Terahertz waveform selection of a pharmaceutical film coating process using a recurrent network

Xiaoran Li[1], Bryan M. Williams[2], Robert K. May[3], Michael J. Evans[3], Shuncong Zhong[4], Lynn F. Gladden[5], Yaochun Shen[6], J. Axel Zeitler[5] and Hungyen Lin[1]

[1]Department of Engineering, Lancaster University, Lancaster LA1 4YW, United Kingdom

[2]Department of Computing and Communications, Lancaster University,Lancaster LA1 4WA, United Kingdom

[3]TeraView Ltd., Enterprise Cambridge Research Park, Cambridge CB25 9PD, United Kingdom

[4]School of Mechanical Engineering and Automation, Fuzhou University, Fuzhou 350116, China

[5]Department of Chemical Engineering and Biotechnology, University of Cambridge, CB3 0AS, United Kingdom

[6]Department of Electrical Engineering and Electronics, University of Liverpool, L69 3GJ, United Kingdom

***Abstract* – Waveform selection plays an important role in the processing of in-line terahertz measurements of pharmaceutical tablet coating processes. This paper presents a approach to optimise waveform selection by utilising an artificial recurrent neural network and transfer learning. The results show that the averaged coating thickness gradually increases throughout the coating process. In comparison with the conventional method, our approach allows more than double the number of waveforms to be selected without compromising on the accuracy when compared against off-line measurements. Moreover, the processing time of waveform selection decreases so that it can be applied for real-time coating monitor in the pharmaceutical industry.**

I. INTRODUCTION

We have previously demonstrated in-line measurement of tablet coating thickness for production [1] and lab-scale [2] coating process using terahertz radiation. A criteria selection algorithm (CSA) using off-line determined thresholds is used to automatically select suitable waveforms from the data stream, which represent reflections from the coated tablets that are both in the focus and aligned normal to the terahertz optics. This is a critical step in the measurement as the selected waveforms are then analysed to determine coating thickness. Using the CSA does allow one to monitor coating thickness throughout the process, producing data consistent with off-line data. But depending on the threshold values, it can also reject potential candidate waveforms resulting in limited thickness measurements taken. On the premise of the availability of large dataset combined with the time dependent nature of the waveforms, we present a machine learning approach using recurrent network for waveform selection.

II. METHODOLOGY

Details of coating experiments have been covered elsewhere [3]. In short, in-line terahertz waveforms for two runs of the same coating processes (runs A and B) were acquired at 120 Hz. Off-line measurements were taken by removing randomly from the coating pan at several time points using terahertz pulsed imaging (TPI) [4]. Since the in-line measurement dataset contains not only waveforms reflected from the coating tablets, but also waveforms from the surface of the coating pan, in order to train the network to discriminate between a hit (reflected from tablet) and a miss (reflected from pan surface), off-line acquired waveforms from run A were used to represent the hit class while in-line waveforms of an empty coater were used for the miss class. The in-line dataset was used for the validation.

In external validation, the number of selected tablet waveforms fluctuated significantly in cross-validation, thus indicating an unstable training due to insufficient training data. We therefore used Fresnel's equations to simulate terahertz waveforms within realistic values of coating and core refractive indices and thicknesses to supplement the training with additional tablet waveforms.

Bi-directional long-term short memory (BLSTM) network is a typical recurrent neural network. As terahertz waveforms are time dependent in nature, a BLSTM network is used here to select tablet waveforms acquired from a production coating process [5]. Fig 1 shows the structure of BLSTM network. At the the top of the network is a sequence input layer followed by BLSTM layers to learn long-term dependencies between time steps. After this layer, there is a fully connected dropout layer, which is added to prevent network from overfitting. The classification output layer contains activation functions to define how the sum weight of the input is transformed into the binary output classes.

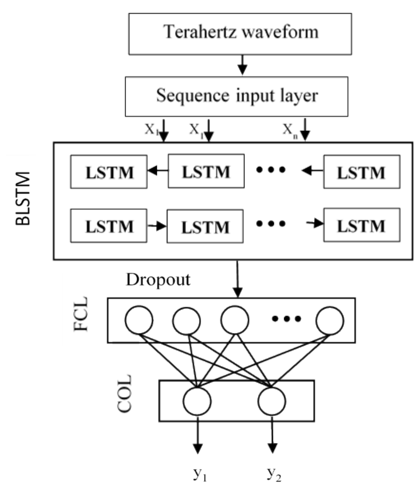

Fig. 1. BLSTM network used for classification. FCL: fully connected layer; COL: classification output layer.

The training results using augmented training dataset show that the averaged coating thicknesses increase over coating time, however, compared with off-line measurements, the network tends to identify waveforms with thick profiles as tablets This highlighted that the off-line measurements do not truly represent in-line waveforms. This is due to differences in measurement between off-line and in-line: off-line measurements are taken with the sample placed at the focus and perpendicular to the terahertz sensor, while in-line waveforms are acquired with tablets tumbling inside a rotating coating pan.

Off-line waveforms therefore served as a guide to the network on what in-line waveforms would generally look like. To train the network to learn these differences, transfer learning is used to refine the trained network. In particular, the weights of the network trained using off-line supplemented with simulated data were updated using a small amount of in-line data (4% of the off-line training dataset) of run A classified by the CSA.

III. RESULTS

The refined network is applied to in-line dataset of Run B. Fig 2 compares the 30 seconds average of coating thickness obtained by the BLSTM network (green circles) against the CSA (black circles), off-line TPI and weight gain measurement. In general, there is good agreement between BLSTM selected waveforms, off-line TPI and weight gain measurements after 80 minutes. As expected, a steady increase in coating thickness is observed in line with coating time. At the ending stage of the coating process (250-300 minutes), selected thicknesses deviate in slope compared with the CSA, but it is still consistent with off-line measurement. Fig 3 shows the histograms of tablet coating thicknesses from 60 to 220 minutes. Compared to the CSA [1], BLSTM is able to select twice the number of tablet waveforms without compromising on the accuracy when compared against the off-line measurement. This work therefore shows promise for in-line waveform selection

Usually, the processing time of the CSA to classify a single in-line waveform is 1 ms. It takes approximately 35 minutes to analyse one batch of in-line dataset with 5 hours' coating process, which is not efficient. The processing time of BLSTM for the same in-line waveform is 0.1 ms, which is 10 times quicker. Thus, BLSTM network has the potential to significantly improve classification efficiency, leading to real-time monitoring of the coating process.

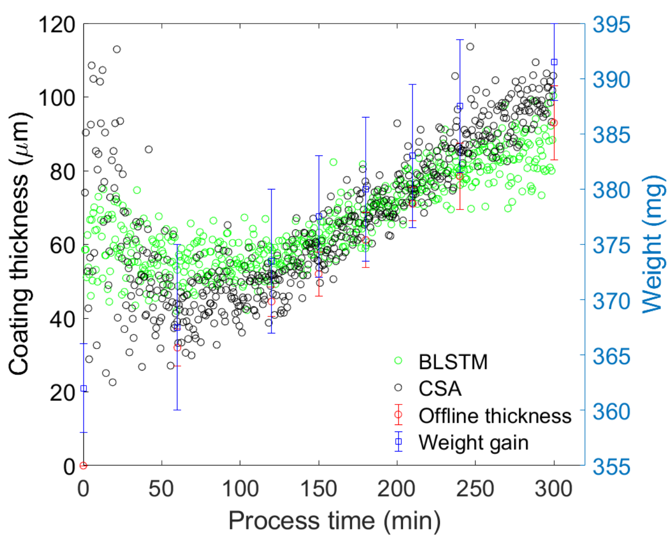

Fig. 2. 30 second average of the film coating thickness from waveforms selected by BLSTM, CSA and off-line measurements

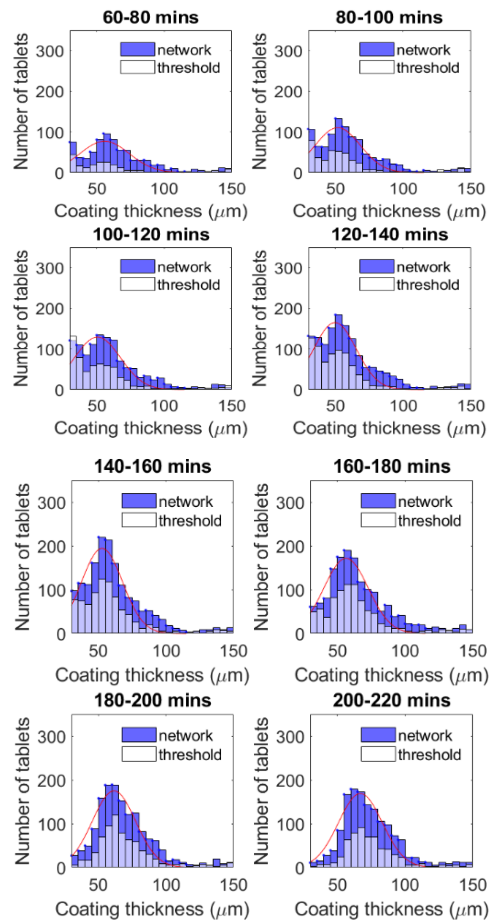

Fig. 3. Histogram of coating thicknesses from 60 to 220 minutss from waveforms selected by the CSA and BLSTM

ACKNOWLEDGEMENTS

X.L. and H.L. acknowledges financial support from the EPSRC (Grant No. EP/R019460/1, H2FC Supergen Flexible Grant EP/P024807/1).

REFERENCES

[1] R. K. May et al., "Terahertz in-line sensor for direct coating thickness measurement of individual tablets during film coating in real-time," Journal of Pharmaceutical Sciences, vol. 100, no. 4, pp. 1535-1544, 2011.

[2] H. Lin et al., "Measurement of the intertablet coating uniformity of a pharmaceutical pan coating process with combined terahertz and optical coherence tomography in-line sensing," Journal of Pharmaceutical Sciences, vol. 106, no. 4, pp. 1075-1084, 2017.

[3] H. Lin et al., "Impact of processing conditions on inter-tablet coating thickness variations measured by terahertz in-line sensing," Journal of Pharmaceutical Sciences, vol. 104, no. 8, pp. 2513-2522, 2015.

[4] D. Alves-Lima et al., "Review of Terahertz Pulsed Imaging for Pharmaceutical Film Coating Analysis," Sensors, vol. 20, no. 5, p. 1441, 2020.

[5] R. Asaoka et al., "Using deep learning and transfer learning to accurately diagnose early-onset glaucoma from macular optical coherence tomography images," American journal of ophthalmology, vol. 198, pp. 136-145, 2019.