th>
<th>Percentage difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>Test 1:Test 5</td>
<td>0.000204</td>
</tr>
<tr>
<td>0.012</td>
<td>Test 3:Test 5</td>
<td>0.000394</td>
</tr>
<tr>
<td>0.109</td>
<td>Test 2:Test 4</td>
<td>0.000515</td>
</tr>
<tr>
<td>0.635</td>
<td>Test 2:Test 3</td>
<td>0.000144</td>
</tr>
</tbody>
</table>

Table 4 - Cross-correlation results for position traces with different fluids (n = 5).

Figure 26 – Coil position results for four different fluids (viscosity indicated) when a 30 ms voltage pulse is applied to the coil. Each test was repeated five times. The similarity of the traces is indicative of the consistency of the injector’s behaviour.
The water test (Figure 26) revealed an overshoot in the position trace, evident when compared to the tests with the other fluids. While some of the compliance may be due to the lower bulk modulus of water in comparison to glycerol, its cause was most likely the presence of an air bubble, stuck on the side within the ampoule. These air bubbles are normally removed by immersing the ampoule in water during assembly and often disappear during repeated use. The effect on the recorded position was minimal, and the steady-state jet speed was still as consistent as the tests with glycerol. A method where the ampoule could be tested for air bubbles, such as that developed at MIT [112], would allow for its effect to be reduced.

4.5.2 Energetic Analysis

By using the same jet force measurement described in Section 3.4.2, I determined the energy carried by the jet. Three other points of reference for the energy in the system were measured in standard testing. These were the electrical energy (the integral of the power of the electrical current running through the coil), the coil energy dissipated as heat (calculated from the power of the current running through the coil’s resistance), and the kinetic energy of the coil calculated from the potentiometer measurements of the coil’s speed. Through the combination of these four measurements, I looked at how the electrical energy was converted within the system as the coil dissipated energy as heat, gained and lost kinetic energy, and the jet gained kinetic energy and then left the system as it emitted out the orifice. A two phase waveform was used to mimic what in testing was revealed as a jet profile that penetrated the pig skin surface.

The jet’s energy over time is presented in Figure 27, as calculated from the recordings of the force transducer. The peak voltage during the first phase was 35.1 V, and the follow-through phase voltage was 8.3 V. The peak jet speed (the jet speed during the penetrating first phase of injection) was 131 m·s⁻¹, and the follow-through speed (the jet speed during the dispersing second phase) was 60 m·s⁻¹. The energy measurements are presented in Figure 27. This figure shows that as the electrical energy was introduced, the coil dissipated some of that energy as heat, but also gained and lost kinetic energy. Additionally, the jet possessed kinetic energy as it left the system. The integral of these measurements is presented in Table 5, indicating the total energy that was spent at each stage of the injection process.
The efficiency of the system was estimated from these measurements as 12.2 %, the percentage of the applied electrical energy was imparted to the jet.

The energetic analysis provided insight into how the system converted electrical energy during an injection. The demonstrated efficiency of the system was reasonable, given its size, the sources of loss that it encounters such as the orifice geometry, and the friction of the system. Most of the energy was lost, dissipated as heat, as the coil transferred the electrical energy into the system to develop the fluid pressure, typical of moving coil motors such as that which I used to apply the force to the fluid.

Improvements in the efficiency of the system would be best achieved by improving the form of the motor so that it suits the application better. For instance, a linear synchronous motor would likely be smaller and provide better efficiency than the motor in the VFJI system.

**4.5.3 High Speed Video of the Jet**

With the new orifice insert as part of the VFJI, I was interested in the form of the jet that would be produced. I used a high-speed camera (Phantom M310, Vision Research Ltd.) to image the jet emitted from the orifice at a speed of 30,000 fps and a resolution of 128x600 pixels. A light source intended for

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<tr>
<td>Integral over 100 ms period</td>
<td>4.72</td>
<td>3.32</td>
<td>0.18</td>
<td>0.18</td>
<td>0.58</td>
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Table 5 - Total energy that passes through the three measurements of energy within the injector system.

![Figure 27 - Energy analysis of jet injection. The blue line in A indicates the change in energy associated with the current that passed through the coil during the injection to produce the injection force. The purple line is the coil energy dissipated as heat. The black line is the gain or loss in kinetic energy that the coil experienced during the injection (10 pt. average), and the red line is the kinetic energy of the emitting jet. B presents the same results, zoomed in on the coil and jet energies.](image)
high-speed imaging (GS Vitec MultiLED PT-V8-15) provided enough backlight to contrast the jet with the surrounding air. I imaged the jet in-plane. The peak jet speed of the emission in this test was 135 m·s⁻¹, and the follow-through jet speed was 50 m·s⁻¹.

Frames from the imaging (Figure 28) showed the shape of the jet at the peak jet speed and the follow-through speed. The shape maintained a fairly constant diameter with parallel edges as it progressed across the frame width. The jet appeared to be affected by some shear forces during its emission. This may have been due to deformities at the emission surface. Distension of the ampoule end was present in the image, visible as the difference in the orifice position between the two images shown.

The high-speed camera imaging of the jet revealed that it was remarkably non-divergent, at least in the plane normal to the imaging and within the first 1.4 mm of travel after exiting the ampoule. This shape was likely a result of the consistently cylindrical section at the end of the orifice insert. In contrast, the commercial ampoule, as used in the LJI, had a gradually decreasing diameter (Figure 29) as the flow approached the orifice. Due to this geometry, the jet of the LJI spread out perpendicular to the jet flow once it had exited the orifice. The spreading of the jet may be a cause of the difference in pressure loss observed between the VFJI and the LJI, but more tests would be required to determine this. The consistency of the jet shape at different jet speeds, evident in Figure 28, will help with future investigations into the effect of the shape of a jet on the penetration of gels and skin. The distension of the ampoule, present in the images, is likely due to movement of the thread at the base of the ampoule as pressure was applied, as this unfortunately introduced some compliance at low pressure until the

![Image](image_url)

Figure 28 - High speed camera images of jet emitted from the VFJI orifice. A: The jet when at peak jet speed (135 m·s⁻¹). B: The jet during the follow-through phase (50 m·s⁻¹).
Thread was locked tight. An investigation into this distension may reveal it to be proportional to the pressure in the ampoule, allowing it to be used as a pressure transducer.

### 4.5.4 Comparison to Lab Jet Injector

The results of the pulse tests performed with the VFJI described in 4.3, and a similar set performed with the LJI are presented in Figure 30. The tests were performed when the temperature in the room was between 22 °C and 25 °C. The figure shows a comparison of the jet speeds achieved with the VFJI compared to that achieved with the LJI. The VFJI achieved a maximum jet speed much higher than the...
LJI. Although the speed reached in direct comparison with the LJI over its range is lower with water, there is less variability with viscosity when using the VFJI. In fact, the range of jet speeds achieved with increased viscosity is more consistent in the VFJI results than the range recorded when using the LJI.

4.5.5 Jet Speed Range and Discharge Coefficient

Extending upon the work that compared the VFJI to the LJI, I performed the same pulse tests as 4.5.1 with fluids containing 95% glycerol (viscosity: 0.311 Pa·s) and 100% glycerol by volume (viscosity: 0.635 Pa·s) in the ampoule. The relationship between voltage and jet speed, as well as the discharge coefficient at different forces, are presented in Figure 31. For medium- to high-applied force, there was little further decrease in the steady-state jet speed recorded with the VFJI as the viscosity increases.

The results revealed that the discharge coefficient is less variable than steady-state jet speed. Due to their higher density, glycerol jets (density of 1260 kg·m⁻³) are expected to have lower jet speeds even when ignoring viscous effects. The calculation of discharge coefficient accounts for any variation in density between fluids, causing the decrease in variability I observed. When applied force is below 100 N, the fluid of the highest viscosity (0.635 Pa·s), exhibited a much slower steady-state jet speed than water, and the discharge coefficient dropped below 0.5, significantly lower than values calculated for the other fluids tested. The results with this fluid showed a non-linear dependence of jet speed on the steady-state force, where the slope reduces as steady-state increases above 200 N (Figure 31A).

4.5.6 Effect of Changing Orifice Diameter

I performed a set of pulse tests, similar to that presented in section 4.5.5, with three other orifice inserts screwed into the end of the stainless steel ampoule. As the orifice diameter and the fluid in the ampoule changes, the steady-state jet speed and the discharge coefficient of the flow varied (Figure 32). When the 100 µm orifice insert was fitted, the recorded jet speeds at low power were slower with the 0.109 Pa·s and 0.635 Pa·s fluids loaded. A decrease in recorded jet speed was evident when I applied lower levels of force and used the 150 µm orifice insert, and the discharge coefficient decreased at low levels of force across all orifice inserts.

Apart from these trends observed when the orifice diameter and force are at low levels, the results for both estimated jet speed and discharge coefficient remained remarkably similar for different orifice inserts, across the central range of applied forces. For instance, I found it striking that the discharge coefficient results with the different orifice inserts overlapped when the fluids with 0.001 Pa·s, 0.012 Pa·s, and 0.108 Pa·s viscosity were in the ampoule. In these plots, the consistency of discharge coefficient across different orifice diameters revealed that the discharge coefficient was proportional to
the applied force. With the VFJI, viscosity had a greater effect on the jets formed through the 100 µm diameter orifice than any of the other orifice inserts. Glycerol jets were significantly slower at low applied force, but reached a similar jet speed as the other less viscous fluids when the applied force is above 500 N. As the orifice diameter increased, variability between the fluids decreased, with the 310 µm orifice unaffected by viscosity (other than a slow down with the 0.635 Pa·s fluid at low speed). Overall, the range is similar to that experienced with the orifices of Lichtarowicz et al. [105] who recorded coefficients between 0.6 and 0.9 over a wide range of geometries.

Schramm-Baxter et al. [77] recommend jet power \( \frac{1}{2} \pi \rho D_o^2 v^2 \) whereby \( \rho \) is the density of the fluid, \( D_o \) is the diameter of the jet and \( v \) is the velocity of the jet) as an indicator of a jet's ability to inject into gels and pig skin, correlating jet power with depth of injection [77]. I present the results of evaluating the jet power resulting from the pulse tests in Figure 34. The results showed that, for the most part, the greater the orifice diameter, the greater the jet power. The nature of this relationship is uniform across the results.

The plot of discharge coefficient versus Reynold's number (Re) suggests that at least part of the trend in discharge coefficient can be correlated to the Re. However, the increase at higher Re numbers doesn't match the scale between the two least viscous fluids. Therefore, my data analysis focused more on the fluid's across the viscosity range and across the orifice diameters rather than the trend that was observed as the Re of the flow changed.

![Figure 31](image_url)

**Figure 31 – A:** The jet speeds achieved during voltage pulse tests across all viscosities, plotted against the steady-state force.

**B:** The discharge coefficient at four of these viscosities plotted against the force applied in steady state to the injector.
Figure 32 - Relationship between steady-state force and both jet speed (1), and discharge coefficient (2) with different orifice diameters using a range of viscous fluids (A: 0.001 Pa·s, B: 0.012 Pa·s, C: 0.108 Pa·s, D: 0.635 Pa·s). The orifice diameters measured 100 µm (blue cross), 150 µm (orange cross), 200 µm (black cross), and 310 µm (green cross).
Figure 33 - Relationship between steady-state force and both jet speed (1), and discharge coefficient (2) using different viscous fluids over a range of orifice diameters as indicated (A: 100 µm, B: 150 µm, C: 200 µm, D: 310 µm), a representation of the data from Figure 32. The fluids tested had viscosities of 0.001 Pa·s (blue plus), 0.012 Pa·s (orange plus), 0.109 Pa·s (black plus), and 0.635 Pa·s (green plus).
Figure 34 - Jet power achieved in steady-state with different viscous fluids across four tested orifice diameters. A: the results with the fluid with a viscosity of $0.001 \text{ Pa}\cdot\text{s}$. B: the results with a fluid of $0.012 \text{ Pa}\cdot\text{s}$ viscosity. C: the results with a fluid of $0.109 \text{ Pa}\cdot\text{s}$ viscosity. D: the results with a fluid of $0.635 \text{ Pa}\cdot\text{s}$ viscosity.

Figure 35 - Plot of discharge coefficient ($D_C$) versus Reynold's number. The blue crosses (×) are the results with an orifice of $100 \mu\text{m}$ in diameter, the red diamonds (♦) are the results with an orifice diameter of $200 \mu\text{m}$ and the green circles (○) are the results with an orifice diameter of $310 \mu\text{m}$.
4.6 Discussion

As the VFJI was tested, it became evident that the pressure loss within the ampoule has a major effect on the performance of the injector, particularly in terms of the jet speed achieved. As mentioned previously, the jet speed is a critical determinant of success in piercing the stratum corneum. The loss is dependent upon the viscosity of the fluid being injected as well as the geometry of the internal fluid chamber of the ampoule. The comparison of the LJI and the VFJI in Figure 30 demonstrates how a geometry change can lead to a substantial reduction in pressure loss. The outcome is an improvement in the efficiency of jet injection with viscous fluids.

Viscosity has little effect on the jet speed achieved with the VFJI at low pressure. At higher pressures, an increase in the percentage of glycerol of the ampoule fluid is accompanied by a decrease in the jet speed. However, this decrease is mostly due to glycerol's higher density when compared to water. In comparison, the results of testing with the LJI demonstrate a different trend. The influence of viscosity on jet speed is close to uniform across all speeds, and it is always more than what is experienced with the VFJI. I conclude that the change in geometry from the commercial to the new stainless-steel ampoule has drastically reduced the pressure loss due to the viscosity of the fluid. The cause of this will be further investigated in Chapter 5.

The results of testing with the 200 µm orifice insert begin to reveal the capability of the new VFJI. Tests with the new fluids (0.311 Pa·s and 0.635 Pa·s) exhibit a large pressure drop at low speeds. With the 0.635 Pa·s fluid, the effect results in a non-linear dependence of jet speed on steady-state force as a large pressure drop dominates the determination of jet speed at forces below 200 N. The trend indicates that viscosity will affect jet delivery much more during the follow-through phase of jet injection than the high-force, high-speed penetration phase. I suggest that the cause of the pressure drop below 200 N is due to one or both of two phenomena. The first potential cause is that the nature of the flow changes when highly viscous fluids are formed into a jet within the ampoule at low speeds. The change is likely to be related to the change from a turbulent to a laminar flow as viscosity increases and Reynolds number drops, allowing the boundary layer at the wall to slow down the average speed of the flow. However, I believe that the discharge coefficient is best observed across viscosities rather than Reynolds number (Re) as the results did not show a strong correlation with Re. This lack of dependence on Re is likely due to the dominance of the sudden contraction form of the flow in comparison to the Re-dependent pipe flow that would occur in the latter section of the orifice geometry. The contribution of internal ampoule flow effects is further investigated in Chapter 5.
The results reveal that a 100 µm orifice is not well suited to injection of viscous drugs above 0.1 Pa·s. The test that confirms this is the one in Figure 33A-2 with glycerol (0.635 Pa·s viscosity), which demonstrates a discharge coefficient of around 0.2. While the VFJI can still get the fluid up to a speed that would be able to pierce through the stratum corneum, it requires a much greater force than other orifice sizes need to reach that speed, and the results demonstrate a significant increase in loss with the smaller orifice.

It is particularly surprising that jet speeds and discharge coefficients are similar for the majority of the tests as the orifice diameter changes. When I started these tests, I expected that there would be a greater difference of discharge coefficients. This expectation was due to the results from my previous tests with the original injector [99] that had yielded a similar range of discharge coefficients with fluids of lesser viscosity and without changing the orifice diameter. The difference between tests with different orifice diameters at low power is important, but so too is the similarity of results otherwise. The invariability is evident in the graph of volumetric jet speed achieved with fluids with 0.109 Pa·s viscosity. This viscosity is similar to that of olive oil, which I would expect to resist flow. However, the jet speeds at a constant force remain consistent as the orifice diameter changes. It appears that, within the range presented, the nature of a pressure drop across an orifice depends little upon the diameter of the orifice, even as viscosity increases. I conclude that a device with an orifice diameter in the moderate range of what is demonstrated here, and with the geometry that I used, can reliably inject a wide range of viscous fluids, as the effects of high viscosity are easily accommodated.
4.7 Conclusions

At the conclusion of this chapter’s work, I had developed a jet injection system for viscous fluids, the VFJI. The new system made use of stainless steel components to greatly reduce the compliance of the system in comparison to the LJI. It used a commercial orifice insert to allow the orifice diameter to be changed. The control system of the VFJI combined both a feed-forward model and a feedback system, allowing a wide range of viscous fluids to be injected with the system through the use of two bridged amplifiers.

I conclude that an orifice diameter around 200 µm is best for viscous fluid jet injection. Straying too far below 200 µm will reduce the range of viscous fluids that can be injected with the system as it becomes harder to load highly viscous fluids and to get them up to speed with a portable motor. The set of results presented in this chapter make clear the impact of viscosity on jet formation, and that orifice diameter remains dominant over viscosity in the determination of the power of a jet formed within a jet injector, at least for the geometry of the ampoule and orifice inserts that I used.

The general consistency of discharge coefficients away from the extremes gave me great confidence in the device’s ability to form highly viscous jets that could pierce through the skin, over a wide range of orifice diameters. The results also highlighted that the new orifices exhibited more reduced pressure losses than I expected given their sharp geometry. This result is further investigated in the next chapter. The shape of the jet, produced with the new orifices, suggested a much more collimated jet, likely to further intensify the impact of the jet, and improve its ability to pierce through the surface of the skin.

It is clear the system produced repeatable results, easing investigation into the nature of viscous drug delivery. After creating the device and testing it, I moved onto investigating the impact of ampoule geometry as fluid is forced out the orifice, for both the LJI ampoule and that of the VFJI. I present that investigation in the next chapter.
5 The Effect of Orifice Design on Jet Formation

5.1 Introduction

5.1.1 Purpose and Computational Fluid Dynamics Approach

The testing of the new viscous fluid jet injector (VFJI) presented in Chapter 4 measured the viscous loss occurring in the injector for two ampoules: a commercially available disposable cartridge jet injector (DCJI) ampoule and a stainless steel ampoule with an interchangeable commercially available orifice. However, this testing provided no indication about the location and nature of the viscous loss in the ampoules. The Navier-Stokes equations, which describe the motion of the fluid in the ampoule, could enable me to investigate the viscous loss. Unfortunately, these equations have no analytical solution, and no simplification was applicable as neither inertial nor viscous effects dominate across the full range of viscous fluids I intended to investigate. This range invalidates the assumptions used to form linear approximations for Stokes flow, and those required to apply the Bernoulli equation alone. Therefore, I pursued a computational fluid dynamics (CFD) approach to investigate the causes and location of the loss by applying the Navier-Stokes equations to a discretisation of the flow field in the ampoule. I identified the finite volume method (FVM) as the best option for discretisation as, unlike the alternative finite element method, it is conservative. This property ensures that the flux throughout the flow field is conserved [113]. I chose the program ANSYS FLUENT (ANSYS Inc., Canonsburg, PA, U.S.A.), a commercial CFD solver, to implement this method as it supported axisymmetry, was readily available and had been used previously in the literature [114], [115]. The viscous loss I was investigating was primarily of two forms: turbulent loss (a result of eddies forming in the flow field); and frictional loss (a result of the interaction of the fluid with the wall, and the smooth flow of the fluid particles past each other). I intended to investigate both of these sources of loss in the two ampoules tested in Chapter 3.

The FVM divides the problem domain into a set of elements with nodes at the corners. A set of discrete control volumes are defined, centred on the nodes in the surrounding elements, as illustrated by Figure 36. The volumes extend halfway towards the next node in each direction, abutting the other node’s control volumes. The method solves the appropriate equations on each of these volumes in order to
determine the solution over the whole domain [113]. The FVM as part of a CFD simulation can provide approximate solutions to many fluid mechanics problems and, if these results are validated, the resultant model can provide insight into the physical behaviour that underlies the predicted response of a system. In my application, the equations of conservation of mass, momentum, and energy are applied to the control volumes via a pressure-based solver, and the Gauss divergence theorem (which conserves flow throughout the domain) is used to convert the volume integrals into surface integrals. The integrals are discretised, and the equations are solved numerically until they reach a steady-state within a set tolerance level.

5.1.2 Literature Review

Often, empirical measurements guide the choices of geometries for high-speed jets [103]. However, extensive CFD modelling has been used to model the behaviour of fluids in fuel injectors. These are similar to drug jet injection geometries in that they involve a reduction to an orifice diameter near 150 µm and an emitting jet. However, the ratio of this reduction is of a smaller scale (ratio of 9:1 rather than 18:1), and involves passing through the gap between a needle and the wall of the cylinder (of around two times the orifice diameter) and, in multi-hole injectors, flowing around an angle of up to 90°. Models for fuel injectors have included both single-hole [111], [114], [116]–[120] and multi-hole fuel injectors [121], and involve a geometry where the fuel is forced past a cylindrical needle and out through an orifice into the engine's cylinder. Often the contraction to orifice diameter in these devices

Figure 36 - Illustration of application of finite volume method (FVM) to a simple fluid flow problem. The control volumes (dashed orange lines) are visualized around the central nodes (orange dots) of the mesh. These control volumes are also defined around all other nodes.

Equations applied to each control volume
is sharp, causing flow separation and large drops in pressure below atmospheric levels. These drops can cause cavitation, where the drop in pressure forms vapour in the flow. This vapour takes the form of bubbles which greatly modify the flow conditions around them and can burst, producing a shockwave.

Most modelling in this field has applied the finite volume method using commercially available CFD solvers such as FLUENT [114], [119] or KIVA3 [111] with some researchers [118], [121] developing their own code. The guidance from these papers indicates that smooth profiles and small angles reduce turbulence and the likelihood of cavitation, increasing the overall speed of the fluid out the orifice. One group also recommends conical nozzles in comparison to cylindrical nozzles as they avoid boundary layer separation [119]. Some researchers have explored the interaction between the jet and air as they interact in the engine's cylinder [117], as the ratio of these fluids impact greatly on the efficiency of fuel consumption in engines. Most of this work is limited to the viscosities of diesel and petrol fuel, which are of the same order as that of water (~0.00335 Pa·s for diesel at 25 °C [122]).

Jets are also formed from gas flows, and the modelling of this process can provide some guidance for liquid simulations. As part of a compressible flow simulation, the internal geometries used in aeroacoustics to form jets were studied by Viswanathan and Clark [123]. Aeroacoustics is the study of using turbulent flows to generate noise, so the focus was more on the turbulence than the speed of the emitted jet. While only exploring the effect of a reduction in diameter of a half, Viswanathan and Clark investigated three different profiles: a conic profile, a geometry designed by the American Society of Mechanical Engineers (ASME), and a cubic profile. Their investigations revealed that the cubic profile exhibited the lowest pressure loss, with the boundary layer staying close to the wall as the diameter reduced. They also showed that the turbulence induced by the contraction acts near the wall and was related to the geometry of the profile.

Other gas simulations have included the effect of viscosity in different geometries. Viscous flow in a convergent-divergent nozzle was simulated by Khan et al. [124], and their results indicated that the onset of shock in the nozzle and the resultant boundary layer formation had a significant effect on the results of the flow. Their modelling suggested that separation of the flow from the wall significantly affects the nature of the flow and they suggested that close attention should be paid to the nature of this separation and its reattachment to the wall. One study at supersonic speeds in a gas flow [125] indicated that heat loss from the flow helped to reduce viscosity near the wall, increasing the speed of the resultant flow through the orifice. This effect occurred mainly through a reduction of the extent of the boundary layer itself. From this study, I observed that the temperature of a fluid can affect its
viscosity, with viscosity generally increasing with increasing temperature in gases and decreasing with increasing temperature in liquids.

CFD has recently been applied to investigate the mechanics of the formation of a jet for needle-free injection by several groups. Jet injection was a focus of work by Seehanam et al. [126] where they investigated the formation of jet speeds faster than that of sound in air. Their investigation covered the development of the required fluid pressure through both the impact of a projectile on an ampoule of fluid as well as the impact of a projectile on a piston coupled to a similar ampoule of fluid. They looked at both a conical and stepped nozzle with a focus on the transient development of the jet within the first 90 µs after impact. They revealed that the piston method reduced the transient driving pressure for a projectile of the same momentum, but did not reveal which shape provided the quicker jet speed.

Another paper, by Li et al. [127], used FLUENT 6.0 (Fluent Inc., Lebanon, NH, U.S.A.) to simulate the behaviour of their insulin powder when it was accelerated in a de Laval nozzle. These nozzles have the geometry of a tube that is narrowed in the middle. They focussed on the speed of the powder (which was greater than the speed of sound in some locations) and its temperature before impacting the skin. While the nature of their problem was somewhat similar, powder can be expected to behave very differently from fluids, and their nozzle was quite different to that used in fluid jet injection. The nozzle was both much longer (around nine centimetres), and thinned, then expanded, as the drug travelled along it. Therefore, the work of Li et al. provided little guidance for the work I wanted to pursue.

However, Nakayama et al. [128] have recently developed a computational model of an air-pressure driven jet injector of water, looking at the development of pressure in the ampoule, the production of the jet and the interaction of the jet with the air outside the ampoule. Their CFD model used a moving wall coupled to a mechanical model to create pressure in the ampoule and a stepped orifice to produce the jet. They focussed on the stagnation pressure of the jet, and revealed that the standoff distance of the nozzle does not affect its impact force, and found that friction had an important effect on the dynamic profile of the pressure applied to the skin. They also showed that the orifice diameter had little effect on the speed of the jet when a consistent pressure is applied, as long as it stayed close to the standard orifice diameters used in jet injection. This observation is in accordance with the results presented in the previous chapter. However, Nakayama et al. did not vary viscosity when they characterised their model and explored just one geometry, with little focus on the exact nature of the flow in the ampoule.

CFD also allows me to predict the level of shear that is experienced by the drug as it passes through the orifice. Shear can cause proteins such as monoclonal antibodies to denature, which reduces their effectiveness as a drug treatment [90]. Chavan et al. have suggested that the ability to reduce shear is a
benefit of jet injection as the drug does not travel along the relatively long wall of a needle [129]. However, during jet injection the drug does still travel along the walls of the nozzle at speeds much higher than those experienced in a needle, and the shear associated with this is of much greater intensity. A study by Thomas and Geer [130] investigated the effects of shear on proteins during the creation of drug formulations in factories. This study concluded that air/liquid interfaces were the major source of the denaturation of the protein, and hydrodynamic shear was a secondary cause during drug processing. The work showed that shear stress rates up to $32,000 \, s^{-1}$ could be experienced by protein solutions without denaturation. A study by Bee et al. [90] exposed the drug to even higher rates of up to $250,000 \, s^{-1}$ and still did not show any significant denaturation. They predicted that rates above $10^{-7} \, s^{-1}$ would be the minimum required for denaturation without cavitation or an air-liquid interface. Unfortunately, there is no record of a study that looked directly at the effect of shear during jet injection, though Baxter and Mitragotri [131] called for such studies in order to ensure that jet injection is a viable method for delivery of high-concentration protein drug solutions.

### 5.1.3 Outline of Investigation

In this chapter, I present my work using CFD to simulate the expected flow through the ampoule of a jet injector. I first simulate a commercial ampoule (U-100, Injex Pharma Gmbh) that was used in the work by Taberner et al. [9] and modelled in Chapter 2. The mean jet speed is calculated by rotating the results of a 2D axisymmetric model around the centre of the flow, calculating the volumetric flow rate and dividing it over the area of the orifice. This value, when compared to the jet speed expected by the Bernoulli equation, is indicative of the viscous loss inherent in the design of the approach to the orifice (Figure 37). I compare the simulation results for the commercial ampoule to experimental results and then investigate the causes of loss in the ampoule. I then evaluate the shear rate experienced by the simulated drug to indicate the magnitude of shear, allowing me to estimate its effect on drug delivery of protein solutions. Following this investigation, I apply the same method to the stainless steel ampoule presented in Chapter 3 with a $200 \, \mu m$ orifice insert (ZMNS-8-M3.5-SS-BN, O'Keefe Controls Ltd.). I compare the results of the simulations with the experimental results from Chapter 4 and comment on their match. I then use the model to pinpoint the major sources of pressure loss for both modelled ampoules and use these results to suggest ways in which the losses can be reduced in the future design of ampoules for jet injectors.
Figure 37 - Diagram indicating area of device where viscous energy loss occurs.
5.2 Commercial Ampoule Simulation

5.2.1 Structure and Settings of Computational Model

A commercial CFD package (ANSYS FLUENT 13.0, ANSYS Inc., Canonsburg, PA, U.S.A.) was used to investigate the nature of viscous loss in the commercial ampoule. This program was chosen as it supported axisymmetry and had been used previously in the literature. ANSYS Workbench is the central environment that provides access to the many programs that handle different parts of the CFD process within ANSYS (Figure 38).

The first step was to get an accurate 3-D model of the internal wall geometry of the commercial ampoule. Michael Byrne, a lab technician at the ABI, imaged the Injex ampoule using a micro-CT (Bruker Skyscan 1172) and formed a 3-D model in SolidWorks (Figure 39). I fit a 2-D profile to the model along its length with the radius set by the average of the radius in the 3-D model. The profile exhibited a 23 µm RMS error along its length, which covered 5.5 mm from the orifice end. I assumed that the physics of the flow could be adequately captured by a 2-D axisymmetric simulation using this profile, which is much less computationally expensive than a full 3-D simulation.

I imported the 2-D SolidWorks model directly into ANSYS Workbench. I chose to mesh the geometry with a minimum element size of 0.1 µm and a maximum element size of 7.5 µm as these settings gave a fine mesh with a moderate number of elements (131,000). The final mesh is presented in Figure 40. I used tetrahedral elements throughout the mesh. Along the ampoule wall boundary, I applied an inflation layer condition to the mesh (visualised in Figure 41) to increase the size of the elements that are further away from the wall of the model. In the inflation layer, the elements were thin, and the sides parallel to the wall were long in comparison to the orthogonal direction. This pattern was used because the velocity gradient normal to the wall is much larger than that parallel to the wall. My inflation layer forced 20 elements between the wall and a parallel boundary 15 µm from the wall, with the elements increasing in size at a rate of 1.05. I chose this number of layers as the resultant jet speed profile output from the solver was smooth, and this number provided a smooth transition to the mesh density nearer the centre of the flow. The inflation layer ensured that the first element had a dimensionless wall distance (y+) of around 4, placing it comfortably within the viscous sub-layer for flows of water. I defined circles of influence to refine the mesh in areas that in previous simulations had been a source of high residuals during the solution. These areas were where the diameter approaches that of the orifice, and along the narrow section near the orifice (see Figure 40). They were refined to an element size of 2.5 µm.
Figure 38 - Flow diagram of ANSYS Workbench environment.

Figure 39 – Micro-CT reconstruction of the inside of the commercial ampoule. The orifice and direction of flow are indicated.
The flow in the simulation progressed from the left hand side towards the right hand side of the mesh in Figure 40, moving from where the pressure is applied to where the jet emits out of the orifice at speed. Momentum, mass, and energy are conserved across the domain. The primary transfer of energy in the domain was from that of pressure potential energy to kinetic as the jet gathers speed as well as from kinetic energy to heat due to interactions with the wall and within the fluid itself.

The next step was to define the boundary conditions with in FLUENT as indicated on the mesh in Figure 40. I applied a 'wall' boundary condition along the inside wall of the ampoule, which ensures no movement across the boundary and assumes that the wall is stiff. The heat transfer setting along the wall was made to be adiabatic, so heat is not transferred across the boundary. This setting ensured heat arises only from viscous dissipation as the flow is developed. At the left-hand-side of the model, where the pressure from the piston is applied, I defined an inlet boundary condition using a user-defined constant gauge pressure of 10 MPa, but allowed flow across the boundary. At the orifice, I defined an outlet condition, setting the relative pressure at the boundary as 0 Pa. The inlet restricted the flow so it was perpendicular to the boundary and the outlet restricted any backflow. I set the simulation as axisymmetric and set an axis boundary condition along the bottom of the profile. FLUENT used this boundary to make a 7.5° wedge of one element by rotating the flow profile around it.

To account for the influence that the surface of the polycarbonate wall has on the flow, I measured the roughness of the standard Injex ampoule. Firstly, I cut an ampoule in half using a band saw to expose the inside of the ampoule. I used a surface roughness tester (Surftest SV-2100, Mitotuyo Ltd.) to measure the RMS roughness of the inside surface. The roughness height is the required input in
FLUENT. This input was set to 0.912 µm along the wall, equivalent to three times the measured RMS roughness, [132]. I input this value into the software and, with this completed, all boundaries were defined, and the problem was ready to be solved.

Turbulence was accounted for by Menter’s shear stress transport (SST) model [133], a two-equation turbulence model that simulated the transfer of momentum due to eddies in the flow with an extra viscosity termed the eddy viscosity. This particular model is effectively a combination of two other turbulence models: the k-epsilon turbulence model and the k-omega turbulence model. Both models define two equations that calculate the kinetic energy in the turbulence (k) and the dissipation of this energy (noted as epsilon or omega, depending on the model). More information about the structure of these models can be found in [133] and [134]. In the SST model, the k-epsilon model is used in the free flow far from the wall and the k-omega turbulence model is used in the near-wall section of the boundary layer. The SST model is structured this way to avoid the sensitivity of the k-omega model to inlet turbulence properties and the sensitivity of the k-epsilon model to severe pressure gradients (such as those encountered in the ampoule during jet injection). As a result, the model is also able to be used right down to the wall without the extra damping functions that would be required if the k-epsilon model was used alone.

The solver was set to a minimum number of iterations of 25 and a maximum number of 40,000. The time increment at each stage was set by the solver and the iterations increased until a steady state was reached.

Figure 41 – Screenshot of inflation layer outline (thick blue dotted line) within ANSYS meshing along curve of commercial ampoule wall. The red box shows where along the profile the inflation layer is shown.
reached. The residual target was set as a RMS average of $1 \times 10^{-7}$. A review of the results of early simulations revealed that this was sufficient to achieve a steady-state profile for the jet speed out the orifice. Three of the four cores of my computer’s processor (Intel Xeon W3520) ran the simulation in parallel using double precision floating-point numbers. Within the simulator, I extracted the results for four fluids: water and solutions of glycerol at 60 %, 85 %, and 100 % fraction by volume with water.

The fluids were defined in ANSYS as materials, with the density and molar mass set using the material tables available in ANSYS. Glycerol’s viscosity is temperature dependent. I included viscous heat in the equations of the CFD solver and defined the viscosity of the various glycerol-water solutions with an equation that depended upon the temperature of the fluid. The equations were obtained from a paper by Chen and Pearlstein [135]. Their results revealed that that an increase in the temperature of glycerol from 25 °C to 50 °C reduces the viscosity of the fluid from 0.635 Pa·s down to 0.124 Pa·s, much nearer to that of an 85 % glycerol solution at room temperature (0.108 Pa·s).

To ensure mesh and time independence, I re-ran the simulation several times with 10 MPa as the applied pressure at the inlet and with water as the fluid. Each time, I changed mesh parameters and output the resulting orifice speed profile. In these simulations, I set the maximum element sizes to 6 µm, 7.5 µm, 9 µm, 12 µm, 15 µm, and 20 µm and the element size in the refinement regions to 1.6 µm, 2.5 µm, 3 µm, 4 µm, 6 µm, and 8 µm respectively. To compare the results, I measured the RMS velocity difference between the resultant orifice speed profiles for each test. The results provided an indication of how consistent the solver was as the mesh changed in complexity.

### 5.2.2 Mesh Independence

Mesh convergence testing results (Table 6) revealed that the results converged as the node and element count increased. The mesh used in the tests later in this chapter (maximum mesh element size of 7.5 µm – simulation 5) was within 0.2 m·s⁻¹ RMS difference of the finer mesh (maximum mesh element size of 6 µm – simulation 6), even though it had many fewer elements. Based upon the results of the convergence study, I assumed that the mesh I used (as in simulation 5) was sufficient to gain a result within 1 m·s⁻¹ RMS error of that expected if computational resources were unlimited. The differences were less with fluids with greater viscosity than that of water.

The simulations took around seven hours to converge to a steady-state flow, with the high-viscosity glycerol simulations up to two hours quicker.
### 5.2.3 Turbulence Variation

To test the sensitivity of the simulation to turbulence introduced at the inlet, I modified the boundary condition to have different levels of turbulence intensity and re-ran the simulation. To do this, greater fluctuations in velocity are introduced along the velocity profile at the inlet. I set the turbulence intensity to 1%, 5%, and 10% across three different simulations. These percentage values refer to the RMS velocity of the turbulent fluctuations as a percentage of the mean velocity of the flow at the boundary. The RMS velocity differences from the 1% jet speed profile of the 5% and 10% simulation jet speed profiles are shown in Table 7. For all simulations, water was the fluid in the ampoule.

<table>
<thead>
<tr>
<th>Turbulence setting at inlet</th>
<th>1%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Jet Speed (m·s⁻¹)</td>
<td>135.4</td>
<td>135.3</td>
<td>135.3</td>
</tr>
<tr>
<td>RMS Velocity Difference from 1% (m·s⁻¹)</td>
<td>n/a</td>
<td>0.0601</td>
<td>0.0900</td>
</tr>
</tbody>
</table>

Table 7 - RMS velocity differences in jet speed profiles at orifice between simulations with 5% turbulence and 10% turbulence compared to the simulation with 1% turbulence. The mean jet speed is also indicated. The turbulence is applied at the pressure boundary condition.

The sensitivity analysis showed that little difference is observed as the turbulence at the inlet changes. The maximum difference recorded with 10% turbulence intensity was a 0.0900 m·s⁻¹ RMS velocity difference. Simulations with fluids with greater viscosity in the ampoule showed lower RMS velocity difference than that presented in these results.
5.3 Results from Computational Model of Commercial Ampoule

5.3.1 Jet Speed Profiles

I applied an inlet pressure of 10 MPa in ANSYS for four different fluids; water, and simulation of 60 %, 85 % glycerol, and 100 % glycerol fraction by volume with water. I exported the jet speed profiles from ANSYS in CFD-post. The results are presented in Figure 42, where they show that the simulated jet profile changes shape as viscosity is increased. The jet speed profile when water is forced through the orifice is similar to plug flow with high gradients near the walls and a wide central maximum of the jet speed. The Reynolds number (Re) of this flow at the orifice is approximately 24,100. The flow of glycerol (Re of ~13.1) still has a steep section near the wall, likely caused by viscous heating and the temperature dependence of the viscosity of glycerol. However, its approach to its lower central maximum does not flatten out like the profile for water. Meanwhile, the 85 % glycerol jet (Re of ~138) and the 60 % glycerol jet (Re of ~1,800) profiles sit somewhere in between these two profile types, with the central maximum extending up and out as the glycerol concentration decreases, increasing the mean jet speed of the flow.

It is important to consider the entrance length, or the length of pipe required for development of the flow [136]. Only the flow of glycerol is expected to have fully developed by the time it reaches the orifice, as its entrance length is 180 µm. Empirical loss equations such as the Darcy-Weisbach equation [137] do not apply in this case as the flow does not have constant physical properties — its temperature varies across the flow. Therefore, the flow profile of glycerol at the orifice presents as a modified form of laminar flow with high gradients at the sides due to viscous heating. The undeveloped

![Figure 42 - Jet speed profiles at the orifice of the commercial ampoule resultant from simulations with applied pressure of 10 MPa (indicated viscosity is that measured at room temperature).](image-url)
form of the flow for fluids of lower viscosity than glycerol is partially responsible for their atypical shape.

5.3.2 Comparison with Experimental Results

I intended to use the mean jet speeds determined through fluid testing with the jet injector to validate the model. As I did not measure the pressure when obtaining the mean jet speeds of flows through the commercial ampoule (Figure 43), I had to assume that the friction coefficient is around 0.17 in order to estimate the pressure in the fluid. This is consistent with the range in Section 3.6. Thereby, I could use the experimental results to assess how well the simulation replicates the results of experiments.

The results (Figure 43) match well for the range of fluids with viscosity up to approximately 0.1 Pa·s at room temperature (25 °C), with the simulated mean jet speed within the error bars of the experimental mean jet speed. In this case, the error bars in the figure indicate the change in mean jet speed that would occur if the friction coefficient and orifice diameter were set to the extremes of both the approximation of friction coefficient and the bounds of error in measuring the orifice diameter. However, for fluids with room temperature viscosities higher than 0.1 Pa·s, the simulation starts to overestimate the loss that occurs in the ampoule. The results with glycerol are particularly different and will be further discussed in section 5.4. In the meantime, I will further analyse the maps presented in CFD-Post that indicate the nature of the flow.

![Figure 43 - Comparison of simulated and experimental mean jet speeds across a range of viscosities (at room temperature) for the commercial ampoule.](image-url)
5.3.3 Qualitative Results

The coloured maps over the simulation area in Figure 44 and Figure 45 provide some explanation for the profiles presented in the previous section. The map presented in Figure 44A shows the magnitude of the turbulence kinetic energy for water when the applied pressure is 10 MPa. According to the map, the main concentration of the loss is near the wall along the ‘neck’ of the 2-D profile approaching the orifice. With glycerol (Figure 44B), the turbulence loss is diminished. However, the walls enforce a laminar flow pattern upon the jet speed profile, a phenomenon that is in accordance with the flow’s Reynolds number of approximately 11.3. The pressure profile presented in Figure 45 shows that the commercial ampoule does a good job of smoothing out the pressure as it drops to zero along the approach to the orifice. The pressure maps for water (0.001 Pa·s viscosity) and glycerol (0.635 Pa·s viscosity) simulations indicate no significant difference between them and so only one is shown here.

5.3.4 Shear Rate

The simulation results also predict the shear rates as the fluid is accelerated through the orifice. The commercial ampoule profile develops shear along the wall as the flow gradually approaches the orifice diameter. In this approach, the fluid reaches a maximum shear rate of $1.32 \times 10^8$ s$^{-1}$ in the simulation with water and an average peak shear rate for the fluid of $1.57 \times 10^6$ s$^{-1}$. This second parameter indicates the peak shear that the average particle in the flow would experience. The simulation also

![Figure 44](image-url) - Visualisation of turbulence in commercial ampoule flow. A shows the turbulence kinetic energy of the simulation with water. B is the turbulence kinetic energy of the simulation with glycerol.
predicts that only 3.79% of the water flow experiences a shear rate over $1 \times 10^7$ s$^{-1}$. The simulation with glycerol predicts a maximum shear rate of $9.82 \times 10^7$ s$^{-1}$ and an average peak shear rate of 649,000 s$^{-1}$.

Figure 45 – The simulated steady-state pressure profile for the commercial ampoule with water as the internal fluid.
5.4 Investigation of the Simulation Settings with Glycerol

5.4.1 Process of Investigation

In order to better understand the discrepancy between the simulation results and the experimental mean jet speed results, I investigated the effect of a wide range of parameter values and model options in the modelling environment. I used the simulation of glycerol (viscosity of 0.635 Pa·s) in the commercial ampoule as this simulation exhibited the greatest discrepancy with the experimental measurement.

The base simulation for these investigations is that presented in section 5.2. The unique property of each of the range of simulations follows, with the shortened reference terms in brackets:

- no temperature-dependence of viscosity \(\text{(No TDV)}\)
- disabling the turbulence model \(\text{(Laminar)}\)
- enabling temperature-dependent thermal conductivity, based upon the results of \([138]\) \(\text{(TDTC)}\)
- allowing deformation of the inside wall of the ampoule according to its mechanical properties and the pressure in the fluid \(\text{(deformed)}\)
- solving a model with a coarser mesh, but in full 3-D, rather than axisymmetric 2-D \(\text{(Full 3-D)}\)
- enabling temperature-dependent specific heat capacity and density, based upon the results of \([139]\) and \([138]\) respectively \(\text{(TDD+SHC)}\)
- the use of a second order (instead of first-order) interpolation for all equations \(\text{(Second Order)}\)
- enabling pressure dependent density (making the fluid compressible) \(\text{(Compressible)}\)
- a simulation where the temperature of the fluid initially and at the inlet and outlet is 30 °C \(\text{(30 °C)}\)
- a simulation with 5 µm roughness height at the wall instead of 0.912 µm \(\text{(5 µm Roughness)}\)
- a planar simulation with a symmetry boundary condition at the centre of the flow rather than an axial boundary condition \(\text{(Planar)}\)

I systematically computed the resulting flow field for each of these options in order to discover which (if any) might better reproduce the measured flow properties.
5.4.2 Results from Range of Simulations with Glycerol

The mean jet speeds at the orifice extracted from the results of the simulations are presented in Figure 46 and Table 8. The results show that the simulation predicted a much lower mean jet speed when the effect of the viscous heating on the viscosity of the fluid was ignored, implying that this effect played a significant role in the determination of jet speed with viscous fluids. A small decrease was observed when the turbulence model was turned off and when a full 3-D model was used. No significant change was predicted when the thermal conductivity was made temperature-dependent and both the specific heat capacity and density were made temperature-dependent. Additionally, the mean jet speed changed little when the mesh was deformed, when second order interpolation was used and when the fluid was made compressible. A model solved at the higher temperature of 30 °C showed approximately 10 m·s⁻¹ increase in mean jet speed. However, none of these simulations were within 10 % of the experimental result.

Interestingly, the planar model with a symmetry boundary condition at the centre of the flow predicted a jet speed within 10 % of the experimental result. This model simulates two parallel plates with a distance apart of two times the radius of the flow. The flow profiles from this simulation indicated that

![Figure 46 – Results of simulations with different inputs for parameters and geometry within the simulation.](image-url)
the viscous heating was much more concentrated near the wall, allowing the centre of the flow to reach a speed of 92 m·s⁻¹, and increasing the overall mean speed of the flow.

The shape of the profile was similar for all of these simulations except for the simulation with no temperature-dependent viscosity. In this profile, the flow exhibited no steep gradient near the wall and approached the central maximum with a slowly decreasing gradient, as expected for laminar flow.

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Mean Jet Speed (m·s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TDV</td>
<td>25.2</td>
</tr>
<tr>
<td>Laminar</td>
<td>48.2</td>
</tr>
<tr>
<td>Full 3-D</td>
<td>48.5</td>
</tr>
<tr>
<td>TDTC</td>
<td>49.5</td>
</tr>
<tr>
<td>Deformed</td>
<td>49.6</td>
</tr>
<tr>
<td>Base Simulation</td>
<td>49.6</td>
</tr>
<tr>
<td>TDD+SHC</td>
<td>50.2</td>
</tr>
<tr>
<td>Second Order</td>
<td>50.3</td>
</tr>
<tr>
<td>Compressible</td>
<td>50.4</td>
</tr>
<tr>
<td>30 ºC</td>
<td>60.0</td>
</tr>
<tr>
<td>5 µm Roughness</td>
<td>60.9</td>
</tr>
<tr>
<td>Planar</td>
<td>80.7</td>
</tr>
<tr>
<td>Experimental</td>
<td>79.5</td>
</tr>
</tbody>
</table>

Table 8 - Mean jet speed results for the range of simulations explored in section 5.4.1.

5.4.3 Effect of Viscous Heat

The graph in Figure 46 indicates that a simulation without viscous heat and temperature dependent viscosity would predict a much lower mean jet speed for glycerol than one that included these factors. The expected temperature of glycerol at the orifice is presented in Figure 47. Only 0.4 ºC of heating is predicted near the wall when water is simulated, while the profile with glycerol indicates that there is an expected 70 ºC increase in temperature in some elements near the wall, reducing the effective viscosity of the fluid at this point from 0.635 Pa·s to 0.051 Pa·s, around one order of magnitude. The expected increase in the fluid temperature averaged across the entire fluid volume is 2.7 ºC.

5.4.4 Preliminary Review of Commercial Ampoule Results

The results presented in the previous four sections highlight the behaviour of fluid in the commercial ampoule. I observe from these sets of results that viscosity affects significantly the nature of the flow...
through the ampoule, as would be expected given the range of Reynolds numbers exhibited across the range of fluids. Viscous heat thus plays a significant role in the formation of a viscous fluid jet, allowing a fluid that is quite viscous at room temperature to achieve steep gradients in velocity near the wall. This enables the jet injector to form viscous jets with mean jet speeds capable of piercing through the stratum corneum. However, it is clear that the model is failing to fully capture the physics involved in the development of a jet of fluids with glycerol concentrations above 85%. This limits the model’s applicability to fluids above this concentration and level of viscosity until a cause for the discrepancy can be found. The previous section allows many sources of the discrepancy to be ruled out and an even more thorough investigation will be needed in the future to better model these highly viscous fluids. This could involve a full non-symmetric 3-D representation to match the experimental result, which was not pursued due to the much greater amount of time required to solve these models. Therefore, leaving this question unresolved, I adapted the model to the same geometry as the ampoule I used in Chapter 4 to explore how it expects the flow in this ampoule to behave. It also allowed me to compare the simulation results with another set of experimental measurements of mean jet speed.
5.5 Stainless Steel Ampoule Investigation

5.5.1 Structure and Settings of Computational Model

Following the investigation and validation of the flow in the commercial ampoule, I moved on to simulating the stainless steel ampoule geometry. This geometry had produced faster jets of fluids with viscosity above 0.1 Pa·s than the commercial ampoule in the testing presented in Chapter 4. Only slight modifications to the model were made so that the results with the two different geometries could be compared.

I performed a 10 µm resolution micro-CT scan on the 200 µm orifice insert using the Skyscan 1172 (Bruker Ltd.). I set the voltage of the x-ray source to 100 kV and the current to 100 µA, ensuring maximum penetration of the stainless steel that makes up the orifice insert. I increased exposure time until the inside profile of the insert was clearly visible in preliminary images, leading the exposure time to be set to 3.25 s. The insert was vertically moved randomly eight times during the scan to reduce ring artefact, and each output image was an average of two exposures.

I input the set of 331 images into a program called NRecon (Bruker Ltd.) that reconstructed the images into 2-D slices of the orifice insert. A threshold extracted only the signal associated with the stainless steel of the insert. 3D-creator (Bruker Ltd.) reconstructed the inside of the insert into a 3-D model in DXF format. RapidForm (3D Systems Ltd.) was used to clean up the mesh, ensuring a continuous surface. MeshLab (3D Co-Form Project) was used to reduce the number of mesh elements to 150,000 and apply a Poisson filter to the surface of the mesh to smooth out the noise in the micro-CT images. The applied Poisson filter had an octree depth of 12 and a solver divide of 12. These settings specified the order of the functions used to fit the surface and the equivalent level at which a block solver was used respectively. The result was a smooth model (Figure 48), capturing the geometry of the interior wall. I imported the model into SolidWorks (Dassault Systèmes SolidWorks Corp).

I fit a 2-D profile to the SolidWorks model, scaled it and revolved it around the central axis matching the radius to the average radius of the 3-D model (Figure 48) based upon micro-CT images. The section of the measured geometry at the orifice diameter presented as slightly off-centre (average of 10 µm off-centre), but I assumed that this would have an insignificant effect on the resultant fluid flow in the ampoule. With this in mind, the profile exhibited a 13 µm RMS error along its length. I simplified the model by limiting the 2-D representation to the insert and not including the geometry associated with the flow before the insert. I assumed that this would have a relatively insignificant effect because, firstly, the flow before the insert is relatively slow, and, secondly, the reduction in diameter (~0.5) is small in
comparison to the reduction in the insert (~0.875). It is only in the insert that the flow reaches speeds above 10 m·s⁻¹. I input the SolidWorks 2-D representation into ANSYS workbench as the flow geometry.

The screenshot of ANSYS Meshing presented in Figure 49 shows the flow profile and mesh for the stainless steel ampoule. The maximum mesh element size was set to 6 µm, and the minimum was set to 0.1 µm. By using two mesh refinement nodes with separate circles of influence, I was able to concentrate the mesh elements near the orifice, focussed near the point where the diameter reduces down to the orifice diameter and around the point where the diameter started to decrease from that of the piston. Within the circle’s influence, the element size was forced to be 1.2 µm. An inflation layer was set within 15 µm of the wall of 20 elements with a growth rate of 1.05, identical to that set for the commercial ampoule mesh. Once again, this ensured that the first element had a y⁺ of around 4, placing it within the viscous sub-layer for flows of water. I set the roughness height of the wall to the same as that used in the commercial ampoule simulation (0.912 µm) as I was unable to measure the roughness of the wall directly because it was not a reproducible part. I therefore assumed that the influence of wall roughness on the flow was similar between the two geometries. I investigated mesh independence by gradually decreasing and increasing both the maximum element mesh size and the element size in the mesh refinement areas.

Similarly to the simulations with the commercial ampoule the viscosities of the fluids were altered between 0.001 Pa·s and 0.635 Pa·s and were made temperature dependent. I included viscous heat in
the simulation and set up equations for the temperature dependence of viscosity for each of the fluids. The solver profiled the viscous loss caused by the geometry of the profile across this range.

### 5.5.2 Mesh Independence

The mesh refinement study involved decreasing gradually the overall maximum element size and refined element size, and recording the resultant jet speed profile for water (0.001 Pa·s viscosity) after each refinement. The range of element counts for the simulations covered one order of magnitude, indicating the impact of mesh changes and their convergence. The results are presented in Table 8. The differences were less with fluids with viscosity greater than that of water. The mesh used in my simulations was within 0.5 m·s⁻¹ (simulation 5), so I expected the results to be within at most 1 m·s⁻¹ of this result if computational resources were not limited.

The simulations took around four hours to converge to a steady-state flow, with little change as the simulated fluids changed in viscosity.

<table>
<thead>
<tr>
<th>Simulation</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Element Size (µm)</strong></td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>6</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Refined Element Size (µm)</strong></td>
<td>3</td>
<td>2.4</td>
<td>1.9</td>
<td>1.65</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Nodes (000's)</strong></td>
<td>18.7</td>
<td>55.3</td>
<td>78.5</td>
<td>111</td>
<td>199</td>
<td>228</td>
</tr>
<tr>
<td><strong>Elements (000's)</strong></td>
<td>18.3</td>
<td>54.7</td>
<td>77.8</td>
<td>110</td>
<td>198</td>
<td>227</td>
</tr>
<tr>
<td><strong>Mean Jet Speed (m·s⁻¹)</strong></td>
<td>111.1</td>
<td>113.8</td>
<td>114.3</td>
<td>115.4</td>
<td>116.0</td>
<td>115.9</td>
</tr>
<tr>
<td><strong>Jet Speed RMS Difference from Simulation 6 (m·s⁻¹)</strong></td>
<td>4.99</td>
<td>2.47</td>
<td>1.90</td>
<td>0.932</td>
<td>0.266</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 9 - Details of mesh convergence study with water as the fluid in the ampoule. RMS velocity difference in jet speed profile is shown as compared to the simulation with the most elements.

### 5.5.3 Turbulence Variation

I followed the same process as that used for the commercial ampoule (section 5.2.3) to test the effect of the inlet turbulence on the steady-state jet speed at the orifice when using the stainless steel ampoule. The results are shown in Table 10.
The difference with turbulence was slightly more with the stainless steel ampoule than observed with the commercial ampoule. However, the relative effect is still minor with a maximum RMS velocity difference of 0.190 m·s\(^{-1}\). Simulations with fluids with greater viscosity in the ampoule once again showed less RMS velocity difference than those with water.

<table>
<thead>
<tr>
<th>Turbulence setting at inlet</th>
<th>1 %</th>
<th>5 %</th>
<th>10 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Jet Speed (m·s(^{-1}))</td>
<td>116.0</td>
<td>115.9</td>
<td>115.9</td>
</tr>
<tr>
<td>RMS Velocity Difference from 1 % (m·s(^{-1}))</td>
<td>n/a</td>
<td>0.149</td>
<td>0.190</td>
</tr>
</tbody>
</table>

Table 10 - RMS velocity differences in jet speed profiles at the orifice between simulations with 5 % and 10 % turbulence and that with 1 % turbulence for the stainless steel ampoule. The turbulence is applied at the pressure boundary condition. Two fluids were tested in the simulation: water and glycerol.
5.6 Results from Computational Model of Stainless Steel Ampoule

5.6.1 Jet Speed Profiles

The jet speed profiles output from the simulation of the flow in the stainless steel ampoule are presented in Figure 50. The predicted shape of the jet speed profile for water is significantly different from the predicted jet speed profile at the orifice of the commercial ampoule, with a consistently sloped section when moving away from the wall towards the centre of the flow. The slope increases as the room temperature viscosity of the flow is increased from 0.001 Pa·s to 0.012 Pa·s (Re of 2,070). Importantly, the flow is less like plug flow than the jet speed profiles output from the commercial ampoule simulations.

The sloped section is not evident in the jet speed profile from the simulations of glycerol (Re of 24.4). The approach to the central maximum evident in the commercial ampoule results appears again in these results, with the region of plug flow greatly reduced as viscosity increases. The effect of viscous heating can again be seen near the walls when glycerol is simulated.

5.6.2 Comparison with Experimental Results

I compared the results of the simulation with the results of the experiments with the stainless steel ampoule from Chapter 4 (Figure 51). The friction coefficient was set to 0.11, according to results at the injection pressure from the literature for rubber on stainless steel, assuming a smooth profile with no lubrication [140]. The error bars in Figure 51 represent jet speeds calculated at the extremes of the

![Jet speed profiles at the orifice of the stainless steel ampoule resultant from simulations with applied pressure of 10 MPa.](image)
approximation of the friction coefficient and the measurement of the orifice diameter. The simulation results where the fluids of 0.001 Pa·s (water) and 0.012 Pa·s viscosity are simulated correlate well with the results from experiments. However, as the room temperature viscosity of the simulated fluid increases above 0.03 Pa·s, the simulation starts to underestimate the jet speed, especially when the flow of glycerol is simulated (room temperature viscosity of 0.635 Pa·s). For the highly viscous flow of glycerol, the simulated jet speed when the applied pressure is 10 MPa is 50 m·s⁻¹ while the experimental mean jet speed is around 87 m·s⁻¹. I conclude that the simulations are once again overestimating the viscous loss present in the flow at these high viscosities. This suggests that the error observed with the commercial ampoule simulation is not just a problem with the creation of the geometry, but likely a result of limitations in the physics described in formulating the simulation itself.

5.6.3 Comparison with Results from Commercial Ampoule Simulation

With both the commercial ampoule and the stainless steel ampoule simulation results assembled, it is possible to compare the expected performance of both injectors. We can also review the experimental results to identify the performance of the CFD model itself. Figure 52 overlays Figure 51 on Figure 43, allowing this direct comparison. The commercial ampoule is expected to perform better with low viscosity fluids, and the experimental results show that indeed it does. In the experimental results, as the viscosity increases, the stainless steel ampoule starts to achieve higher mean jet speeds with the same applied pressure. Therefore, there exists a viscosity at which the stainless steel ampoule starts to exhibit less loss than the commercial ampoule. In the experimental results this occurs at approximately 0.02 Pa·s. However, the simulation results suggest that this cross-over point is close to 0.635 Pa·s, much
higher than the experimental results. The mismatch between simulation and experiment occurs at around the same point for both geometries.

**5.6.4 Qualitative Results**

As with the commercial ampoule simulation, I used the visualisation tools within ANSYS to identify the sources of loss in the stainless steel ampoule simulations (Figure 53). The turbulent kinetic energy for the water simulation (Figure 53A) indicates that the sharp edge of the geometry has caused a much greater turbulent loss along the nozzle. This high degree of turbulence is especially apparent when comparing to the loss evident with the commercial ampoule (Figure 44A). The difference is large enough that different scales are required to show the intensity. As the viscosity of the fluid increases, once again the walls impose a laminar profile on the flow near the centre.

The pressure profile with the stainless steel ampoule differs between water and glycerol (0.001 Pa·s and 0.635 Pa·s viscosities respectively). The simulated pressure drops below atmospheric to around -12 MPa at the sharp edge for water, and -5 kPa for glycerol, indicating that cavitation could be expected at this interface (Figure 53B and Figure 53C). The impact of this on the simulation's validity will be further discussed in Section 5.7.3. The simulation suggests that the sharp edge has formed a *vena contracta*, where flow separation occurs at the edge leading to a large drop in pressure and turbulent conditions near the wall. No drop at all is observed in the commercial ampoule simulation results as they show a consistently smooth pressure profile (Figure 45).
Figure 53 – Visualisation of stainless steel ampoule flow looking at different flow properties. A: Turbulent kinetic energy for 10 MPa applied pressure simulation with water. B: Simulated steady state pressure for water simulation. C: Simulated steady state pressure for glycerol (viscosity of 0.635 Pa·s) simulation.
5.6.5 Shear Rate

The shear rate is predicted to be higher with the sharp edged stainless steel ampoule geometry when water is in the ampoule, as the results show a maximum shear rate of \(4.03 \times 10^8\) s\(^{-1}\) (\(1.32 \times 10^8\) s\(^{-1}\) in the commercial ampoule results). The average peak shear rate is \(3.98 \times 10^6\) s\(^{-1}\) (\(1.57 \times 10^6\) s\(^{-1}\) in the commercial ampoule results) and the predicted percentage of the flow experiencing a shear rate over \(1 \times 10^7\) s\(^{-1}\) is 2.89\% (3.79\% with the commercial ampoule). The simulation with glycerol predicted a maximum shear rate of \(9.81 \times 10^7\) s\(^{-1}\) (\(9.82 \times 10^7\) s\(^{-1}\) with the commercial ampoule) and an average peak shear rate of \(779,000\) s\(^{-1}\) (\(649,000\) s\(^{-1}\) for the commercial ampoule). The colour maps showing the shear rates for the flow in the stainless steel ampoule are presented in Figure 54.

![Figure 54 - 2-D colour map of shear rate near the orifice of the stainless steel ampoule. A: the results of the simulation with water. B: the results of the simulation with a 0.635 Pa-s fluid (glycerol).](image-url)
5.7 Discussion

5.7.1 Discussion of Simulation Methods for Both Ampoules

Firstly I will review how the method itself was executed, before discussing its results. We can see the stability of the model with regard to the inlet turbulence in the results presented in 5.2.3 and 5.5.3. The flow has developed in the domain of the simulation enough that the nature of the turbulence model in the simulation reflects what would occur during the flow development in the actual ampoules. The turbulence model provides important information on the interaction of the flow with the wall. However, the results are dependent upon the accurate determination of the geometry of the inside boundary. My use of micro-CT ensured that geometric model in the simulation was accurate to within 10 µm, small enough for the scale of the simulation. I would recommend this approach for future research as accurate reconstructing of orifice geometry plays an important role in achieving results that reflect experimental conditions.

While the density does increase with increasing glycerol concentration increased, the degree of this change (1000 kg·m⁻³ to 1260 kg·m⁻³) was much less significant than the change in viscosity over the range (0.001 Pa·s to 0.635 Pa·s), so the results of simulations were much more likely to reveal effects due to viscosity rather than density.

Mesh and time convergence is critical in ensuring that the simulation results I collect are precise enough to meet the requirements of the application. Both ampoule simulations demonstrated that a significant increase in the number of elements changed the simulated mean jet speed by less than 0.5 m·s⁻¹. Also, the general trend as mesh size decreased was a decrease in the RMS difference between simulation results for the jet speed profile at the orifice. Therefore, I decided that the mesh for each ampoule that solved in less than eight hours achieved enough precision to be fit for purpose.

The computational model was limited by its use of the axisymmetric assumption about the flow. Any 3-D geometry that is not captured by the symmetric form would influence the experimental results and not those of the simulation. The accuracy of the imaging in the micro-CT limits the accuracy of the geometry that is used. The walls are assumed to be adiabatic, which means that the heat transfer of the ampoule material has not been accounted for. This may influence the results as the heating near the wall is an important factor in the determination of predicted jet speed. The flow is assumed to be Newtonian though the high shear rates near the walls may result in non-Newtonian behaviour. Additionally, as a result of this structure, the model can only be used as a conservative estimate of the
flow speed for a shear-thinning fluid such as a monoclonal antibody. Nonetheless, the model indicates what properties of such a fluid will influence its jet speed.

5.7.2 Jet Speed Profiles for Commercial Ampoule

As viscosity increases, the shapes of the jet speed profiles output from the commercial ampoule simulation change. With water, they are something close to plug flow, but with glycerol they tend towards a more laminar flow with steep sides. These steep sides, caused by the viscous heating near the wall of the ampoule, affect the mean jet speed achieved by the flow as it exits the ampoule. As I mentioned in section 5.4.4, this viscous heating effect is an important phenomenon that previously has not been well discussed in the jet injection literature, though one diesel injector paper has addressed its contribution to flow in both a cylindrical and tapered geometry [141] and the phenomenon has been observed in the flow of glycerol [142]. If a drug formulation is found to have a constant or increasing viscosity as temperature increases, then the jet speed expected when it passes through a jet injection orifice should be expected to be much slower than otherwise. Additionally, the simulation presents what it expects the jet speed profile to be for flows of a wide range of viscosities. With all of this, we can review the results to guide future design decisions. The results indicate that viscous fluids drag along the wall of the commercial ampoule, suggesting that a shorter section of geometry at or near the orifice diameter will improve the performance of the ampoule at higher viscosities than water.

As expected, turbulent loss is evident in the water ejection simulations. The turbulent kinetic energy map, presented in Figure 44A, shows that turbulence stays close to the wall with the gradual reduction in diameter of the commercial ampoule as the flow approaches the orifice. The way in which the reduction occurs is therefore the likely cause of the smooth pressure profile of the commercial ampoule simulation. However, the turbulent losses are much reduced when a viscous fluid jet is being formed. This phenomenon is observed both in simulation results and experimental results.

The maximum shear rates indicate that the flows through the commercial ampoule exceed the level of shear stress rate which has been proven to cause no significant damage to the protein during production (32,000 s\(^{-1}\) vs. upwards of 100,000,000 s\(^{-1}\)) [130]. The shear rates also exceed the minimum required level for inactivation predicted by Bee et al, of 1 \(\times\) 10\(^{-7}\) s\(^{-1}\). However, the high shear was only evident in the simulation results as the flow progressed toward the orifice and the diameter reduced with simulations of both ampoules revealing that only \(\sim3\%\) of the flow will be exposed to shear rates above the 1 \(\times\) 10\(^{-7}\) s\(^{-1}\) level. Additionally, the period of time at which the drug is exposed to high shear is an important determinant of its deactivation [143] and the period that the fluid would be exposed is less than 100 \(\mu\)s. Therefore, I do not expect that there would be a significant deactivation of protein.
during jet injection, an expectation which is in accordance with the results of Jin [144] and the work of Hogan et al. [91].

The simulation results for mean jet speed and the experimental results from tests for the commercial ampoule (Figure 43) were well matched until the room temperature viscosity exceeded 0.1 Pa·s. Therefore, we must limit any predictions from the computational model to viscosities up to this limit in order to be confident of the results. Further validation could be provided by a system that allows the experimental measurement of velocity profiles from jets formed by jet injectors. This would allow the jet speed profiles themselves to be validated rather than mean jet speed. I hope that in the future that such a system could help experimentally verify the profiles presented in this chapter, further reinforcing the prediction capabilities of any computational model.

The discrepancy between the glycerol simulation result and the experimental result indicates that the model is overestimating viscous loss, especially as it starts to become the main determinant of jet speed. The mismatch suggests that there are processes occurring in the boundary layer near the wall that are causing a greater jet speed in the experimental device than observed in the computational model. I can suggest two possible causes of the discrepancy. Firstly, the geometrical representation in the computational model may not accurately represent the actual profile of the ampoule. Although the roughness is accounted for with the turbulence model, this could be underrepresenting the flow separation that occurs as the diameter of the flow reduces, thereby increasing the effective viscosity. Secondly, the heating of the fluid itself could be represented inaccurately within the simulation. The planar simulation showed much more intense heating nearer to the wall and, as a result, indicated a mean jet speed much closer to that of the experimental measurement. In this study, the wall is assumed to be adiabatic, but the impact of the temperature distribution along the wall of the ampoule may be significant, especially if the conductivity of different ampoule materials is taken into account. Further investigation of the heating properties of glycerol and its interaction with the wall could reveal that the model has incorrectly distributed the viscous heating over a broader area, reducing the effect that viscous heating has on the viscosity of the glycerol in the flow. Future investigations in these areas could explain why the flow of glycerol is so different in the experimental results, and help to extend the range of fluids for which the computational model can predict the behaviour. This would be necessary to use the model to design ampoule geometry profiles for the jet injection of highly-viscous fluids.

5.7.3 Extension to Stainless Steel Ampoule

The results matching the experimental mean jet speeds compared to the predictions of the simulation (presented in Figure 51) indicate that the model deviates as the viscosity of the fluid inside the ampoule
is increased, with mismatch occurring at 0.1 Pa·s. Once again, this suggests that physics that are not captured in the model are allowing the stainless steel ampoule to achieve greater mean jet speeds and perform better as viscosity increases.

The pressure profile with the stainless steel ampoule suggests a cause of a discrepancy between experimental and simulated results. The sharp decrease in diameter that occurs in the stainless steel ampoule is associated with a pressure profile that drops well below zero near the sharp edge of the profile (Figure 53C and Figure 53D). This is below -1 kPa indicating that cavitation is likely to occur at the corner [145] and the effect of cavitation in the domain is not covered by the current physics of the model. While it applies to both water and glycerol, it is possible that a bubble at this corner could decrease the gradient of the jet speed profile near the wall as it allows slip along the wall itself, enabling viscous fluids to achieve higher mean jet speeds than they would otherwise. A similar increase in the gradient near the wall of the jet speed profile for water would have much less effect. A cavitation model like that pursued in the fuel injector literature [114], [116], [121] could be added to the domain, but this was considered a much more onerous undertaking and was not pursued in this investigation.

Nonetheless, in the future, understanding the cause of the increased performance of the stainless steel ampoule geometry at high viscosities may reveal that the sharp edge is significantly beneficial and thus drastically change the approach that has previously been taken with designing ampoule geometries. In the meantime, the results expose a limitation of the model and indicate that it is best applied to fluid flows with smooth pressure profiles that do not drop below the pressures associated with cavitation.

A direct measurement of the RMS roughness of the stainless steel ampoule wall would allow the model to better capture the effect of this roughness on the flow of the fluid through the ampoule. This could be measured on an orifice that is manufactured at the same plant and can be cut in half to allow the roughness tester access to the surface. Unfortunately, including the measured roughness height is unlikely to change the comparison to the experimental results significantly because the results with a 5 µm roughness height input for the commercial ampoule revealed a difference in mean jet speed of only 11 m·s⁻¹. An increase of this magnitude in the mean jet speed with glycerol in the stainless steel ampoule would still leave the simulation prediction well within the current error of the model in comparison to the experimental results.

The match with water allows me to make some assertions about the behaviour of fluid in the stainless steel ampoule. With water and low viscosity fluids, turbulence is much more prevalent than in the commercial ampoule as flow separation occurs. This forms what is known as a *vena contracta* [146], where the radial momentum of the fluid forces it towards the centre, increasing the speed of the fluid in the centre, but limiting the speed of the fluid nearer the wall (which is of much greater volume). This is
the cause of the shape of the jet speed profile (Figure 50), where a secondary slope is evident and the central maximum extends less towards the wall than otherwise. This effect is much reduced with a smoother geometry such as the commercial ampoule, increasing the mean jet speed.

The results with of the stainless steel ampoule simulation show that the ampoule exhibits less viscous loss than the commercial ampoule. I suggest that the cause of the improved performance with the stainless steel ampoule is related to the length of the ampoule that is at or near the orifice diameter. The viscous drag of the wall is less prevalent in the stainless steel ampoule simulation results, enabling high viscosity fluids to form jets of higher speeds. However, more guidance in this matter would be gained by building a simulation system that optimised the design of the ampoule and a manufacturing system that could make an arbitrary shape. This would allow a computational design process that minimises the loss in the ampoule either for a specific drug or a range of drugs, improving the performance of whichever jet injector the process was applied to, regardless of the jet injector's source of power.

Finally, the shear rate experienced in the stainless steel ampoule is greater than the commercial ampoule according to the simulation results. Therefore, the use of a smooth profile similar to that of the commercial ampoule will reduce the average shear rate experienced by the drug.

5.7.4 Guidance for Ampoule Design

The results suggest that when it comes to designing jet injector ampoules for viscous fluids, CFD is capable of providing guidance, at least for flows of a non-negative pressure profile and of room temperature viscosity no greater than 0.1 Pa·s. I expect that the simulation of a short approach to the orifice diameter with a smooth rounded profile would predict reduced loss across the range of viscosities investigated here. Thereby, the turbulent loss that occurs with water would be reduced due to reductions in the downstream flow separation and eddy dissipation loss and the wall friction losses that occur with viscous fluids would reduce as the flow is less exposed to the effects of the wall. Through reducing both of these effects, the resultant ampoule will achieve higher jet speeds, regardless of viscosity. This design would also have the benefit of reducing the shear rate experienced by the drug during jet injection. A simulation of this profile would be required to confirm these expectations, and I consider that future work should focus on improving the match with experimental results before investigating better geometries.
5.8 Conclusions and Future Work

The importance of the inner geometry of the ampoule used in a jet injector is clear from the results presented in this chapter. A better designed ampoule must reduce pressure loss, allowing higher jet speeds to be developed with lower applied force. Simulations can guide design so that turbulent and wall friction losses are reduced. The simulation presented in this chapter helped to explain some of the results shown in Chapter 4, did not require excessive computational power to run, and provided insight on the nature of the flow in an ampoule. For drug delivery by jet injection, information about this flow obtains greater importance as the drug being injected increases in viscosity.

The simulations indicate that viscous heat is a significant factor in determining the jet speed achieved by a particular fluid in a jet injector. Profiling the temperature dependence of a drug’s viscosity will be crucial to predicting the ability of drugs to pierce the skin and should be considered by formulators when creating drug solutions. Further experiments with a range of fluids that differ in their temperature dependence will provide further information about this phenomenon.

The simulations also provide useful guidance for the design of ampoules for low-viscosity drug delivery. The results suggest that a short and smooth diameter reduction works best to reduce turbulent losses. This profile also reduces the shear rate experienced by the drug during jet injection. Future investigations should use this knowledge to reduce the pressure drop regardless of viscosity.

To improve the simulation, the cause of the reduced viscous loss with viscous fluids experimentally must be identified. From here, a velocimetry study could be used to validate the shape as well as the mean jet speed results. With the simulation performing well and the results validated across the full range of viscosities, it would be possible to identify the geometry profile that reduces pressure loss the most across all available liquid drugs. The better performing profile would allow for injectors to require lower power in order to form a jet capable of piercing the stratum corneum, allowing the injector to be smaller and more versatile.

I conclude from my work in this chapter and the previous chapter (Chapter 4), where I tested the VFJI, that the predominant impact of viscosity when forming a viscous jet is the loss that occurs as the diameter decreases near the orifice of the ampoule. My feed-forward model accounts for this loss so that an equivalent mean jet speed is achieved with the VFJI no matter how viscous the fluid in the ampoule. However, forming an equivalent jet does not mean that the fluid will behave the same when it is injected into skin. Therefore, in the following chapter, I pursue an investigation of the effect of viscosity on dispersion underneath the skin’s surface while controlling for mean jet speed. These tests
were performed with the knowledge of the different shapes that the jet speed profiles have across the orifice (Figure 42 and Figure 50), as well as the potential for variation due to the inherent viscosity of the fluid itself.
6 Dispersion of Viscous Fluids Underneath Skin

6.1 Introduction

I have demonstrated that the new viscous fluid jet injector (VFJI) is able to produce a jet of a viscous fluid at a speed capable of piercing the skin (as defined by Schramm et al. [86]) (Chapter 4). I have also detailed the expected shape of the jet speed profile across the orifice for a range of viscous fluids and with different ampoules (Chapter 5). The next step in fully exploring the effect of viscosity was to gain knowledge about the dispersion of the jet under the skin. As previously mentioned in Chapter 2, targeting of drugs to specific layers of the skin has been shown to improve their clinical performance, in combination with other factors such as inflammation [12], [53]. For example, vaccines present with better antibody titres in the bloodstream when they are targeted to the epidermis [3]. Therefore, the effectiveness of delivery is dependent on the dispersion.

Artificial skin analogues are often used for the testing of jet dispersion. The most common of these is polyacrylamide gel [9], [12], [13], [21], [33], [74], [77], [79], [147]. In both my work and that of another research group [79], silicone gels have been used, but they eject fluid post-injection as the gel relaxes. Previous research has provided some guidance as to the proper percentage of acrylamide to use in preparing a human skin analogue gel [36], [74]. However, this is mostly in the form of connections between desired stiffness and acrylamide concentration; how these parameters translate to human skin properties is not detailed. Therefore, the results of gel testing are limited to being a guide as to the response of skin at a basic level, and serve as a useful way to test ideas initially.

Across the range of recommendations, whether a 10% or 20% acrylamide gel is used, the jet pierces through the surface cracking the gel in a plane, as shown in Figure 55. The angle of the plane is impossible to determine beforehand, and the injected fluid is mostly contained in the crack.
Despite their limitations, much has been learned about the nature of fluid dispersion after jet injection based on experiments in polyacrylamide gels. Mitragotri and Schramm-Baxter et al. [74] demonstrated the effect of changing the stiffness of a gel on the penetration depth and in-plane dispersion of an injected fluid. They increased the percentage of acrylamide in the gel to increase the stiffness and observed reduced penetration depth and increased width of dispersion perpendicular to the jet. Another study [77] connected jet power and nozzle diameter with gel dispersion in 30% acrylamide gels. Ideally, a control system could rely upon certain jet parameters to be well-correlated with injection dispersion measurements. For this to be true, the variability of the response to the jet must be less than the expected change due to the modified jet parameter, for example, jet speed. The literature demonstrates that gel media has variability that is sufficiently low to allow jet speed to be well-correlated to jet penetration depth [13], [21], [33], [36], [77], [81].

Unfortunately, the gel results presented in literature do not translate well to the behaviour of jet injected fluids in animal skin models. Wagner et al. [75] reports that fluid penetration depth is highly dependent upon thickness of the dermis and depth to the muscle fascia. The shape of the dispersion in porcine skin lateral to the jet direction is bulb-like, similar to that evidenced in acrylamide gels in the plane of fracture. However, the plane fracture evident in gels is not observed in porcine skin, and the bulb appears to originate from the bottom of the eroded hole and then disperse up, rather than uniformly around the end point [82]. Taberner et al. [9] present data that suggests that it is possible to effectively deliver to a required layer underneath the skin surface in rat models. While the result does not demonstrate millimetre accuracy on depth with the jet, at the very least, it shows that layer targeting is possible.

Figure 55 - Diagram of injection into acrylamide gel. A: The injection from above, indicating the plane nature of dispersion. B: Illustration of how the in-plane dispersion looks from the side.
Baxter and Mitragotri [21] tested the stiffness of skin, and then correlated it to the fluid dispersion. They used a linear approximation of skin stiffness in their analysis. Their results indicated that greater stiffness led to a shallower penetration depth and reduced fluid absorption. However, no connection was drawn between gel results and porcine skin results. Baxter and Mitragotri [21] recommended measuring stiffness to gain a better idea of the source of variation between injections, and to try connect the dispersion to jet power mechanics. They achieved this with some degree of repeatability, mainly at targeting a layer of skin, rather than a specific depth.

Porcine skin tests usually use skin taken from the abdomen or upper torso of a pig. Some modelling by Schramm-Baxter [74] has indicated that, unlike gels, porcine skin behaves like a porous medium when injected, a viewpoint reinforced by the experimental data of Stachowiak et al. [33]. To some degree, the movement of fluid in the tissues can be predicted by Darcy’s law, which describes the flow of a slow, incompressible, viscous fluid through a porous medium, commonly applied to the flow of ground water after injection of gas or another fluid [148]. The equation for Darcy’s law is:

\[ Q = -\frac{\kappa A}{\mu} \cdot \frac{\Delta P}{L} \quad (6-1) \]

where \( Q \) is the flow rate of the fluid (or the absorption rate in the tissue), \( \kappa \) is the permeability of the tissue, \( \mu \) is the viscosity, \( \Delta P \) is the pressure difference between the jet and the end of the hole, and \( L \) is the length of the hole. A Darcy model assumes a homogenous porosity throughout the medium, and the layered nature of skin probably invalidates this assumption, without even taking into account the variability in porosity between samples [149]. Comley and Fleck [70] propose that a jet injection causes the porosity of the surrounding tissue to increase significantly, allowing the fluid to disperse more than it would otherwise, allowing a modified Darcy’s law to model the dispersion if the porosity value is dynamic. They hypothesize that the cause of the increase in the porosity is due to the formation of micro-channels in the tissue, as a consequence of the applied pressure. Their work has been supported by that of Chang [82] who uses a similar model to inform her studies of the extraction of interstitial fluids from skin. Darcy models are normally restricted to flows of Reynold’s number (\( Re \)) less than 10, indicating that they have limited ability to model highly turbulent flows such as the high-speed liquid jet of jet injection (\( Re \approx 10,000 \)). However, post-injection, the flow of the fluid is much slower, the Reynold’s number decreases, and the Darcy model may be able to describe the flow more accurately.

The question that this chapter intends to answer is this: can we expect a more viscous fluid jet, going the same speed and of the same volume as one of lower viscosity, to disperse differently during and after piercing through the surface of the skin? To answer this question, I performed tests in both
polyacrylamide gels and porcine skin. For each of these media, an acceptable jet injection profile was chosen, and it was used to form jets that can pierce through the medium. I repeated the test after changing the fluid in the ampoule to one of a different viscosity. The resultant dispersion patterns were analysed to determine whether it is possible to relate measures of the dispersion pattern to the viscosity of the fluid.
6.2 Injection into Acrylamide Gels

6.2.1 Methods

The gel tests used a 10% polyacrylamide gel in a 10 mL transparent plastic container. The cylindrical container measured 24 mm in diameter and 23 mm in height. I prepared the gels on the day of injection as they tend to shrink due to evaporation if left too long after preparation.

I injected the gels using a two phase waveform that used the feed-forward model detailed in Chapter 4. The user interface that presented the position trajectory is exhibited in Figure 56. Brilliant Blue FCF 1.8% dye was used at 5% concentration in the fluid. The target jet speed for the first phase was 124 ms\(^{-1}\) with a second-phase follow through speed of 50 ms\(^{-1}\). The target period for the first phase was 10 ms, and the total target volume for both phases combined was 150 µL. A previous series of tests had revealed that the water jet prescribed by these parameters penetrates to around halfway down the gel and disperses in the 24 mm diameter of the gel container. I randomized the order of the fluids for a series of tests (n = 10) of with viscosities ranging between 0.001 Pa·s and 0.347 Pa·s, and only those within 10% of their intended waveform targets were included in the analysis.

Immediately after injection, I placed the gels on a flat table with a white background and took a photo of the dispersion underneath the gel surface. A ruler, in focus with the dispersion, provided scale for the measurements of the dispersion. I imported the photos into ImageJ (W. Rasband, N.I.H., Bethesda, MD, USA).

![Figure 56](image.png)

*Figure 56 - Two-phase trajectory is input into the feed-forward model to form the two-phase waveform. The control system uses the model to try to track the trajectory. The input values on the left are those used for the gel tests.*
U.S.A) and used the set scale tool in order to begin measurements. I measured the width, the height, the depth from the surface of the gel to the start of the oval-shaped dispersion (Figure 57). Finally, I applied a threshold to the image that selected pixels of hue between 121° and 184°, and saturation between 0.28 and 1.0 (normalised). This threshold was chosen to select the blue bolus in the gel and none of the other elements inside the container. I measured the area over the threshold, giving, in total, four measurements to compare across viscosities.

I initiated a linear regression analysis to determine whether there was any correlation between the viscosity of a fluid and its dispersion pattern, extracting the p-value as the measure of influence.

<table>
<thead>
<tr>
<th>Measure</th>
<th>1st Phase Jet Speed (m·s⁻¹)</th>
<th>Time above 100 m·s⁻¹ (ms)</th>
<th>2nd Phase Jet Speed (m·s⁻¹)</th>
<th>Volume (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>123.37</td>
<td>11.60</td>
<td>50.37</td>
<td>149.21</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.50</td>
<td>0.37</td>
<td>1.88</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 11 - Mean and standard deviation of jet measurements for gel tests (n = 10).

6.2.2 Results

I ascertained the variability in the two phase waveform from the recordings of the coil position. The standard deviations and means of first-phase jet speed, second-phase jet speed, time above 100 m·s⁻¹, and volume injected are presented in Table 11.

The viscosities of the fluids tested sit equidistant along a log scale of base ten between 0.001 and 0.1 Pa·s. Therefore, I applied a log transformation to the viscosity data. An outlier was removed because the image was distorted by fluid that had seeped along the wall of the container.

The p-values for the viscosity affecting a dispersion measure are presented in Table 12. Only area was correlated to viscosity. For each factor of ten that viscosity is increased, dispersion area is expected to increase between 5% and 46%.

<table>
<thead>
<tr>
<th>Width</th>
<th>Height</th>
<th>Depth (Surface)</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.2 mm</td>
<td>14.3 mm</td>
<td>17.9 mm</td>
<td>188 mm²</td>
</tr>
<tr>
<td>1.3 mm</td>
<td>1.2 mm</td>
<td>1.4 mm</td>
<td>23 mm²</td>
</tr>
<tr>
<td>0.18</td>
<td>0.912</td>
<td>0.0504</td>
<td>0.0229</td>
</tr>
</tbody>
</table>

Table 12 – Mean and standard deviation for each test set (n = 10) and p-values representing evidence against the hypothesis that viscosity has no effect on a dispersion measurement in gels.
6.2.3 Preliminary Discussion

In the context of the dispersion investigation presented in this chapter, the gel tests were preliminary and helped inform the method pursued for the porcine skin tests. As previously mentioned in this text and in others [74], polyacrylamide gels only represent skin inasmuch as they provide a model that mimics the stiffness of skin. Fluid jets can then pierce through and disperse under the surface, giving a rough indication of their behaviour in a linear approximation of skin tissue properties. Porcine skin tests provide a better approximation of human skin conditions [95], so I focused on these after the initial tests in gels presented above.

The range of fluid viscosities covered in the gel tests was quite wide, from a fluid that behaves very similarly to water, to one that is more similar to the viscosity of motor oil. The log transform was chosen as previous tests with viscous fluids [99] revealed that the effects of viscosity in jet injection operate more on a log scale than a linear one. The discreet nature of the fluid choice meant that there was no effect on the recorded variance of the set.
The performance of the two-phase feed-forward model is presented in Table 11. The mean of both the 1st phase and 2nd phase jet speeds were within 1 m·s⁻¹ of the intended value, and demonstrated standard deviation of less than 2 m·s⁻¹. This consistent performance ensured that the focus could be on viscosity rather than the performance of the electro-mechanical system. Measurements of the time the jet spent above 100 m·s⁻¹ and the volume ejected demonstrated similar consistency.

Perhaps the difference in volume injected could explain the predicted change in area as viscosity is increased? It would be unusual for area to increase with increased viscosity, as viscosity is a measurement of resistance to flow, and would be expected to correlate with a decrease in dispersion area after injection. I expect that, if this is the case, the difference would be at the lower end of the confidence interval, near 5%.

The absence of a clear relationship between viscosity and dispersion measurements amongst the gel tests implies that the momentum of the incoming jet on the gel is the main determinant of the jet dispersion pattern, in addition to being a possible determinant of the ability of a jet to penetrate skin. I would limit this conclusion to the range of viscosities tested. Darcy’s law would indicate that we can expect viscosity to have an effect, especially as the range of viscosities explored here should increase the flow rate by 300 times according to equation (6-1). I suggest that the momentum of the jet is a more important determiner of the fluid dispersion in gels than the viscosity. If the reasoning of Comley and Fleck [70] is correct, I believe that the increase in permeability of the gel media due to the jet injection is

![Figure 58 - Photo of jet dispersion in gel. A 30 % glycerol fluid with 5 % blue dye was used in this test.](image)
of much greater consequence than the change in viscosity in the range explored here.

Often, the shape of the gel dispersion was obscured by the fluid left on the surface that seeped into the
gap to the side of the gel (Figure 58). The area was then measured by manual segmentation. In future, I
recommend placing absorbent towel around the edge of the injection site to ensure that there is no
seepage to the sides. Using this method, the fluid that did not pierce through the surface of the gel could
be weighed

The deepest points of the dispersion patterns deviated little in the xy plane from the injection points. All
dispersion patterns were approximately circular around a central point at the bottom of the eroded
hole apart from one. The outlier had two boluses which were connected, with one above the other. I
found it quite difficult to make gels with similar properties. Often the gels would cure and shrink, likely
forming a preferred plane and anisotropy in the process. In future, I would recommend making a large
volume of liquid gel that has been well homogenized, and then removing individual samples to cure
separately.
6.3 Injection into Porcine Skin

6.3.1 Methods

When determining the distribution of the fluid underneath the surface of a skin sample, the opacity of skin makes it much harder than with gels to get a good representation of the fluid's dispersion. Therefore, I used micro computed tomography (micro-CT) with the help of radiographic contrast (iohexol 0.647 kg·L⁻¹) to image the dispersion pattern. Porcine skin was used as the skin model for human skin due to its similarity in structure and mechanical properties [150], [151].

I harvested the porcine skin from post-mortem pigs at the Vernon Jensen unit of the University of Auckland. Another research group had performed anaesthetic testing on the pigs (in accordance with the requirements of the University of Auckland Animal Ethics Committee). The samples came from the upper torso of the pig and were collected from two pigs, both aged between 9 weeks and 12 weeks old and weighing in between 20 kg and 30 kg. The age of the pig was similar to that used in other studies of injection methods [150], [152]. Skin properties are unlikely to have been affected by the anaesthetic testing. Once harvested, I froze the skin at -80 °C. All tests were conducted within four months of harvesting. This followed previous procedures used within the literature [9], [21], [147]. While the pig skin is not under *in vivo* load during injection, the samples were large enough (~500 mm²) to resist the pressure of the injector and mimic *in vivo* load at the injection point. Baxter et al. have shown that pig prepared in this way can be an adequate guide to the response of human skin once thawed [21]. Further information about the differences between human and porcine skin is available at [151].

I prepared the fluids so as to cover a wide range of viscosities while including enough contrast fluid so that, when injected, the images revealed the pattern clearly. Each fluid I prepared contained 15 % of the Omnipaque™ iohexol, and the other 85 % was made up of a fluid with a glycerol concentration of 30 %, 60 %, 75 %, 85 % or 95 % fraction by volume. I attempted to create a range equidistant along a log scale of viscosity, though the behaviour of the mixtures was hard to predict. I measured the viscosities of the fluids using a RheolabQC rheometer (Anton Paar GmbH, Graz, Austria) with a 27 mm rotational measurement system (2 mm gap).

The night before testing, I removed from the freezer the pig skin samples intended for use the next day and left them in a 4 °C fridge overnight to defrost. The next morning, the samples were sealed in a plastic bag and immersed in a water bath at 24 °C. An hour later, using the same sample containers as the gels, I traced the outline of the container on the skin sample and cut the skin to the appropriate size for the circular container. Each day, five containers were filled and refrigerated at 4 °C.
I removed samples from the fridge one hour before they were to be injected. The mean temperature in the room where the injection was performed was 24 °C with a standard deviation of 0.5 °C across the test set. I placed the sample in the contact force cradle and forced the end of the ampoule onto the centre of the sample with 0.5 N of contact force. The contact force level was chosen as the intermediate level between the two presented by Jean Chang in her PhD thesis [82]. I had conducted preliminary tests to ensure that the contact force level led to repeatable injection with water. The sides of the cradle were tightened, keeping the sample at the correct contact force during injection.

In order to achieve the same jet speed as viscosity varied, the voltage applied had to be changed. I based the voltage applied on the feed-forward model described in Chapter 5. However, the addition of the contrast agent into the solutions and the resistance of the skin samples modified the fluid’s behaviour requiring me to make slight modifications to the values. Preliminary pig skin tests indicated a 110 ms⁻¹ water jet successfully pierced through the stratum corneum and distributed itself in the sub-cutaneous fat. I focussed on sub-cutaneous fat delivery, as the layer is an area of high contrast when imaged with a micro-CT and a region commonly targeted for drug delivery. A series of tests established what voltage was required to achieve a consistent steady state jet speed of 110 ms⁻¹ across all tested viscosities. I applied the required voltage for 25 ms, rapidly forming the jet for a short period and delivering a volume around 90 µL. This period was chosen as it is long enough to develop a stable jet speed; at this speed and period, I was able to pierce through the stratum corneum consistently without piercing fully through the sample.

<table>
<thead>
<tr>
<th>Day</th>
<th>1st Fluid Viscosity (mPa·s)</th>
<th>2nd Fluid Viscosity (mPa·s)</th>
<th>3rd Fluid Viscosity (mPa·s)</th>
<th>4th Fluid Viscosity (mPa·s)</th>
<th>5th Fluid Viscosity (mPa·s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>22.4</td>
<td>22.8</td>
<td>47.1</td>
<td>4.75</td>
<td>47.1</td>
</tr>
<tr>
<td>2nd</td>
<td>4.75</td>
<td>101</td>
<td>4.75</td>
<td>22.8</td>
<td>22.4</td>
</tr>
<tr>
<td>3rd</td>
<td>101</td>
<td>47.1</td>
<td>101</td>
<td>47.1</td>
<td>22.8</td>
</tr>
<tr>
<td>4th</td>
<td>47.1</td>
<td>22.4</td>
<td>22.4</td>
<td>101</td>
<td>4.75</td>
</tr>
<tr>
<td>5th</td>
<td>22.8</td>
<td>4.75</td>
<td>22.8</td>
<td>22.4</td>
<td>101</td>
</tr>
</tbody>
</table>

Table 13 - Order of testing into pig skin over the five days of testing.

The order of the fluids injected on each day was randomized and is exhibited in Table 13. After the injection had taken place, I transported the porcine skin sample to a micro-CT scanner (Bruker Skyscan 1172, Bruker micro-CT, Billerica, MA, U.S.A.) and placed it in the chamber. Earlier in the day, I had pre-heated the x-ray source and aligned the micro-CT camera. A flat-field was taken, and a 0.5 mm aluminium filter was placed over the camera lens to improve contrast. The micro-CT scanner required 12 minutes for the x-ray source to stabilize. During this period, I prepared the sample and CT machine for scanning. Through the micro-CT software, I moved the sample in the chamber, aligning the top of the
image with the surface of the skin. This positioning ensured the image captured the injection site, the
dermis, the sub-cutaneous fat, and the first layer of muscle fascia. Once the source was stabilized, I
initiated scanning. The machine rotated the sample 0.42 degrees at a time, taking a series of frames over
the period of an hour. Each frame was an average of two images, and eight random vertical movements
were executed during the scan to reduce ring artefact. I recorded chamber temperature at the beginning
and end of each scan.

A series of 1048 images resulted, each with a resolution of 1048 by 1480 pixels and a pixel size of
9.86 µm. All had been gathered perpendicular to the jet direction. I used the proprietary Bruker
software (NRecon) to reconstruct the images into a series of slices, each a cross-section of the jet in the
skin. I set the dynamic range for the series of reconstructed images by declaring the lower and upper
bounds as those images created with an attenuation coefficient of 0.005 and 0.013 respectively. This
range was selected based upon a histogram in NRecon that identified the image intensity lost as the
attenuation coefficient increased. The minimum, 0.005, sat between the intensities that I associated
with the tissue and those I associated with the bolus, and the maximum, 0.013, was set above the
intensities associated with the bolus. The program used the range to separate the signal of the bolus
from the signal of the tissue and repackage the separated signal into the reconstructed images.

I performed twenty-five injections and twenty-five scans over five days, with five viscous fluids tested
each day. The accumulated data was introduced into MATLAB. I progressed to analysis of the
distribution of the contrast in the skin, first projecting the intensities in the skin perpendicularly to the
jet direction and then parallel to the jet direction. As described by Figure 59, the x and y directions form
the plane perpendicular to the jet direction with the jet progressing down in the z direction.

I intended to place the origin at the injection point on the surface of the skin. Unfortunately, the centre
of the micro-CT images did not necessarily match the injection point. Therefore, I post-processed the
micro-CT images to identify the injection point. First, I imported the reconstructed data into a program
called 3D-creator (Version 2.5; Bruker, 2009). This program forms 3D models out of reconstructed
micro-CT images. I set a threshold of pixels with intensity above 61 based on the histogram of intensity
values where the minimum intensity between background signal and contrast signal at this point; I
stepped through every 16th frame (out of 1048), and set locality to 100, the maximum. The locality
setting ensured that the program only formed the solid out of the central mass of the fluid, rather than
artefacts present in the sample. Therefore, I assumed that the fluid was continuous under the skin. Once
the 3-D model was constructed, I used the healing wizard in RapidForm to remove folded, dangling,
small, and crossing poly-faces, and imported the resultant mesh into MeshLab. This mesh usually had
around three million faces. I reduced the number of faces to 200,000 in MeshLab using Quadric Edge
Collapse Decimation and smoothed the reduced mesh using a Poisson filter in MeshLab. I set the octree depth of the filter to 12, which determines the order of the quadratic terms used in the smoothing [153]. This depth provided sufficient detail at the edges. An STL formatted file was exported from MeshLab and imported into MATLAB, and from there, I could place a mark at the position where the fluid had pierced through the surface of the skin as it left a trail at this point. I modified the coordinate system and then applied the transform to the original data. From then on, the origin of the data was at the injection point, just below the surface of the skin.

I analysed the distribution of each test in the xy plane in MATLAB, with surface contrast fluid segmented out. Subsequently, I calculated a radius around the injection point that captured 63% of the fluid underneath the injection point (see Figure 60A). This percentage was chosen as it allowed the xy distribution to be represented in one number that could be compared across viscosities. The analysis was extended to the z axis by projecting each xy plane onto its depth. I found the depth from zero in the negative z direction that captured 63% of the injected fluid (Figure 60B). The final measure I evaluated was the percentage of the total fluid in the micro-CT data that was underneath the stratum corneum. Pattern-focussed methods such as principal component analysis were not used as the focus was on comparing the distributions between viscosities rather than the patterns that were formed when the skin was injected. The simplistic 3-D model that I used enabled the comparison between viscosities and provided a strong basis for conclusions, without complicating the analysis unnecessarily. The resultant values quantified the distribution of fluid underneath the skin surface, allowing easy comparison.
between the 25 tests.

### 6.3.2 Results

The mean jet speed across all tests was 109.1 m·s⁻¹, and the standard deviation was 3.4 m·s⁻¹. A linear regression on jet speed indicated no evidence of a difference in any measurements over the range of jet speeds tested. The mean volume ejected across the test set was 87.2 µL with a standard deviation of 2.4 µL. Only the percentage delivered depended on the volume ejected. It is expected that, with an increase of 10 µL of volume ejected, there would be between a 1.46 % and 61.5 % decrease in volume delivered.

A few examples of the dispersion patterns analysed in MATLAB are presented in Figure 64. It is upon the data presented in plots like these that the bulk of the data analysis was performed. The projected values of the z intensities on the xy plane produced 25 radii that captured the xy distribution for the 25 tests. These results were separated based upon the viscosity of the fluid injected. I identified two results that were outliers as they did not sufficiently penetrate the skin. The resultant values demonstrated normality (Shapiro-Wilk test p-value: 0.852) and had equal variance across the five sets (Levene test p-value: 0.563). An ANOVA of the data set revealed that the variation due to factors other than viscosity was greater than the variation due to viscosity. The raw data and the results of this ANOVA (and all subsequent ANOVA results) are presented in Appendix I.

A bar graph is presented in Figure 61, visualising the similarity in the results between the different viscosities. Each bar is the mean of the radius described above across the five different viscosities, with the error bars representing two standard deviations. The ANOVA of the results (available in Appendix I)
gave a p-value of 0.12 indicating that there was no evidence against the hypothesis that there is no difference in the mean value across the five viscosities.

Similar to the xy distribution measure, the depth from the origin that included 63% of the injected fluid was evaluated from the set of micro-CT images. As before, the data set demonstrated normality (Shapiro-Wilk test p-value: 0.077) and had equal variance amongst the sets (Levene test p-value: 0.557). Figure 62 presents a bar graph of the mean 63% depth across five different viscosities, with the error bars showing two standard deviations. The plot suggests no observed difference for all comparisons. The ANOVA of the results (available in Appendix I) gave a p-value of 0.62 indicating that there is no difference in the mean value of depth between the five viscosities.

The micro-CT image results presented both the fluid that had been injected, and that which remained on the surface. The contrast intensity that was located under the injection site was able to be presented as a percentage of the total contrast intensity in the whole data set. The result is the percentage of contrast fluid injected. The data set for percentage injected demonstrated normality (Shapiro-Wilk test p-value: 0.102) and had equal variance amongst the sets (Levene test p-value: 0.535). Figure 63 presents a bar graph of the mean percentage delivered across five different viscosities with 2 standard deviations indicated by error bars. The plot suggests that there is no difference in mean percentage delivered. The ANOVA of the results (available in Appendix I) gave a p-value of 0.29 suggesting that there is no difference in the mean value of percentage delivered across the five different viscosities.

I matched the results of the three measurements above with the average temperature recorded during the scan of the sample measured. I conducted a linear regression analysis as done with the gel test results (n = 25). The mean temperature for all tests was 29.5 °C, and the data set demonstrated a standard deviation of 1.4 °C. One outlier was removed, the last test of the fluid of 4.75 mPa·s viscosity, because of the delay the tissue sample experienced before injection (>12 hrs. since thawing). The total data set demonstrated normality across all three measurements (p-values: 0.441, 0.148, and 0.155 respectively). The p-values describing the reliance of the three fits on temperature are presented in Table 14.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Radial Distribution</th>
<th>Depth Distribution</th>
<th>Percentage below Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4.27 mm</td>
<td>-2.77 mm</td>
<td>70.64 %</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.66 mm</td>
<td>0.88 mm</td>
<td>17.60 %</td>
</tr>
<tr>
<td>P-value for effect of temperature</td>
<td>0.954</td>
<td>0.742</td>
<td>0.0979</td>
</tr>
</tbody>
</table>

Table 14 - Mean and standard deviation for tissue measurements, and the p-value that represents the evidence that there is no effect of temperature on the result of the measurement (n = 5).
Figure 61—Bar graph of the mean radius that captures 63% of the radial distribution in x and y across five different viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).

Figure 62—Bar graph of the mean depth that had 63% of the injected fluid above across five viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).
Figure 63–Bar graph of the mean percentage of fluid injected into the skin across five different viscosities. The error bars show two standard deviations. No significant difference was found between the sets of data presented (n = 5).
Figure 64 - Examples of dispersion patterns for the five different fluids with varying viscosities. A: 4.75 mPa·s, B: 22.4 mPa·s, C: 22.8 mPa·s, D: 47.1 mPa·s, and E: 101 mPa·s. The colour indicates the normalized concentration according to the colour bar.
Figure 65 - Examples of the dispersion patterns for each of the five tests with one viscosity (22.7 mPa·s). The colour indicates the normalized concentration according to the colour bar.
6.4 Discussion

During testing, I observed that injections into skin samples had a different mean steady-state coil speed than that recorded during injections into air. The steady-state jet speed is directly correlated to steady-state coil speed. As mentioned, I adjusted the feed-forward model to accommodate the effect of the skin, and the results show a reasonable level of jet speed consistency across the range of viscosities. The linear regression performed indicates that, at the very least, the different jet speeds with different fluids did not affect the results of the analysis of the effect of viscosity. This is reassuring as, along with volume, jet speed is a parameter that is something that would be expected to modify what was measured.

The first observation I make from the results presented in 6.3.2 is that viscosity seems to have very little effect on the dispersion pattern. The second observation is that the dispersion pattern is highly variable over the set of results. Previous results in [9], [74] agree with both of these observations. The control over the consistency of the jet, demonstrated in Table 11, indicates that the varying mechanical properties of the tissue samples are the cause of the variance, rather than any properties of the jet. Skin samples that are from different areas, with different thicknesses of each layer, are likely to exhibit high variability. A fundamental goal of controllable jet injection is to create a device that can be relied upon to inject into a specific anatomical layer underneath the skin surface. Control over the jet is just part of the solution, and knowledge of skin properties is necessary to ensure that a viscous fluid goes to where it is most effective. The results presented in this chapter show that, with more knowledge of skin variability, it would be possible to control the dispersion of fluids in the tissues underneath the skin surface, as skin variability is the main determinant of the dispersion pattern. This could be in the context of a sharp punch model such as that of Shergold and Fleck [81] or a Darcy-type model as used by Comley and Fleck [70] and Chang [82]. If such control is achieved, the only requirement to ensure that a jet formed with a more viscous fluid has the same dispersion pattern as that formed with one of similar viscosity to water is an equal volumetric jet speed between the fluids. The adjustment to the control system that achieves this is the viscous fluid feed-forward model presented in Chapter 4.

The focus of this investigation is not the variability of animal skin. The results show no evidence of a difference in dispersion between any two of the fluids tested. In fact, in the xy plane, a dispersion pattern of the fluid of 101 mPa·s viscosity is closer than the dispersion pattern of the fluid of 47.1 mPa·s viscosity to the dispersion of the least viscous fluid, that with a viscosity of 4.75 mPa·s; the comparisons for depth and percentage delivered are even more variable within sets. The measures used in the analysis were chosen as they represent the radial dispersion, the depth achieved, and the delivery
efficiency. While some skew was observed in the radial dispersion of a couple of the tests, the overall radial symmetry of most tests will nullify the effect of this. Therefore, I must conclude that the tests revealed no dependence of fluid dispersion on viscosity.

Why does viscosity not affect jet injection into skin? I hypothesise that, firstly, the momentum of the jet impacting the skin, and, secondly, the skin’s response to the injection, are the primary determinants of the dispersion. When the primary mode of that response is an increase in permeability of the skin, as asserted by Comley and Fleck [70], the magnitude of the increase in permeability may be significant enough, and variable enough, to be a much more important determinant of fluid dispersion than viscosity. It is possible that at higher levels of viscosity, viscosity would have an effect on jet dispersion in skin during injection. However, a fluid of significantly higher viscosity than explored in these tests would be required. This fluid would lie outside the range of viscosities that liquid drugs typically lie within. Additionally, a jet of a fluid with such a high viscosity is unlikely to be produced with current technology in a portable form. Therefore, the only situation in which the viscosity parameter in equation (6.1) will become significant is if the Reynolds number of the flow reduces below ten, as occurs in our range of viscosities post-injection, when speeds are much lower and more diffusion occurs. This period lies outside that observed during the experiments presented in this chapter.

The results of the temperature linear regression reveal that temperature had no significant effect on the distribution of the contrast fluid under the skin. The overall low effect of temperature matches up with the expected change in viscosity for glycerol over the range of recorded temperatures (1 % to 5 %). The temperature result highlights that the effect of viscosity is of a similar level or smaller than the effect of temperature for this set of tests.

The bar graphs (Figure 61, Figure 62, and Figure 63) and the results of the three ANOVAs show how there is no observed change due to viscosity. From Figure 62, it is clear that depth is the measurement that varies the most despite the viscosity of the fluid. This is concerning as depth is probably the most important parameter when trying to deliver to a layer underneath the skin. The plots remind us once again of the highly variant nature of skin, and the challenge that this poses to jet injection.

The shapes presented in Figure 64 give a good indication of the range of patterns seen throughout the tests. Figure 64E is a typical dermal layer injection, where the pattern is centrally focused on the end of the erosion hole. In many ways, it is similar to a three-dimensional version of a gel test result. However, the impact of the layers on a dispersion pattern is presented in Figure 64B and Figure 64D, with the sub-cutaneous fat layer visible in the bolus. When the jet pierces the sub-cutaneous fat, often the piercing point is not in line with the jet, and the fluid bulges in a non-uniform manner. Figure 64D
shows just how non-uniform this can be with the fluid bursting off to the side at the boundary between the sub-cutaneous fat and the muscle. This feature is an example of how the injected fluid can distribute along a layer interface.

Figure 64A and Figure 64C present the dispersion patterns of injections that pierced through to the muscle. Such injections often have areas above the muscular layer with very little contrast agent; this occurs as the jet does not spread out much until it reaches its stagnation point. Potentially, all the contrast fluid ejected in Figure 64A was not captured by the micro-CT imaging as it seems to continue over the edge of the camera’s field of view. However, this is likely to be a small percentage of the total fluid delivered, and is unlikely to have an effect on the averaged results. In the bolus of Figure 64C, the wider spread in the sub-cutaneous region is identifiable, with only some fluid entering the muscle. Finally, throughout all of Figure 10, the fluid left on the surface of the skin is visible, and the range of how much fluid is left is evident.

Figure 65 presents the range of dispersion patterns that I observed with just the 22.7 mPa·s fluid. This includes the dispersion profile from Figure 64C. The images show just how wide the range is, and include injections that reached the muscle (Figure 65E) and ones that only just penetrated the dermis (Figure 65C). Therefore, these images are a visual representation of the variability that my statistical analysis quantified.

The qualitative analysis of the boluses presented in Figure 64 and Figure 65 highlights the impact of the layers. With jet injection, we are not only trying to get through the stratum corneum. To achieve effective drug delivery by jet injection, more must be discovered about the properties of the two other interfaces: the dermal to sub-cutaneous fat interface and the sub-cutaneous fat-muscle interface. Given more knowledge of properties, such as the breaking stress of these interfaces, much of the variability experienced in skin could be accounted for. From there, a control system that focuses on correct layer delivery would be able to deliver a drug more effectively.
6.5 Conclusions

From the results and analysis presented in this chapter, I draw two conclusions. Firstly, the impact of viscosity on the dispersion of viscous fluids in both gels and pig skin is minimal. Its effect is masked by the variability of skin properties and behaviour. It is the interplay between the high-speed jet and the skin that determines the pattern of dispersion. In order to apply Darcy’s law effectively, the magnitude and variability of the permeability increase during jet injection would need to be quantified.

Secondly, skin presents a challenge to the makers of jet injectors. Layer accuracy is ideal for drug delivery, but not much is known about how the different layers underneath the skin surface behave when interacting with a high-speed jet. The control system of the jet injector requires more information about these properties in order to be more effective. Using the methods presented here, pig skin can be used as a model rather than gels, as micro-CT scanning effectively makes pig skin transparent. Further research should focus on achieving repeatable delivery into a pig skin model and then progress to performing experiments on post-mortem human skin.
7 Conclusions

7.1 Review of Outcomes

The primary objective of my PhD work was the development of a jet injector for viscous fluids. In the pursuit of this aim, I investigated the effect of viscosity on injector behaviour and performance, thereby addressing a significant gap in the published literature. I made solutions of glycerol with a range of different viscosities, and quantified the effect of their viscosity on injector performance. These results will be of use to both designers of jet injectors, and designers of the drugs that they inject, as they provide information about how fluid properties change the behaviour of the jet injection system.

The electromechanical model of the lab jet injector (LJI) provided a prediction of jet speed profile over time given an arbitrary voltage input. By modifying the properties of the jet injector components in the simulation I was able to predict the effect these would have on the movement of the motor’s coil and the pressure in the fluid, and thus the jet speed profile. This model continues to be used to predict the behaviour of the injector being developed in the ABI and MIT Bioinstrumentation labs, enabling researchers to make better design decisions as they further develop injectors for a wide variety of applications. It also reduces down the complex physical interactions of the devices to the main components, allowing researchers to understand the core fundamentals of jet injectors and what affects their performance.

The design and construction of the viscous fluid jet injector (VFJI) resulted in a jet injector capable of accelerating glycerol, a fluid with 0.635 Pa·s viscosity, to a mean jet speed of 170 m·s⁻¹. This was significantly better than expected, and indicated the wide range of fluids that can be made to reach such high speeds. It is possible that the sharp edge of the orifice geometry contributed to this performance and more research is required in this area. The high speed was achieved with a 200 µm orifice, but, due to the replaceable orifice insert incorporated into the design of the injector, I was able to profile the injector’s performance across a range of orifice diameters. While I decided that the 200 µm orifice was best suited to the application, this was only after the elimination of a range of orifice diameters. I was also able to quantify the jet power produced across the range of orifice diameters. The device and the
results of its testing were critical to the following investigations of viscous loss and of the impact of viscosity on jet dispersion.

I set out to discover the source of viscous loss in the ampoule through the use of a computational fluid dynamics (CFD) simulation. The results revealed that turbulent loss dominates when the viscosity of the fluid is low, and that viscous drag near the wall dominates when the viscosity of the fluid is high. Turbulent loss is reduced when the profile of the approach to the orifice is smooth, and the viscous drag is reduced when the narrow section of the geometry is shorter. The application of these insights to the design of internal ampoule wall profiles will reduce the pressure loss that occurs in the ampoule.

The effect of viscous heating is also very important, as the heating due to viscous drag near the wall is predicted to cause localised increases in temperature of up to 50 °C. This level of heating near the wall had not previously been reported but has been revealed as an important determinant of the jet speed achieved, regardless of device. The result means that the temperature dependence of the viscosity of the fluid that is to be injected should be investigated prior to jet injection, and its effect on the flow profile simulated. The results of the simulations with water indicated that the fluid is exposed to shear rates of up to $1 \times 10^8 \text{s}^{-1}$ in the ampoule during jet formation, and identified the locations of strongest shear during jet injection. This high level of shear had never been quantified before, and is indicative of the level experienced in a wide range of jet flows. Although the simulation over-predicted the viscous loss that occurred in both ampoules for fluids of high viscosity, the results were well-matched to experiments for fluids with lower viscosities. These models form a useful foundation for any further work in this area.

The final experimental chapter detailed the investigation of the effect of viscosity on the dispersion of fluids in gels and skin. The gel tests provided limited evidence for a reliance of dispersion patterns on viscosity, but, contrary to previous claims, no evidence was found for a reliance of penetration depth on viscosity. The tests in skin revealed no difference in measures of the dispersion pattern as the viscosity of the injected fluid was changed, as the variability in skin structure was the dominant influence on the shape of the dispersion pattern. From these results, I concluded that if a viscous fluid is at the required speed as it passes through the orifice, its dispersion pattern in tissue will be indistinguishable from that of a low viscosity fluid such as water. I expected there to be a significant difference due to viscosity as the range I was working across was broad, and my view of how jets disperse in the skin has been changed as a result. My work in this area also identified a wide range of dispersion patterns that can arise from jet injection, which could aid further research into the targeting of drugs in the different layers underneath the surface of the skin.
My investigations into the behaviour of viscous fluids in jet injectors, both with the LJI and the VFJI, revealed that the major impact of a fluid's viscosity is the loss that occurs in the ampoule of the injector. The results presented in this thesis can help guide the design of jet injectors for a wide range of drugs, in particular monoclonal antibodies and viscous gels that are currently under development. This work thus comprises an examination of the impact of a fluid’s viscosity on jet injection ranging from the electrical activation of the injector through to the interaction of the fluid with the skin.
7.2 Novel Contributions

7.2.1 Electromechanical Model

In this thesis, I present the first reported electromechanical model of a moving coil jet injector that incorporates the current response that arises from the non-linear inductance of the motor, the effects of the compliance of the ampoule and piston tip, and the impact of viscosity on the behaviour of the injector. The early results of the modelling process were presented at the IEEE Engineering and Medicine Biology Conference in San Diego, CA in 2013 as a poster and were the topic of a paper published in the proceedings of that conference [99]. The complete model, validation and parameter analysis as presented in this thesis have been accepted for publication as a journal paper in Transactions of Biomedical Engineering [10].

7.2.2 Control System

Additionally, I detail the first control system that can use a simple pulse test to estimate the viscosity of the fluid in the ampoule. This system is also the first control system to utilise a viscosity estimate, arising either from the pulse-test estimate or from user input, to ensure that the fluid jet that is emitted in an injection is at the desired speed. This functionality is incorporated into a control system that has been proven to be effective for jet injection. This work was presented as a poster to the annual meeting of the Controlled Release Society in Chicago, IL in 2014 and published in a two page abstract included in the conference proceedings [11].

7.2.3 Viscous Fluid Jet Injector Construction and Testing

- I have designed and manufactured a system that is capable of injecting fluid at a speed of at least 170 m·s⁻¹ using fluids ranging viscosity from 0.001 Pa·s to 0.635 Pa·s. The system performs repeatably, has a user friendly computer interface and allows injection characteristics to be studied in a laboratory environment.
- I carried out a detailed analysis of the effect of compliance on the behaviour of the injector, culminating in the design and manufacture of stiffer components, and quantifying their effect on the injector’s performance. These results established the deleterious effect that compliance has on the control of jet injection, and will help inform the future design of injectors.
- I tested a range of orifices with diameters ranging between 100 µm and 310 µm, discovering that the 200 µm orifice performed the best for the range of fluid viscosities within which most drugs lie. I present the impact of orifice diameter on the discharge coefficient and jet speed formed in the VFJI ampoule, illustrating the trade-off that must be made when choosing orifice diameters. In particular, this highlights the fact that orifices with diameters below 200 µm form
significantly lower mean jet speeds with viscous fluids than orifices of 200 µm diameter and above.

### 7.2.4 Computational Fluid Dynamics Modelling of Ampoule Geometry

- This thesis presents an analysis of jet injector pressure loss across a range of fluid viscosities using computational fluid dynamics. Thereby, it provides the first exploration of the turbulent and viscous effects in the ampoules of jet injectors, over a range that includes flows that are dominated by either turbulent flow or laminar flow. These results support the design of jet injection ampoules with short and smooth geometries in order to reduce both turbulent loss and viscous loss near the wall. However, further investigation is required to confirm the validity of this design approach for viscous solutions (viscosity > 0.1 Pa·s).
- I also identify, for the first time, the effect of viscous heating on the performance of a jet injector. My results provide evidence that the temperature dependence of the properties of the fluid in the ampoule has a significant effect on the pressure loss in the ampoule and the shape of the flow profile across the orifice. Future jet injectors that are designed for specific viscous drugs should take account of this effect.
- By using the same simulation, I reveal the shear rate that the flow is exposed to during injection of fluids of viscosities near to that of water. The effect of shear rate has not been quantified in the context of jet injection before, and its magnitude indicates that it is another factor that is important to take account of when designing jet injectors.
- I plan to write up these results in a journal paper for review towards publication in the journal Medical Engineering and Physics.

### 7.2.5 Fluid Dispersion Testing Across Viscosities

- The investigation presented in Chapter 6 is the first evaluation of the effect of viscosity on fluid dispersion in skin that accounts for the viscous loss that occurs in the ampoule. The results show that viscosity has very little effect on dispersion patterns, if the mean jet speed is held constant.
- I have established a micro-CT imaging protocol to analyse the dispersion pattern arising from a jet injection. This protocol enables future researchers to quantify 3-D jet dispersion in skin using metrics similar to the 2D metrics pursued previously in gels. A focus on skin samples rather than gels for future research will allow for a better anticipation of the behaviour of an injected drug under the skin surface.
- The dispersion study also illustrated the degree of variability in pig skin samples. The variability of results due to skin variability was considerably larger than the variability induced due to viscosity and temperature. A better control system that is informed about skin properties will also allow easier investigation of jet injection behaviour in skin samples.
I plan to write up these results in a journal paper for review towards publication in The Journal of Controlled Release.

7.2.6 Overall Review

Overall, the thesis provides a thorough analysis of the impact of viscosity on jet injection. The principal effect of increased fluid viscosity is to increase the pressure loss in the ampoule. Improvements to geometry of future injector ampoules will mitigate the effect of viscosity on pressure loss and jet speed. The thesis also provides guidance to those formulating drugs for jet injectors, with estimates of the shear experienced by a drug during jet injection and of the impact of viscosity on injectability.
7.3 Future Work

In this work, I have explored many of the physical challenges to needle free delivery of viscous fluids into the skin, but there are remaining questions that must be addressed to ensure that jet injected viscous drugs are effective post-delivery. The most important of these is to better understand the impact of viscous heating on the injected fluid. The discovery of the reasons for the overestimation of viscous loss in my computational fluid dynamics (CFD) model will be crucial to uncovering this knowledge. When considering viscous heating, it is important to remember that glycerol reduces in viscosity when heated, a property that may not be shared with other viscous drug formulations. Therefore, an investigation of the dependence of drug viscosity on temperature will be required for proper formulation of drugs for jet injection. In particular, temperature-related degradation of the drug during jet injection should be investigated more thoroughly. These investigations will also allow the control system of the jet injector to cater for such drugs, as more is known beforehand about how they behave in the high pressure ampoule of the jet injector.

This work also highlights the need for further research in the area of injectate-tissue interaction. In particular there is a need to better understand the skin's mechanical response to a jet injection, with a view to predicting drug dispersion in skin. The 3-D micro-CT imaging and X-Ray video imaging techniques developed at the Bioinstrumentation labs, at the Auckland Bioengineering Institute and at MIT, have provided a better understanding of drug-dispersion during and after injection. If correlations can be found between the drug distribution patterns and skin properties that can be measured from the skin surface, the injector could adapt the delivery parameters accordingly prior to or during each injection. This approach has the potential to increase the effectiveness of injections by ensuring that drugs are delivered to their targeted layers with greater efficiency and precision.

The CFD modelling presented in this thesis can be built upon as techniques such as particle image velocimetry reveal more about the nature of fluid flow in the ampoule and orifice. Micro-CT is a convenient tool for extracting or confirming the geometry of any ampoule for use in fluid-flow models. The CFD model used in this work may also be a useful design tool for iterative optimisation of ampoule geometry for a specific drug or a range of drugs. Finally, the shear rate predicted for the fluid in the ampoule should be compared to the damage experienced by a wide range of drugs during jet injection. Although there is scant evidence for shear-induced drug degradation in jet injection [91], [144], a link between these might require that ampoules be designed to minimise shear rate.

The viscous fluid jet injector itself is ready for further development and miniaturisation. With the knowledge that viscous fluids can be injected at speeds around 110 m·s⁻¹, the motor can be reduced in
size and made into a handheld device. Other research work being conducted by my colleagues at the ABI is resulting in the creation of smaller moving coil motors with higher force density than previous devices. These developments mean that a smaller injector can remain fully capable of injecting a wide range of fluids with different viscosities, while retaining the advantages of electronic control. Recent advances in amplifier construction and battery technology will also reduce the size of the amplifier and control system. These advances, in conjunction with further CFD modelling of ampoule internal geometries, will allow our researchers to develop effective and portable jet injectors, for use with a wide range of viscous drugs.
Appendix: Data from Dispersion Studies

Gel Test Data (next page)
<table>
<thead>
<tr>
<th>Viscosity (Pa·s)</th>
<th>Jet Speed (m·s⁻¹)</th>
<th>Follow-through Speed (m·s⁻¹)</th>
<th>Time above 100 (m·s⁻¹)</th>
<th>Volume (µL)</th>
<th>Area (mm²)</th>
<th>Width (mm)</th>
<th>Height (mm)</th>
<th>Depth from Surface (mm)</th>
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<td>11.5</td>
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Table 15 - Raw data from gel test experiments.
### Porcine Skin Test Raw Data

<table>
<thead>
<tr>
<th>Viscosity of Fluid (Pa·s)</th>
<th>63% Radius in xy (mm)</th>
<th>63% depth (mm)</th>
<th>Percentage underneath Surface (%)</th>
</tr>
</thead>
<tbody>
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## ANOVA Results for Porcine Skin Tests

### ANOVA for 63% radius in xy

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<tr>
<th>Source of Variation</th>
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<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
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<tr>
<td>Total</td>
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### ANOVA for 63% depth

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<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
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### ANOVA for Percentage underneath Surface

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Bibliography


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[72] G. Boyer, H. Zahouani, A. Le Bot, and L. Laquieze, "In vivo characterization of viscoelastic properties of


