PHARMACEUTICAL TABLETTING and QbD

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The Quality by Design (QbD) initiative requires that manufacturers demonstrate understanding of their manufacturing process, but when tableting is sometimes described as a "black art", there is a miss-match between what the regulators expect, and the information that some manufacturers can provide. This article describes the use of hydraulic powder compaction simulators to measure and understand the tableting process, and it illustrates some of the inaccuracies that can lead to production failures

THE PROCESS

To visualise the forces and speeds involved in tableting is difficult; an average 15KN compression force (weight of a large car) on a 9.5mm diameter round tablet, generates a pressure of about 2000 atmospheres, or 60,000 ft of water. Trapped air compressed to this pressure would heat to over 1100 Degrees Centigrade adiabatically. On a large production press running at maximum speed, the load applied to the tablet in the last 1.0 mm of compression, happens in less than 5 milliseconds, and the dwell period, (for a punch head with a 10mm diameter flat on top), is only 3 milliseconds. The press running at half speed only gives 10 milliseconds "compression" and 6 milliseconds true dwell time.

Powerful hydraulic powder compaction simulators are used to study the tableting process in most major pharmaceutical companies. They allow the process parameters that affect tabletting to be individually controlled, so that the effect on the process can be measured. But, what are the important process parameters that make an accurate simulation of production scale tableting? And, what parameters should have a defined range for controlling production? These are the essential decisions to define the "Design Space" for this part of the manufacturing process.

A selection of parameters might be: powder physical properties, powder feed method, punch draw down speed, pre-compression profile, resting time, main compression profile, resting time, ejection profile, push-off speed, die temperature, punch to die clearances, and humidity. It is important to consider the parts of the process where nothing seems to be happening, but relaxation, de-gassing, or heat transfer is important.

Different simulators allow varying levels of control of the process parameters, from full control of each parameter, to only very basic speed or load control of the whole operation.

Practically, the momentum of a large production press turret, and the stiffness of a large machine are difficult to simulate in the laboratory. Tableting forces can be very high and small deflections very significant. To closely control the process, the compaction simulator must be, in its effect, stronger and more powerful than the production machine to be simulated.

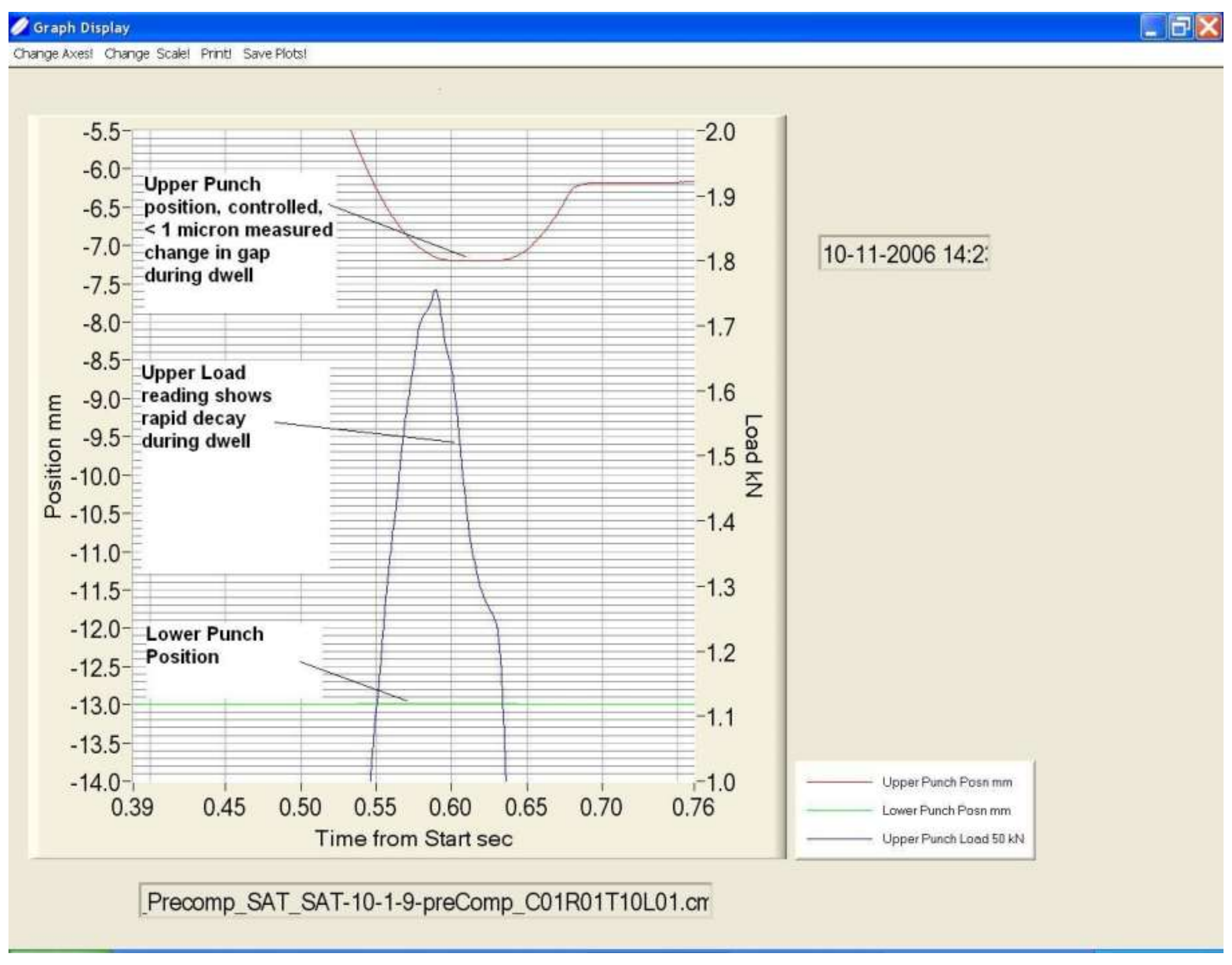
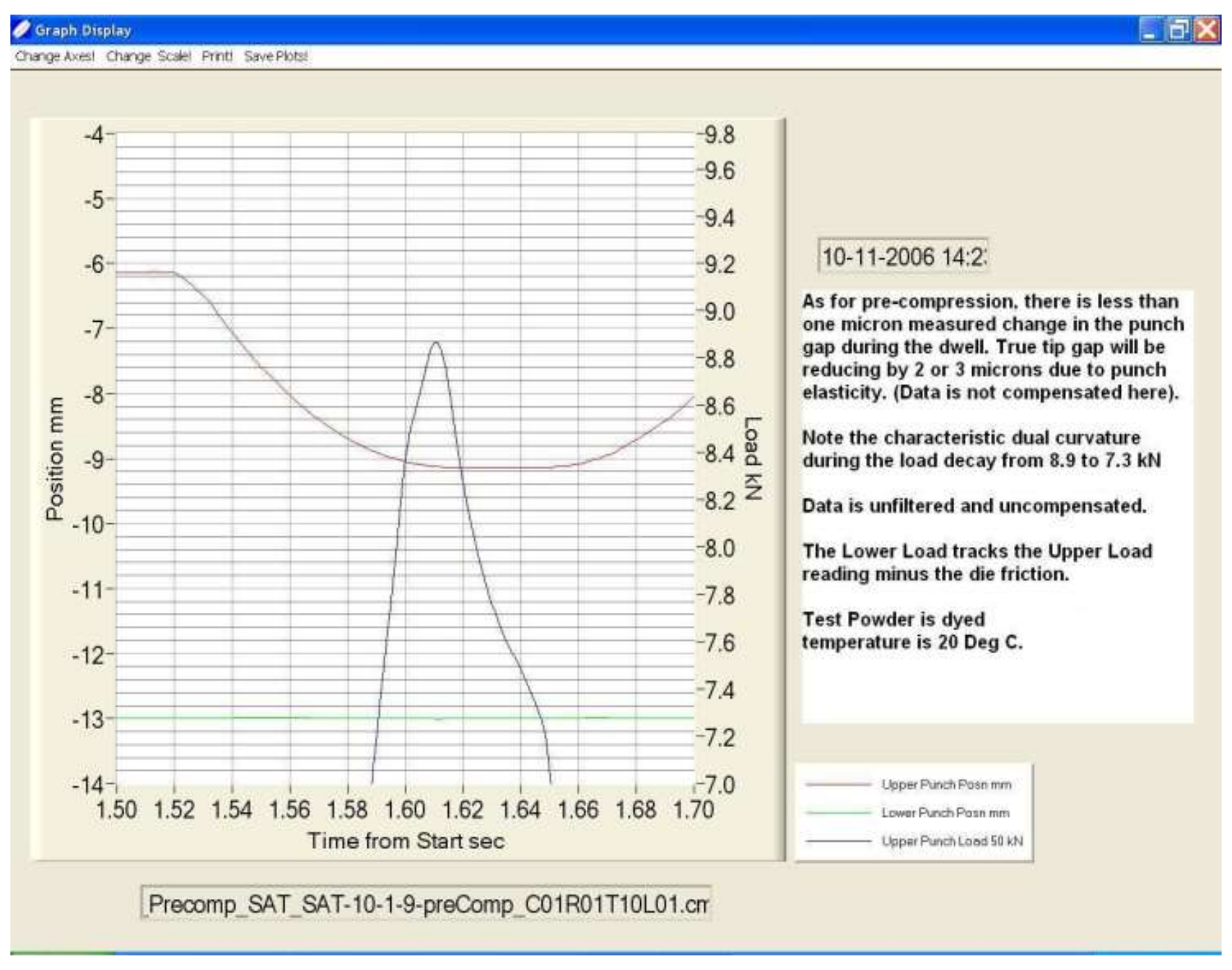


Fig. 1: Load relaxation during pre-compression



As for pre-compression, there is less than one micron measured change in the punch gap during the dwell. True tip gap will be reducing by 2 or 3 microns due to punch elasticity. (Data is not compensated here).

Note the characteristic dual curvature during the load decay from 8.9 to 7.3 kN

Data is unfiltered and uncompensated.

The Lower Load tracks the Upper Load reading minus the die friction.

Test Powder is dyed temperature is 20 Deg C.

Fig 2: Load relaxation during main compression

PROCESS MEASUREMENT

Understanding the measurement is the first step to understanding the process, and it requires some expertise. Production tableting is a dynamic process, and dynamic measurements are more involved than static measurements. For a rapidly changing value, the measurement is affected by: the type of transducer, its mounting, the electronic conditioning, the data acquisition system, and any pre or post filtering of the signal. Loads will be affected by inertia, and temperatures will be affected by conduction. Any derived material properties will be affected by the synchronisation of the transducer signals, but **standard calibrations will not reveal any of these potential errors**.

Figures 1 and 2 show data recorded on a **Huxley Bertram Compaction Simulator**. The relaxation of the load is considerable during the dwell periods at both pre and main compression stages, and the relaxation clearly has different phases, and is time dependent. Relaxation, or compaction, is also occurring during the load build-up, and the strain-rate will determine how the compaction progresses, and what peak temperature and load are achieved. The importance of simulating the correct dwell timing, and timing between the pre and main compression, and the delay before ejection, is also highlighted by these "relaxation" processes.

The pressures, movements, and friction forces can only be measured on the outside of the tablet, but the materials data generated can be used to populate mathematical models, which in turn can be used to predict conditions inside the tablet, and to detail the pressure, temperature and stress distributions in and around the tablet. Refs: (1) and (2).

Figure 3 shows a theoretically generated result for Young's Modulus relative to compaction pressure. The result is then corrected for errors in position due to deformation of the punches, and then to demonstrate data synchronisation errors, a filter is applied to the position signal, causing a time shift equivalent to 0.25 milliseconds during a fast test. Non synchronous data acquisition will also introduce a time shift that can corrupt derived values in high speed tests, but a simple analysis can be used to check the effect.

STRAIN RATE SIMULATION

Strain Rate for a tablet is the speed that the punch "tips" are closing divided by the separation of the punch tips. As the tablet is compressed, the punches are following an approximately sinusoidal profile. When the punches reach the dwell period at the limit of travel, the strain rate reduces close to zero. Compaction is still occurring during the dwell period, so the load reduces, and the elastic strain within the press continues to push the punch tips together. At the end of the dwell period, as the punches start to move apart, any remaining elastic strain within the press is released, which keeps pushing the punches together, and effectively increases the dwell time. Then the upper punch moves away, and after a short delay as the tablet relaxes and cools, the ejection movement starts.

At higher loads, the theoretical punch tip movement is reduced by the elasticity of the punches, the cam wheels, their bearings, and the press structure. In a small lab scale press, the punch speed will also be changed by the dynamic reaction of the drive system to the increasing load. A "spring back" in the drive system will cause an over-speed during the following dwell period, which may hide the error in any average speed indication.

Figures 4 and 5 show the effect of drive system wind-up assuming a transient 10% drop off in speed, calculated from the work done. The "spring-back" is shown in approximately 15ms. The assumed figures are mathematically derived, and not results from a particular press.

The strength, power and momentum of a large production press will tend to generate higher strain rates than cam driven laboratory presses, when operated at the same theoretical punch speed. Unfortunately, this will usually tend to make production tablets more liable to capping or de-lamination relative to development tablets. Conversely, hydraulic simulators, controlling to calculated motion profiles, will tend to generate higher strain rates than a production press, and defects are more likely to be seen on the development tablets than on production.

Powder compounds that are not very compressible, will exhibit a very fast load rise at the end of the compaction, and the strain rate simulation errors due to differences in machine compliance will be magnified. Peak temperatures at incorrect strain rates may also be very different, leading to difficulties in scale-up and production.

Figures 4 and 5 show theoretical "Strain Rate" and "Load" profiles for different types of press, compared to a profile that assumes a perfectly rigid machine. They were generated by using a simple exponential loading relationship, and solving the equations for load, position, and machine compliance. The following data was used:

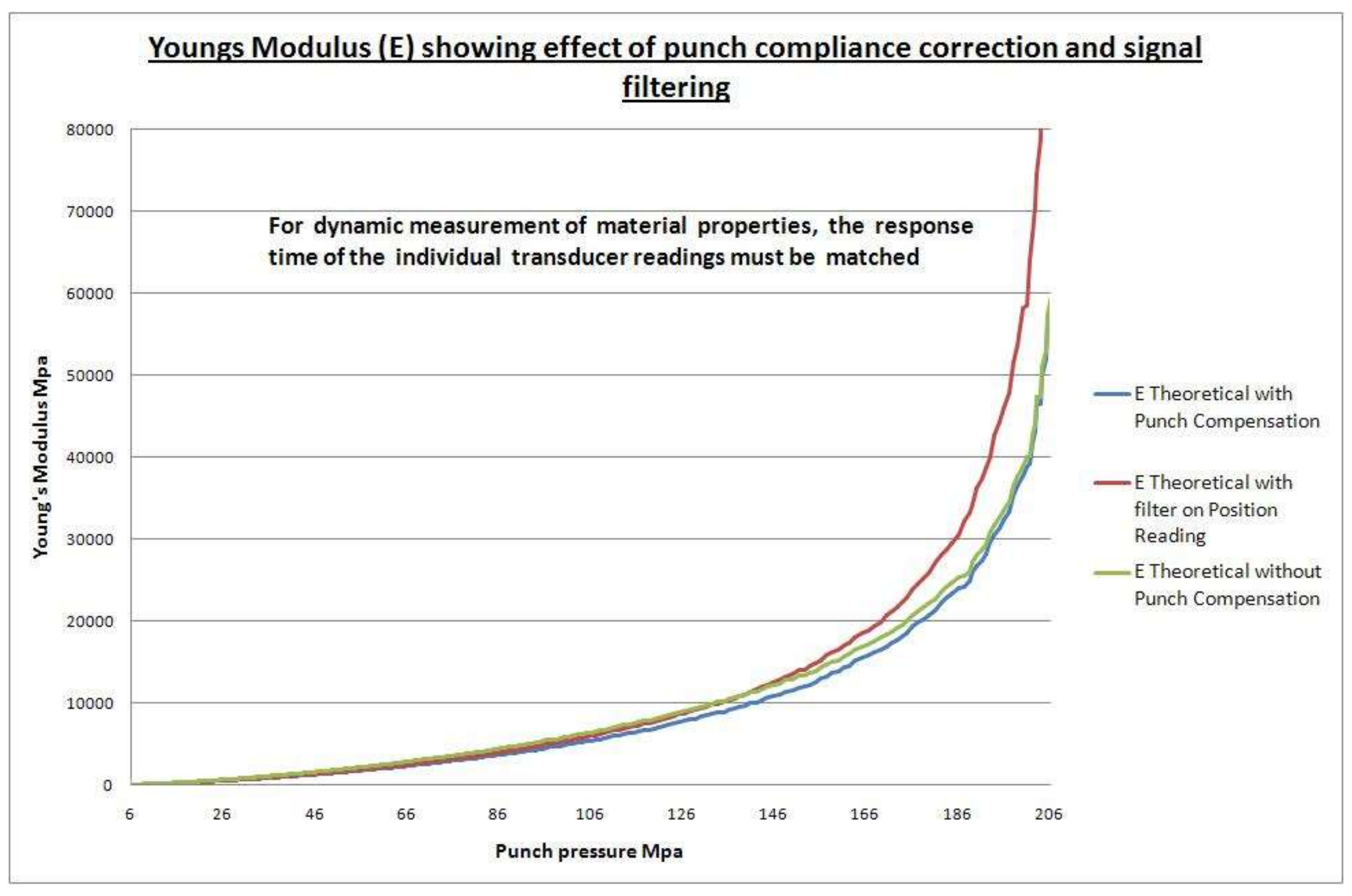


Figure 3 – Errors in Young's Modulus due to uncompensated or unsynchronised readings.

Tablet peak load = 15 KN

Tablet final height, H(f) = 3 mm

Tablet full density height, H(s) = 2mm

Punch Compliance, C(p) = 0.009 mm/KN each – (measured B series, round, flat, 3/8 Dia.)

Lab Scale Cam Operated Press estimated compliance (excluding punches), C(lsp) = 0.040 mm/KN

Lab Scale Cam Operated Press exhibiting estimated 10% speed loss at max load, spring-back in 15ms.

Production Press estimated compliance (excluding punches), C(pp) = 0.020 mm/KN (no speed loss)

Hydraulic Lab Scale Press controls position from punch holders and therefore automatically corrects

for machine compliance, (shown not automatically correcting for punch compliance).

The equation used to generate the load curve is simply:

Load (L) = Loading Constant (K) / (Tablet Height(H) + Total Compliance(C(t))×Load(L) – H(s))

The loading constant (k) is set to give the desired peak load at a tablet height of 3mm in this case.

Total Compliance, C(t) is the Punch Compliance C(p)×2, added to the Press Compliance C(lsp) or C(pp).

The above Load equation then multiplies out to:

$$C(t)\times L^2 + L\times(H-H(s)) - K = 0$$

And can be solved by the standard quadratic solution:

$$X = (-b \pm \surd(b^2 - 4\times a\times c)) / 2\times a$$

Or, $L = -(H-H(s)) \pm \surd((H-H(s))^2 - 4\times C(t)\times(-K)) / 2\times C(t)$

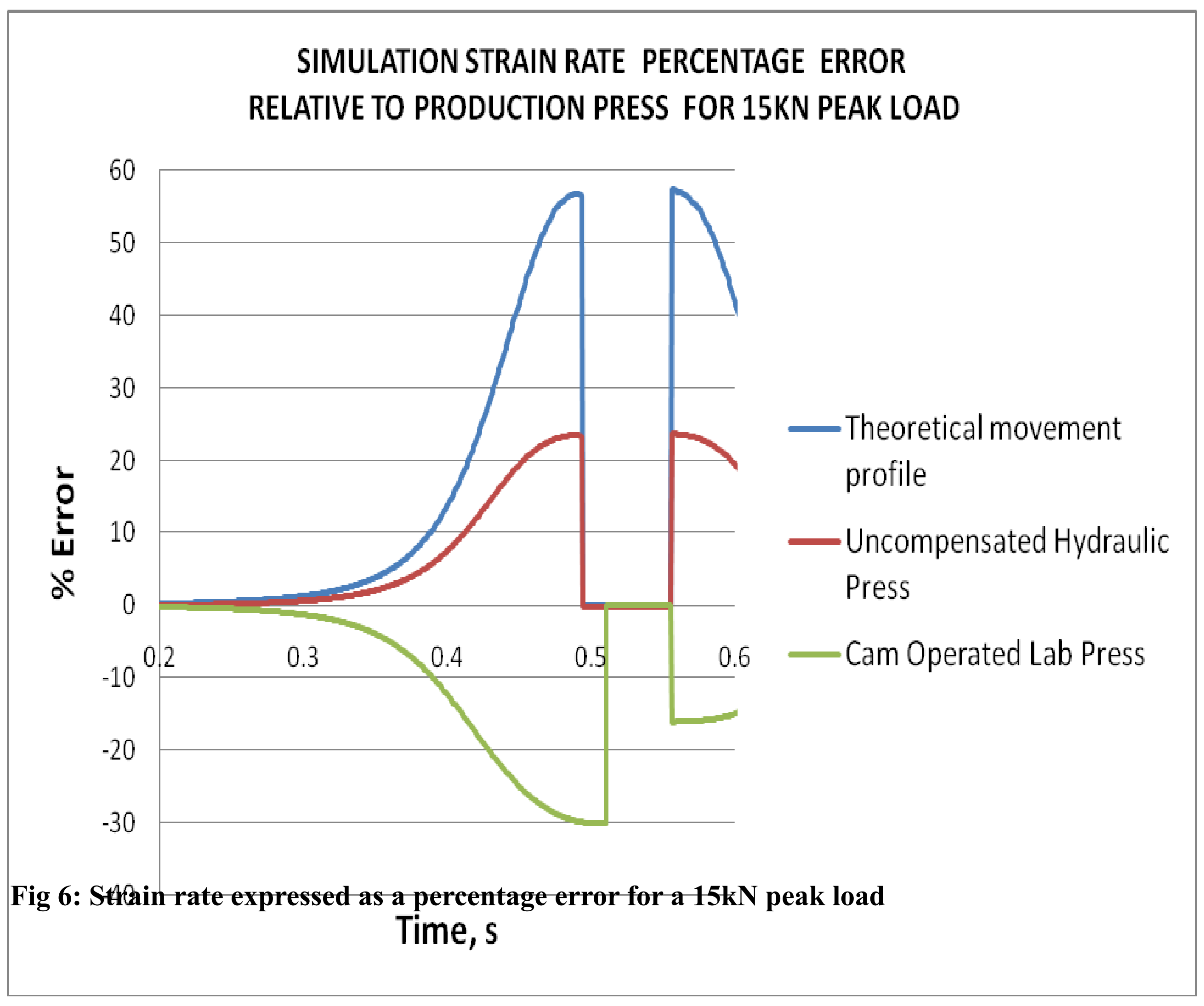
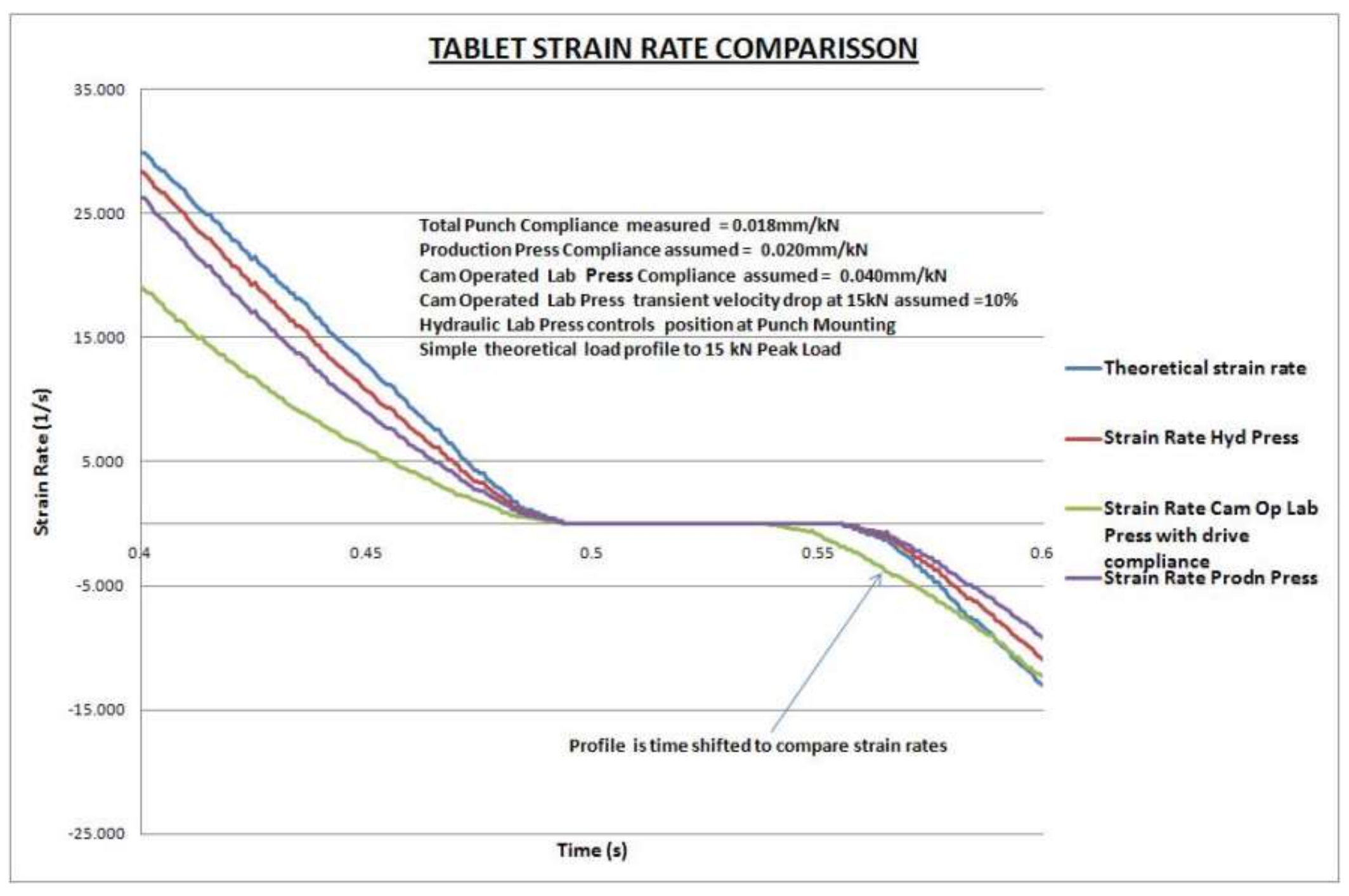


Fig 6: Strain rate expressed as a percentage error for a 15kN peak load



Total Punch Compliance measured = 0.018mm/kN
Production Press Compliance assumed = 0.020mm/kN
Cam Operated Lab Press Compliance assumed = 0.040mm/kN
Cam Operated Lab Press transient velocity drop at 15kN assumed =10%
Hydraulic Lab Press controls position at Punch Mounting
Simple theoretical load profile to 15 kN Peak Load

Fig 4: Tablet Strain Rate variations resulting from machine compliance

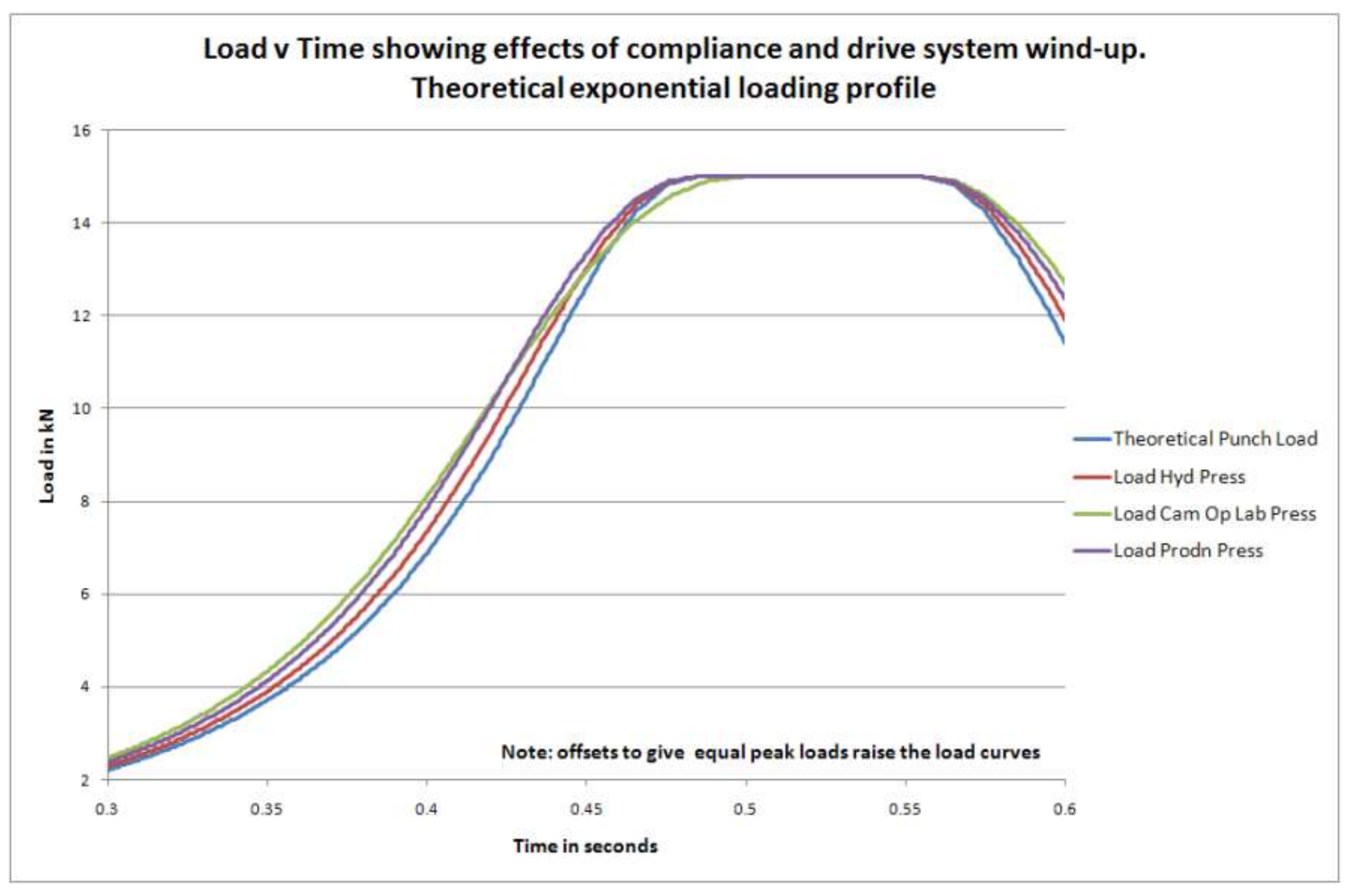


Fig 5: Tablet Load Profile variations resulting from machine compliance. Theoretical gap setting adjusted to give equal peak loads.

Strain Rate is calculated simply as:

Strain Rate = (Delta(H) / (H)) / Delta Time (Units $^1/s$)

The effect of compliance in the drive system of a cam operated lab scale press is simulated by assuming that

the lost speed is due only to elastic effects. In reality it will be due to loading of the motor plus elastic effects.

If a figure of 10% is used for a 15kN load, then the time base can be stretched by using:

Corrected time, $t(c) = t + (0.1\times t \times L/15)$

To simulate a "spring-back" in the drive system during the dwell period, the time base is simply accelerated over the estimated time period until it has recovered.

The theoretical punch motion profile is generated by the Rippie Dannielson equations using a 300mm diameter cam wheel, and a B type punch with a 5mm punch head radius. The profile was calculated using a Compaction Simulator software package.

The data is plotted for a typical tablet peak load of 15kN and estimated stiffness values for the different types of machine. To predict the strain rate errors for any particular combination of Compaction Simulator and production machine, the stiffness of the punches and the compacting roller assemblies should be measured or obtained from the manufacturers. The dynamic speed variation of a cam operated simulator has a larger effect on strain rate, and is the hardest to measure. A clean, unfiltered, accurate punch position signal will allow comparison with a theoretical position profile, but otherwise a high frequency velocity measurement of the turret or cam (depending on design) is required.

CONCLUSIONS

The tabletting process has been regarded in the past as a "black art" for good reasons. It is technically challenging to test the process at production conditions before commercial quantities of powder exist, and physical differences between the development and production presses can significantly affect the process.

Existing Compaction Simulation equipment can be investigated for accuracy by comparison of machine compliances and measurement of drive system performance. The expected errors can then be plotted using a spreadsheet and simple loading equations. To derive material properties from machine test results at production speeds, the effect of filtering and data synchronisation must be checked by investigation and simple simulation.

To make a meaningful simulation of the tablet strain rate in production machines, it is necessary to prove that the simulator can replicate the loading rate of the particular production machine running at the same theoretical speed.

REFERENCES

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