Mathematical Modelling for Faster Auto-Injector Design

By Jonathan Wilkins and Iain Simpson at Cambridge Consultants

A mathematical model has been developed that can be used to predict how key design parameters affect the overall performance of an injection device, bringing benefits in terms of reduced development time, more robust and adaptable designs, and reduced product cost.

There is an increasing demand for advanced injection devices that bring benefits around self-administration and ease of use, and also for injectors that work with new biological drugs that often need to be delivered in larger volumes and/or at higher viscosities than those for conventional drugs. In order to reduce development and manufacturing costs, there is also a desire for 'platform devices' that can meet a broader range of drug and user requirements through simple adaptation of a core design – but unfortunately, a number of devices currently on the market do not meet these requirements. Furthermore, there is often a lack of detailed understanding as to how the key design parameters affect overall device performance. This can lead to product recalls, or present challenges in adapting the designs to meet new needs. Hence, there is a commercial need in the injectables industry for a greater insight into how design fundamentals affect the performance of auto-injector devices.

A fast and effective approach to designing a better injection device is a novel combination of mathematical modelling on a desktop PC, supported by complementary experimental data. The use of mathematical modelling gives insight into the physical behaviour of the device, and allows rapid prediction of the effect of different parameters during the design process. The more established experimental approach provides confirmatory data to support the modelling. We have deployed this methodology in a number of development projects and achieved benefits in terms of reduced development time, more robust and adaptable designs and reduced product cost.

Mathematical modelling allows for fast simulations of device performance, predicting the effect of design parameters, such as injection time, injection force and shear stress on the drug in real time. This allows the engineer to investigate the design space and quickly optimise a suitable set of components for a new injection device.

In this article, we present a Simulink® and MATLAB® (MathWorks) mathematical model of device performance applied to a generic auto-injector that is not tied to any specific commercial device and thus can be tailored to investigate a wide range of interesting design features. We describe our approach and the type of physics used inside the model, and demonstrate how experimental data can be used to calibrate and verify the model.

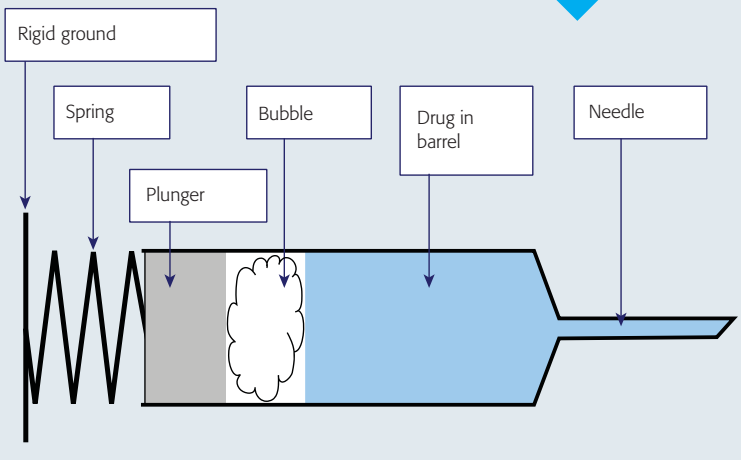
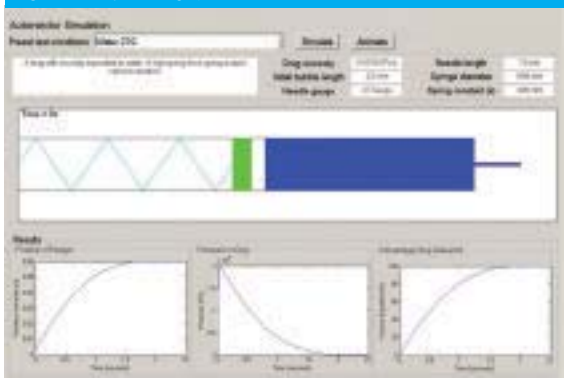


Figure 1: Schematic of the auto-injector

Keywords

Injection device
Auto-injector
Mathematical modelling

Figure 2: Easy-to-use graphical interface for the model



Images: Cambridge Consultants

The Auto-Injector Model

The generic autoinjector considered for the model is shown in Figure 1; it has the following components which are commonly found in most commercial devices:

- A syringe containing the drug
- A needle
- A compliant plunger to seal the drug into the syringe
- A drive spring as the energy source that powers the plunger
- A liquid drug
- An air bubble between the drug and the plunger

The trigger that activates the autoinjector by releasing the spring force onto the plunger is not considered.

The physics of each component can be considered in isolation using ordinary differential equations that vary with time:

- The needle is modelled as a component that creates viscous pressure losses via the Hagen Poiseuille equation, and inertial pressure losses at the entry and exit
- The drug is modelled as a Newtonian fluid
- The plunger is modelled as a rubber component with linear compliance, subject to a maximum compression limit
- The syringe exerts a frictional force on the plunger. For the purpose of the model, a 1ml BD Hypak® syringe was used as a representative commercially available syringe
- The air bubble is modelled as a compliance, with an internal pressure related to the amount of compression via Boyle's Law
- The spring is modelled as a linear compression spring; it is initially compressed and then expands during device activation. It would be a relatively minor change to the mathematical model to replace the mechanical spring with a motor energy source, as used in electronic auto-injectors like the EasyPod® (Merck Serono)

The equations describing each component are assembled into a Simulink and MATLAB mathematical model of the entire auto-injector system where all the components are interdependent. As shown in Figure 2, the user-friendly graphical user interface (GUI) allows for key design parameters to be changed easily, provides a graphical representation of the syringe plunger motion and also plots out metrics of interest such as plunger motion, drug pressure, and percentage of drug delivered as a function of time.

The model allows us to look at the physical behaviour of the auto-injector at different points in time. Some of the parameters that can be predicted are easy to calculate mathematically but difficult to monitor experimentally – for instance, shear stress on a drug. This is important since high levels of shear stress can damage and degrade the molecules within the drug, particularly in the case of newer biotech drugs. An example of shear stress simulation is shown in Figure 3 for a drug with a viscosity six times greater than water, that is being driven by a spring with a stiffness

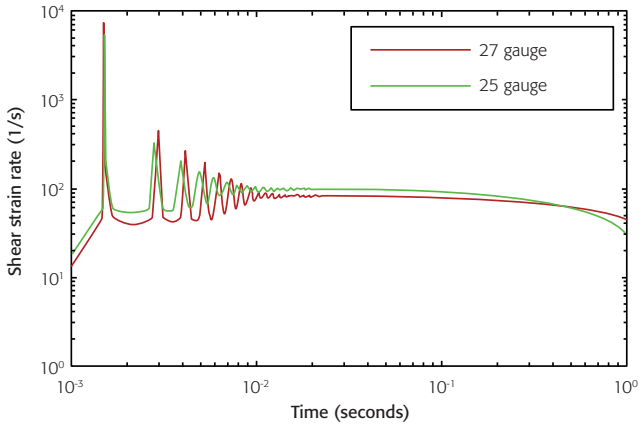


Figure 3: Drug shear strain rate predictions

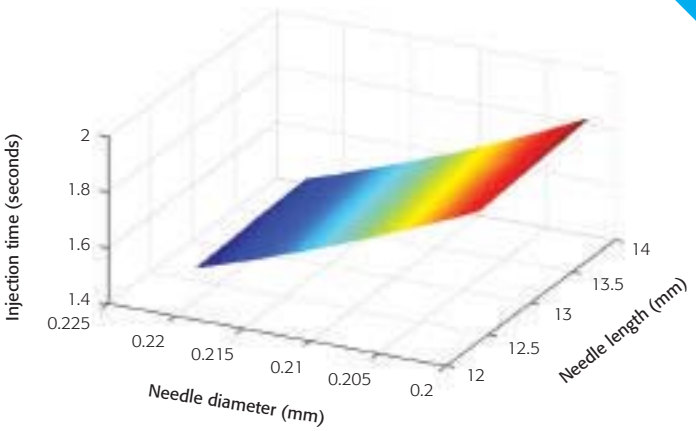


Figure 4: Injection time sensitivities to needle tolerances

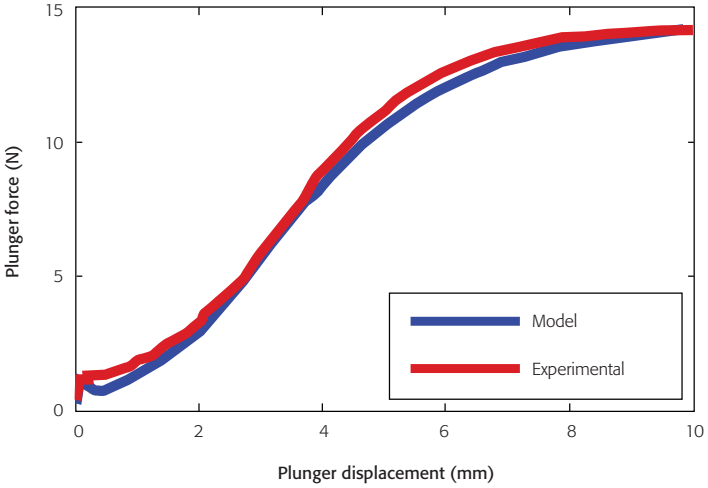


Figure 5: Experimental and simulated plunger forces for a verification test case

of 600 N/m with either a 27 gauge or a 25 gauge needle. Initially, the shear stress is several orders of magnitude higher than the steady state value, due to the 'impact' of the initial spring release that causes rapid compression of the bubble, and subsequent high driving pressures and velocities for the drug in the needle. It is found that the smaller diameter 27 gauge needle has a peak shear strain rate approximately 50 per cent higher than for the 25 gauge.

The model also highlights sensitivities in the design. For example, consider the effect of needle diameter ±5 per cent tolerances (nominally 27 gauge) and needle length ±5 per cent tolerances (nominally 0.5 inches) on the time taken to deliver 1ml of drug with a viscosity equivalent to water. Injection time is an important metric since the patient will prefer a shorter duration injection rather than a longer one.

The contour plot in Figure 4 predicts that injection time is much more sensitive to needle diameter than to needle length. A difference of 23 per cent in injection time results from changing the needle diameter by only -5 per cent to +5 per cent of nominal. This knowledge allows the designer to focus on the needle diameter as the single most powerful design parameter that can be used to adjust injection time.

A designer may have to adjust the design to compensate for changes in the drug formulation. This is particularly true for 'platform devices' where a standard mechanical layout is customised to suit a range of drugs. The mathematical model can be used to predict how the design must be altered to cope with a change in drug properties such as viscosity.

For instance, suppose an initial version of the device platform is developed to work with a viscosity equivalent to water (1 centipoise) and has an injection time of 1.6 seconds. This is achieved by using a spring of stiffness 600 N/m. If a new drug formulation has a viscosity that is five times higher (5 centipoise), and there is a requirement that the injection time should remain constant, then the model predicts that to achieve this, a spring stiffness of approximately 1,250 N/m will be required. This analysis takes minutes to perform with the mathematical model, but would otherwise require a lengthy experimental programme involving many different mechanical prototypes. Having determined the required higher spring force, the rest of the design can then be re-evaluated and modified if necessary to ensure that it can function with the stronger spring.

Experimental Verification

It is important to be able to confirm that the underlying equations representing each component in the model are realistic, and that the output from the mathematical model can be trusted. One way to verify the model is to compare it with experimental data of the force required to drive the plunger on a representative commercially available syringe. The measurements were made on a Mecmesin force-displacement tester that drives the syringe plunger at constant velocity and records the required force. This is a slightly different scenario from the original mathematical model in which a known force from the spring is applied and the velocity of the plunger is calculated; thus a modified

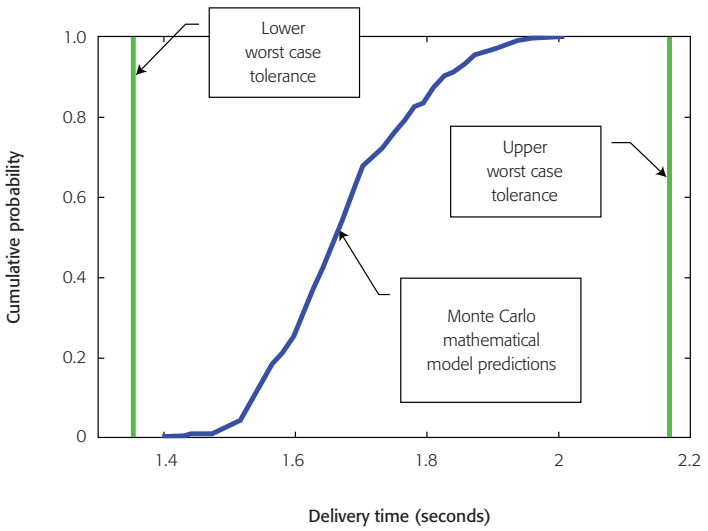


Figure 6: Monte Carlo tolerance analysis predictions

version of the mathematical model was developed specifically for verification where the velocity of the plunger is specified and the plunger force is calculated. The verification model was compared against several different experimental test cases. A sample verification of the plunger force mathematical model predictions and measurements is given in Figure 5 for a test case with a 2.5mm long air bubble in a 1ml syringe, a 30 gauge needle and a test liquid six times more viscous than water. Predictions and measurements are in good agreement.

Case Study: Manufacturing Tolerance Analysis

A common problem with injection device development is to understand the effects of manufacturing tolerances on the design. We can apply the mathematical model to predict the sensitivities of an auto-injector to realistic manufacturing process tolerances to see whether a design will always perform to specification.

For example, the mathematical model can be used to aid the designer in understanding how differences in spring stiffness or shape arising from production variations might affect drug delivery performance.

As an example, consider a device comprising a 1ml BD HyPak syringe with a nominal 27 gauge needle of 0.5 inches in length, and investigate the effect of tolerances on injection time. We assume that each of the needle diameter, needle length and syringe diameters vary with a process variation of Cp = 1.33. Using a Monte Carlo approach, we simulate a sample of 1,000 syringes that embody this distribution of tolerances; the results are shown in Figure 6. The mathematical model is run once for each of these syringes and the injection times are predicted. This takes a matter of hours. Doing this experimentally would take weeks, and would require a lot of test specimens to be made at representative tolerances – which would be expensive.

This Monte Carlo approach is more realistic and gives a narrower range of injection times than a simpler 'worst case' tolerance analysis, where all tolerances are assumed to be at the maximum permissible extremes. The combination of the mathematical model with a Monte Carlo approach means the designer has a more realistic knowledge of the effects of tolerances, and can make statements such as '90 per cent of all devices will have an injection time between 1.5 and 1.9 seconds'. The fact that the real distribution of tolerances is narrower than the 'worst case' values means the designer can achieve a given outcome and still specify less restrictive tolerances in the manufacturing processes. This will result in considerable cost savings, particularly with an auto-injector that is likely to be made in quantities of millions per year.

Conclusion

The mathematical model can be used at the early concept or design stage of injector development to define key components, such as the drive spring or needle, in order to meet the product requirements specification. The model also facilitates platform solutions by allowing the designer to predict rapidly the changes needed in an existing device to meet a change in drug specification. Much of the behaviour that the model can predict is difficult to measure experimentally – such as shear stress in the drug or behaviour over short time-scales – but gives valuable insight into how the device functions. The model is also valuable during the manufacturing scale-up process, as it uses a Monte Carlo approach to simulate the effect of tolerance interactions on device performance.

We believe that more extensive use of mathematical modelling in combination with experimental testing throughout the development process can lead to more robust 'platform' injection devices – hence reducing the risk of product recalls and enabling more reliable and cost-effective adaption of device designs for the delivery of new therapies.

Jonathan Wilkins led a range of drug delivery device developments as Senior Consultant at Cambridge Consultants, from inhalers through to novel injection systems. He has an interest in applying mathematical modelling techniques to speed the development and optimisation times of new products. Jonathan has an Engineering degree and PhD from Imperial College, University of London, specialising in fluid mechanics. He is currently Qualification Manager at Magma Global, developing novel materials and processes for the oil and as industry.

Iain Simpson is Associate Director of Drug Delivery in the Global Medtech Practice at Cambridge Consultants. He has a 20-year track record of multi-disciplinary technology and product development, the last 12 of which have been spent mainly in drug delivery covering parenteral, pulmonary and nasal delivery, as well as more invasive device technology where he has worked mainly in programme management and review roles. Iain has written and presented papers on a range of drug delivery topics including the development of inhalers for children, technology licensing, improving device compliance and usability. He also lectures on drug delivery as part of the Cambridge University Masters in Bioscience programme and is a past Chairman of the R&D Society. Email: iain.simpson@geconsultants.com