White Paper 3

Process Monitoring with DFF Sensor. Raw Data Signal, Force Pulse Magnitude (FPM), Mean FPM (MFPM), FPM Distribution Width (WFPM)

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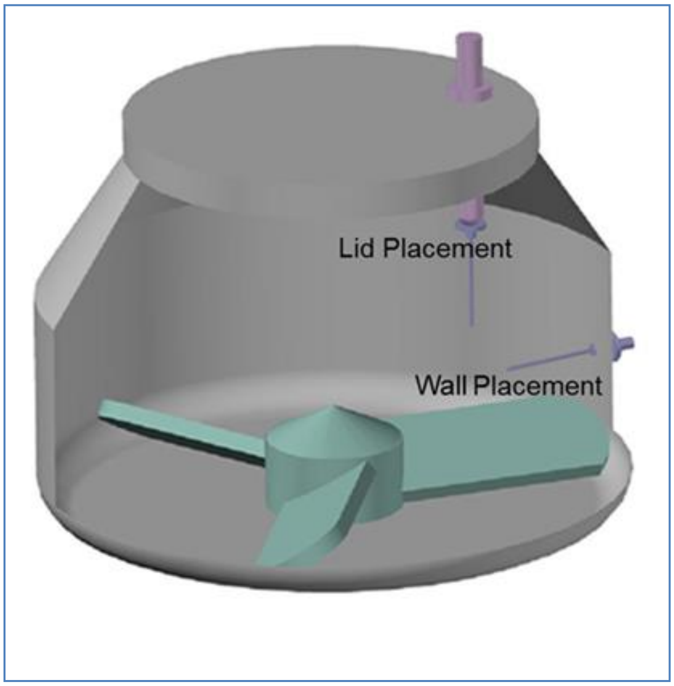
This note describes algorithms for **data interpretation** of and introduces basic characteristics for the time-dependent measurement of flow forces by Lenterra's Drag Force Flow (DFF) sensor, specifically for applications to agitator-based systems such as mixers or granulators, or other processing devices characterized with a specific frequency in operation, such as pumps. As an example, the application of the DFF sensor to monitoring high shear wet granulation (HSWG) is discussed.

Probe Placement

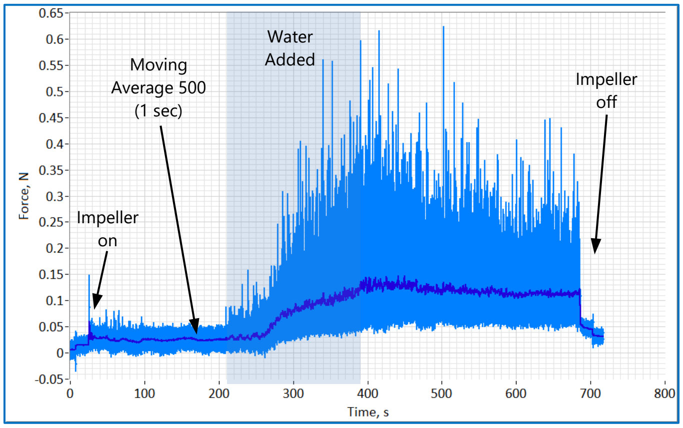
To work as a process analytical technology (PAT) tool, a DFF probe needs to be positioned within the flow. For mixers and granulators the probe is typically installed using a port on the granulator lid or a side port, if available. Lid placement allows for flexible positioning using an adjustable shaft to survey the granulator volume.



Consistent placement in the granulator across the batches that are being compared with respect to the height from the impeller and the radial distance ratio from the shaft are important parameters for consistent process monitoring and scale-up, since particle flow patterns vary in different regions of the granulator. In addition, the probe should be placed away from the port of granulating fluid addition and the chopper.

Raw Data

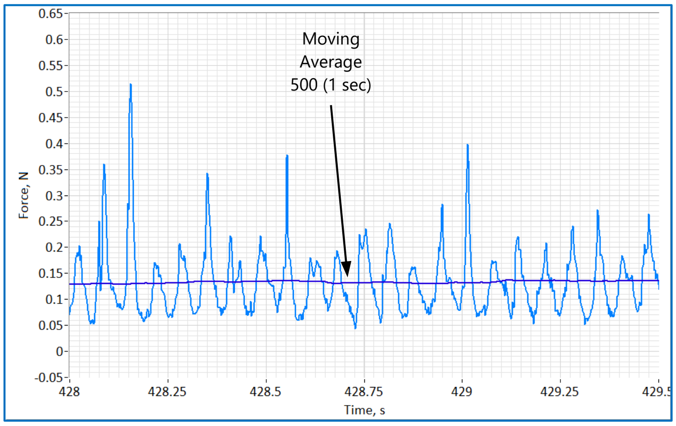
The force on the DFF probe is measured every 2 milliseconds or 500 times per second by the Lenterra Optical Interrogator (LOI) that reflects every measurement point in real time on the computer screen obtaining a live plot that after 800 seconds of continuous measurement may look like that shown in



the figure:

The plot includes 360,000 force measurement points taken during high shear wet granulation (HSWG) of a placebo formulation in a GEA PharmaConnect 10 L granulator (Narang, 2015). The HSWG unit operation included a dry mixing phase ['impeller on' to 'water added'], water addition phase [shaded area labeled 'water added'] that started at time zero and continued for three minutes, and wet massing phase ['water added' to 'impeller off'] while the contents were mixed at the impeller tip speed of 5 m/s.

The detail below contains 750 measurement points taken over 1.5 seconds. A moving average over 500 points or 1 second of time is given in both plots with a dark blue line.



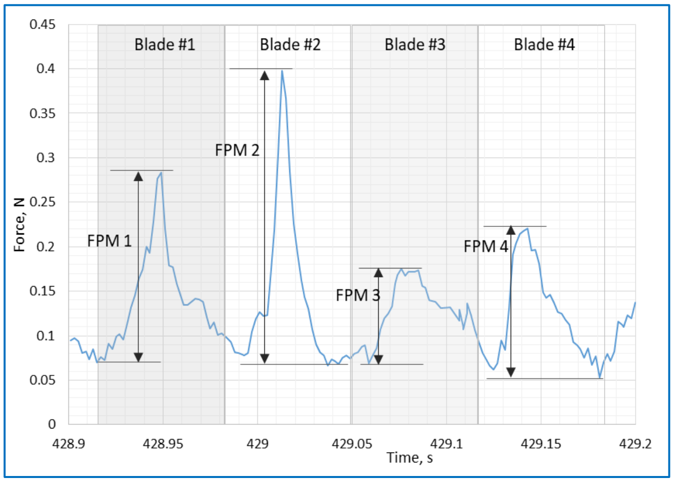
Detailed signal resolves regular force pulses of appearing every 0.066 seconds or at the frequency of agitator blades. When the blade is directly below the probe the velocity of the wet mass is greatest, and the force measured by the probe is highest. Minima occur when flow velocity near the probe is lowest, which happens when the probe is between the blades. One may also observe a fine structure in each pulse that includes a number of narrow peaks of various magnitudes. These are due to elementary impacts of granules. Some of them overlap in time and some other have fairly large magnitudes. Overall, the raw signal can be modeled as a continuous sinusoidal force superposed with random narrow pulses from single granules.

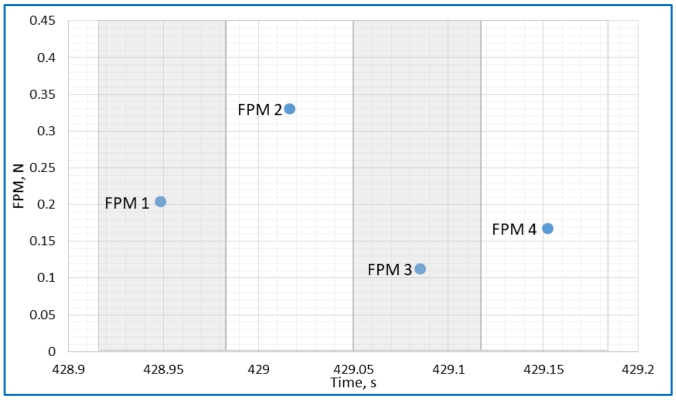
Force pulse magnitude (FPM)

A number of useful metrics can be obtained from analyzing details of the force pulses. These could be a peak magnitude, or total width, or a number of elementary impacts that could be observed over one blade pass. Each such a metric may reflect different properties of the powder or wet mass. For example, the width of the pulse may be connected to the tackiness of the wet mass and the number of elementary impacts – to density of larger granules.

Lenterra's post processing software currently calculates and provides statistical analysis to one of such metrics – pulse magnitude.

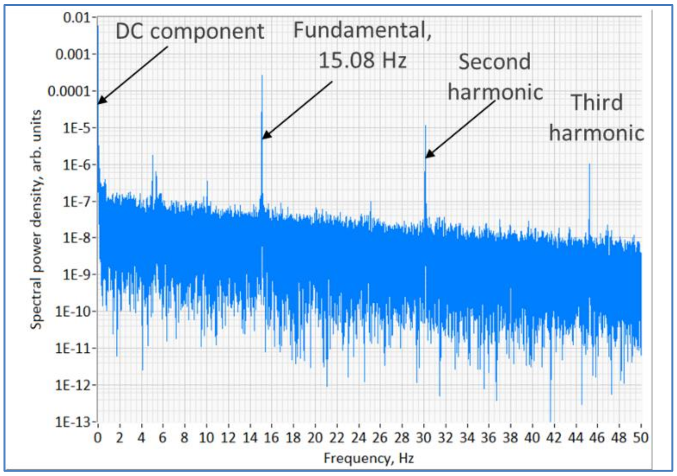
Force Pulse magnitude (FPM) is introduced as a difference between the greatest and smallest values of force measured over one period, or one blade pass in an example of HSWG. Each FPM, therefore, reflects maximum measured force of impact during each blade pass near the DFF probe.





Being a differential measurement, FPM provides a reliable characteristic of the wet mass consistency and densification since it is independent from possible zero drift in the raw signal.

To calculate FPM, one needs to set a period or frequency of FPM. This frequency is found by Lenterra's post processing software by applying **Fourier transformation (FFT)** to the raw signal:



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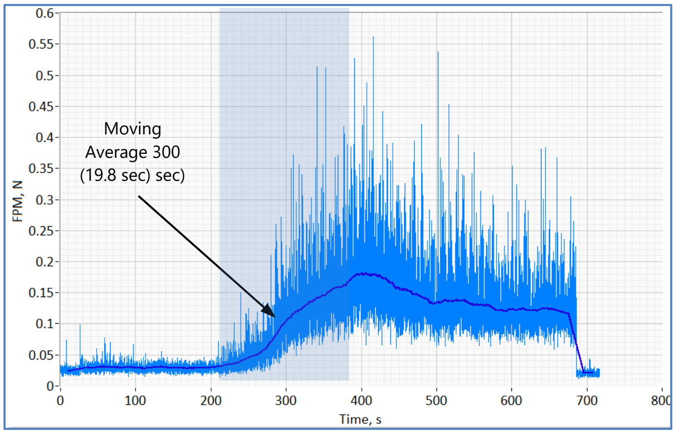
The blade frequency of 15.08 Hz gives the time interval between two blades of 0.066 seconds.

FPM Evolution

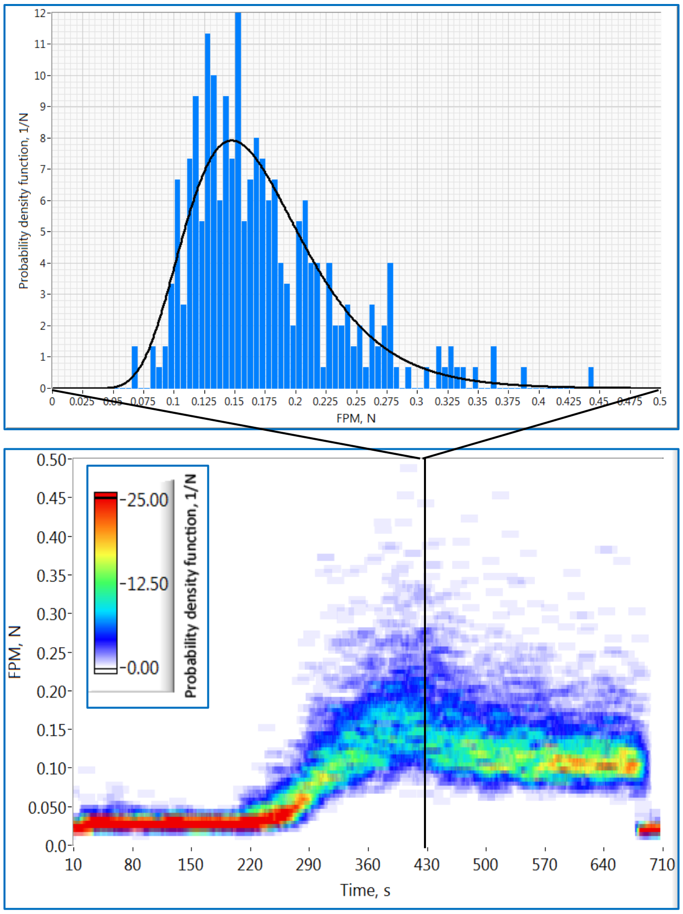


FPM value characterizes an integral impact of granules on the surface of the DFF probe pushed by a particular blade. The evolution of FPM therefore in indicative of the changes in average mass of the granules. Long term evolution of FPM may be better observed by applying a moving average smoothening. In the plot below, a moving average of 300 points (or over 19.8 seconds) shows a low-frequency FPM dynamics that clearly separates the dry mixing phase from intense granulation process that starts with water addition, demonstrates a maximum approximately 30 seconds after water addition ends, and showing that the average peak force steadily decreases on the later stages of granulation. This information may be used for identification of the granulation endpoint.

FPM Histograms

The force magnitudes vary from peak to peak randomly, reflecting the random distribution of granule size in the wet mass. Such a distribution could be observed by selecting a certain number of consecutive FPMs and constructing a histogram. Figure below represents such an “instantaneous” histogram of FPMs calculated for the above presented raw data, for the time interval between 420 and 440 seconds. This histogram contains 300 FPM values.

Evolution of such “instantaneous” histograms carries information about wet mass densification during the granulation process. A reasonable approach in observing FPM distribution dynamics is to construct consecutive histograms for a fixed size array of FPMs shifted by one blade in time. Such, the first histogram is built for an array of N blades counted from blade number 1 to blade number N. The second histogram is built for blades from number 2 to number N+1, and so on. This way we obtain three-dimensional plot (moving histogram) which is presented here as a color map. The color scale shows probability distribution function (PDF) that is the horizontal scale on the upper plot.



The larger is array size N, the more statistically significant FPM distribution is. But when N, measured in time units, significantly exceeds the characteristic time of physical and chemical processes occurring in the course of granulation, rapid changes of wet mass parameters may not be detected. Because of that, consecutive histograms move with a small time increment of one blade. For example, an array of 300 blades (20 s) may seem to exceed the time when the physical and chemical state of the material does not change, but the fact that the following 300-blade-histogram is calculated with an increment of one blade (0.066 s) effectively increases the temporal resolution.

Lognormal distribution function is a typical distribution of particle sizes of granulated powders (Masuda, 2006). Fitting the histogram with a lognormal distribution (black line in the distribution plot above) provides an analytical approximation for a histogram. This "instantaneous" lognormal FPM distribution function is fully defined by two parameters: 1) the mean that is introduced here as "mean FPM" or MFPM:

$$MFPM = e^{\left(\mu+\frac{\sigma^2}{2}\right)} \qquad \text{Eq. 1}$$

and 2) the width, which we call here "width of FPM distribution" or WFPM and calculate as:

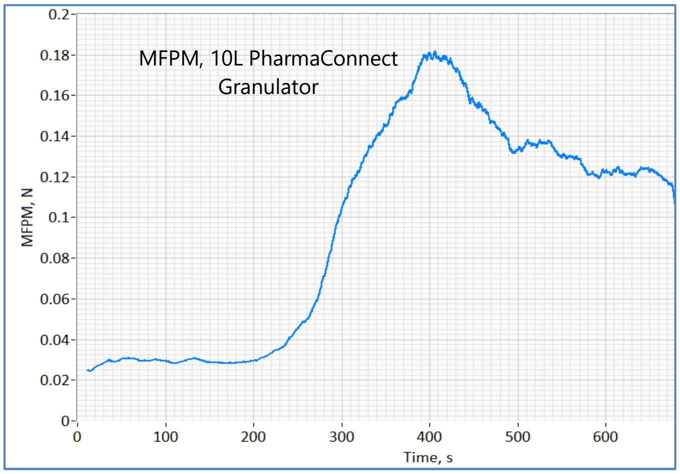
$$WFPM = \sqrt{\left(e^{\sigma^2}-1\right)e^{(2\mu+\sigma^2)}} \qquad \text{Eq. 2}$$

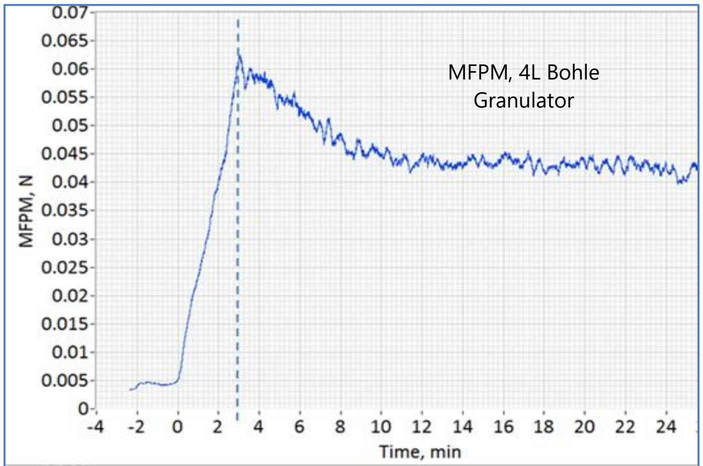
where μ and σ are, respectively, the standard mean and standard deviation of the FPM's natural logarithm, found from the array set of actual FPMs.

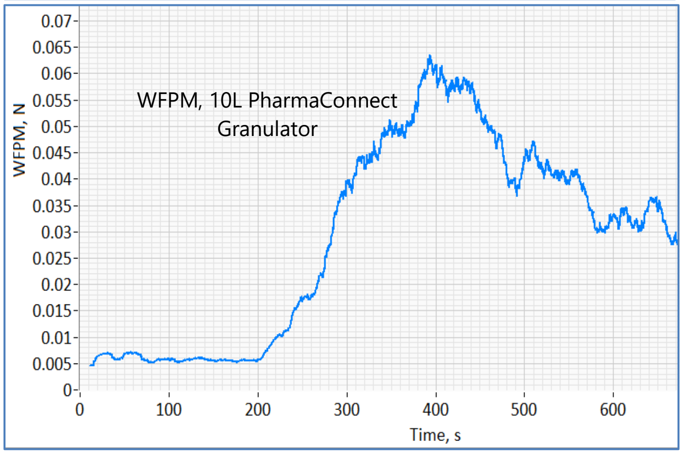
The MFPM and WFPM values are referred to the time instant that is selected as mid-range for the array. For example, time instant assigned to the distribution given in distribution on page 3 is (420+440)/2=430 seconds.

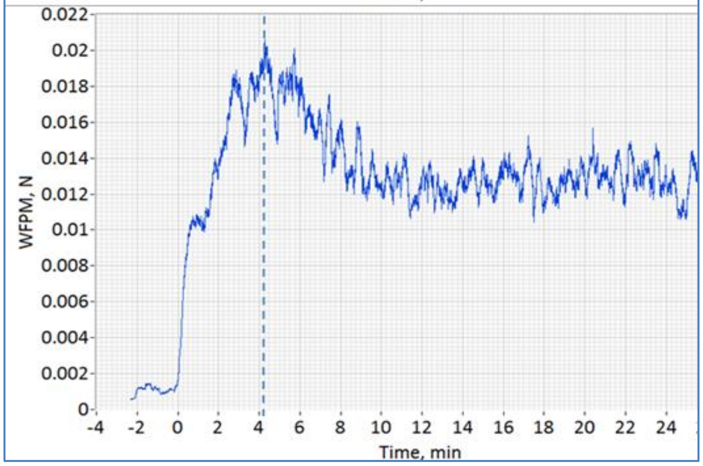
Shown here MFPM and WFPM plots, calculated for above referenced raw data (array size 300), show resemblance to each other and to a 300 points moving average FPM plot seen on page 3. In fact, FPM moving average is calculated very similarly to a lognormal mean or MFPM.

WFPM, is an independent from average FPM metric – the width of particle mass distribution may or may not correlate with the average mass of the particle. In the example of high shear wet granulation, one would expect however the distribution of particle masses being widest at the time of highest tackiness in the wet mass, when most massive agglomerates are formed. For the same reason, the mean value of the granule masses is also highest at the same time. However, depending on the formulation and the granulator type, MFPM and WFPM distributions may depart from each other. An example of such situation shown here is MFPM and WFPM evolutions measured by a DFF sensor in a 4L









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Bohle-Mini-Granulator, for the same placebo formulation that was used in the above test with GEA PharmaConnect™ 10L granulator. MFPM has a sharp peak at 3 min, immediately after the end of water addition, while the WFPM continues to rise for approximately 1 minute after water addition stops. In this situation one may consider to select the granulation end point between these two maxima

Conclusion

The DFF sensor detects the drag flow force of the particle mass with very high sensitivity and temporal resolution. This sensor detects not only the bulk flow properties but also individual force impacts on the sensor that can provide information about particle mass, size, density, and momentum. The high measurement rate of 500 Hz allows to monitor the magnitude of the force pulses created by particle impacts. Temporal distributions of these force pulse magnitudes (FPMs) provide a convenient means to monitor the process dynamics. The DFF sensor has been used to fingerprint HSWG processes to aid in process monitoring, processing endpoint determination, and scale-up.

Bibliography

Masuda, H., Higashitani, K., Yoshida, H. (eds) (2006). *Powder Technology Handbook* (3rd ed.). Boca Raton: CRC Press.

Narang, A.S., Sheverev, V.A., Stepaniuk, V.P., Badawy, S., Stevens, T., Macias, K., Wolf, A., Pandey, P., Bindra, D., & Varia, S. (2015). Real-time assessment of granule densification in high shear wet granulation and application to scale-up of a placebo and a brivanib alaninate formulation. *Journal of Pharmaceutical Sciences, 104,* 1019-1034.

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