IJBPAS, November, Special Issue, 2021, 10(11): 501-513
ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

BIO-CELL CULTURE PROCESSES IN REAL-TIME MONITORING APPROACH WITH MACHINE LEARNING TECHNIQUES

NAGALAKSHMI.T[1*], SURAPANENI KRISHNA MOHAN[2], MALIK MUSTAFA MOHAMMAD[3], ZATIN GUPTA[4], ASHISH KUMAR TAMRAKAR[5], AND BESLIN GEO.V[6]

1: Assistant Professor in Computer Science and Engineering at Koneru Lakshmaiah Education Foundation, Greenfields, Vaddeswaram, Guntur, India

2: Departments of Biochemistry, Molecular Virology, Research, Clinical Skills & Simulation, Panimalar Medical College Hospital & Research Institute, Varadharajapuram, Poonamallee, Chennai - 600 123

3: Assistant Professor in Faculty of Computing Science, Gulf College, Sultanate of Oman

4: Assistant Professor in Computer Science at KIET Group of Institutions, Ghaziabad, UP, India

5: Assistant Professor in Computer Science & Engineering at BIT-Raipur (Chhattisgarh) India

6: Electronics and Communication Engineering at Hindustan Institute of Technology and Science, Padur, Chennai-603103, India

***Corresponding Author: Nagalakshmi. T; E Mail: maha.shanmugam@bmsit.in**

Received 20th July 2021; Revised 22nd Aug. 2021; Accepted 30th Sept. 2021; Available online 1st Nov. 2021

https://doi.org/10.31032/IJBPAS/2021/10.11.1044

ABSTRACT

lyrical procedures, & control strategies to ensure that patients receive safe and reliable goods. Raman spectroscopy is a versatile assessment technique used in biopharmaceutical production to anticipate important parameters in the culture of cell processes in actual time. Raman spectroscopy depends on chemometric concepts that must be properly calibrated to ensure accuracy. The current calibration approach is difficult to apply since it requires running numerous properly crafted experiments to generate appropriate calibration groups. Furthermore, the current technique results in the calibration technique are only reliable in the operating conditions in which they were calibrated. In clinical production, when items have a

short overview of production, this poses a distinct issue. To calibrate Raman models, a new machine learning approach based upon Quick Learning Technique is proposed in this study. Unlike older methods, Quick Learning Technique-based generic Raman models could be employed with confidence for a variety of modalities, cell lines, culture medium, & operating circumstances. Several validation tests including actual time predictions of crucial cell culture performance metrics illustrate the reliability of Quick Learning Technique-based generic systems. The suggested Quick Learning Technique methodology represents a paradigm leap in the calibration of industrial Raman models.

Keywords: Quick Learning Technique; Chemometric Models; Raman models

INTRODUCTION

Raman spectroscopy is a PAT instrument that is extensively utilized as a versatile actual period analytical technique in biopharmaceutical production **[1-3]**. By providing actual period, system-based predictions for crucial variables, spectroscopy of Raman offers another in the manual specimen and offline assessment. The application for Raman models that Raman spectra of correlate to important culture effectiveness factors make it possible.

In 2010, **[4]** described the initial app for spectroscopy of Raman in cultured cells procedures for actual time prediction of glucose, glutamine, glutamate, lactate, ammonium, viable cell density, and other compounds. Many additional researchers, both in business & academia, have worked to boost the effectiveness of Raman models of surveillance & management applications ever since **[5-8]**. The historical evolution for spectroscopy of Raman and its numerous app in bio-manufacturing are exterior of a focus for this work; nevertheless, the viewer has directed to **[9]** as well as the references therein of a full explanation on this subject. Spectroscopy of Raman depends on a calibration system to spectral of correlate emissions to analytics-based evaluations equipment for absorption as a method of actual-time analytics.

The lengthy, time-consuming, & resource-intensive process of calibrating industrial Raman models has spurred industry & academia researchers to search out alternate calibration techniques. The majority of this strive had been focused on decreasing investigation by considering Raman concepts that are universal may be utilized in the range of these situations. The researchers of **[10]** measured Raman models of levels of metabolites via merging sets of information collected over 5 L, 200 L, & 2,000 L vessels of various sizes,

lowering the amount for at-measure tests. Predictions tracked the broad trends in real concentration profiles through testing, although with considerable discrepancies. Finally, we increased the scope of **[11]'s** generic models to include additional parameters like ammonium, viable cell density, & total cell density. **[12]** utilized information from three CHOK1SV GS - KO lines of cells that were grown at similar system media. A system was evaluated for a line of cells as well as the scale of the procedure that was not originally part of the group of calibration.

This research shows that there has been a recent spike in interest in finding a reliable process of calibrating industrial generic systems. While the researchers of the abovementioned research looked at generic models under various settings **[13]**, the systems were all calibrated utilizing the same approach. By pooling information from 3 various hosts of cells & after that, instruction the PLS system on the group of global, scientists calibrated a general model of cell hosts in **[14]**. Similarly, In **[15]** calibrated the generic model for cell lines using global sets of data produced by 3 different cell lines to calibrate a PLS system.

They suggest a unique approach of calibrating Raman systems to solve the constraints for existing global systems. The proposed strategy is based on two main concepts: optimizing the utilization of current sets of data & calibrating local systems rather than global systems. To this end, a novel framework for the general calibration process based on Quick Learning Technique is presented. The Quick Learning Technique platform is built on database sampling & local modeling **[16]**. Unlike global models, the Quick Learning Technique maintains global information in a centralized database (or library) but then measures the local system at the actual period utilizing only the appropriate 2 information from the library in response to query 1.

The local model is discarded that once model predictions are ready, as well as the Quick Learning Technique waits for a new point of inquiry to lead to the point out of the latest local group & ultimately, the calibration of a new local system. Because the Quick Learning Technique framework only chooses appropriate for calibration samples from the library, a resilience or genericity of a local model is assured indefinitely the library includes varied groups of data. In other meaning, the suggested Quick Learning Technique architecture maintains the resilience & correctness of the generic system. Finally, because the systems are calibrated with a set of local, the computational cost of

calibrating & installing the Quick Learning Technique architecture is unaffected by library capacity.

It's worth noting that throughout the Quick Learning Technique architecture, there are numerous methods for calibrating local systems. PLS systems, e.g., could easily be utilized to capture connections in local sets of data. Even though PLS-based calibration systems are usually accepted in the biopharmaceutical business, there are significant difficulties with their application. PLS systems, for starters, require linear connections among spectral & analytical measures, that might or might not be accurate in actuality. Second, the calibration piece's preparation is important to the success of PLS systems. This-Because the preprocessing increases the signal-to-noise ratio & enhances the linearity of connections among pre-processed spectra & analytical measures. The second filter of derivative, for instance, eliminates quadratic spectra patterns. During industrial Raman model calibration, pretreatment filters like the standard normal variate filter & Savitzky Golay smoothness were widely utilized.

Finally, many verification investigations including actual time predictions of essential factors of cultured cells operations illustrate the efficiency of the proposed Quick Learning Technique-based generic Raman model calibration technique. The suggested Quick Learning Technique approach represents a paradigm transfer in the calibration of commercial generic Raman models, that has never been done before from the best of the authors' information.

MATERIALS AND METHODS

In this investigation, 3 mechanisms were regarded: mAbs, proteins of fusion, as well as a bi-specific T-cell engager antibody design. Several altered Chinese Hamster Ovary-based cultures were examined for every modality — 6 cell lines of mAbs, two lines of the cell for Bi-specific T-cell engagers, & 2 lines of the cell for proteins of fusion – for every mechanism. All ten lines of cell utilized in this research were Amgen’s exclusive lines of the cell (Amgen incorporated., USA). The Amgen Production Process group determined a unique medium mixture for every line of the cell. The media mixtures differed significantly amongst lines of cell in general. Furthermore, for every line of cell, many analyses were evaluated. A few of these tests were specifically developed of calibration, and others were part of typical programs. Analysis was performed in batch-fed-batch bio-reactors as well as per-fusion bio-reactors. This research examined stainless & single-utilized bio-reactors of various volumes, geometries, &

dimensions. Process Development of Amgen established the best-operating conditions for every bio-reactor. Moreover, all of the trials were carried out at 4 Amgen locations on 3 separate scales: bench of scale, the scale of pilot, & scale of commercial.

Data Acquisition

Its spectrum was recorded inside the bio-reactor utilizing a stainless optic probe that was immediately immersed in a liquid. To implant these probes into corporate settings, suitable Good manufacturing practice changes were performed. The spectrum gathering was carried out with the help of an iCRaman program (KOS Incorporated Ann-Arbor, MI). This spectrum was recorded over a spectral region of 100-3-425 cm1 with an exposition length of 10 seconds & 75 scans added of a total of 750 seconds. The Raman spectra sample frequency ranged from 15 to 120 min, depending on the place, volume, & method. **Figure 3** shows representative Raman spectra acquired at various points of time for 6 various lines of the cell as an example (a).

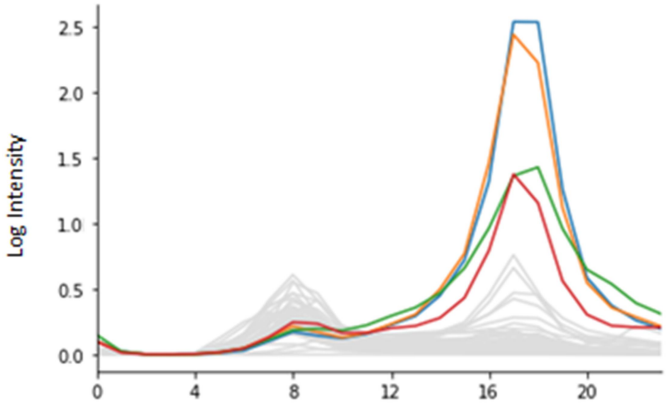

Figure 1: The graph of log transformations

Measurements

Spanning numerous Amgen locations, process sizes, modalities, & lines of the cell, these trials provided about 5, 000 quantitative observations of critical parameters & 120, 000 spectral data. Whereas the majority of the spectrum scans were taken at 15-60 minute intervals, analytic measurements were taken at a 1–6 hour period. Analytic tests were taken even less frequently in regular programs, only with 12-samples per day. In addition, not that all parameters were measured at every interval of time. This could be owing to equipment fault or the fact that such observations were not part of the research's objective. There has been missing data within measurement techniques as a whole.

A timestamp comparison of a set of data was done to adjust for varied sampling frequencies & incompleteness. Analytic observations were temporally paired to Raman spectra using a custom script built-in MATLAB (Math-works, Natick, MA) depending upon their documented collecting timings - an analytic observation was judged paired to a Raman spectrum if they could be acquired inside 60 min of everyone.

The 1-hour criterion was chosen since variations in analytic measures & Raman spectra were determined to be minimal in that time frame. Furthermore, just those temporal analytic observations that did not show some lost observations were compared. Periodic similarities were identified for 3, 800 items based on the above-mentioned parameters for 120, 000 spectral scanning & 5, 000 analysis results. Unrivaled entries were destroyed, whereas matching ones were saved in MATLAB. It should be noted that utilizing data re-conciliation techniques, it is feasible to recover data from mismatched data; nevertheless, the application of these techniques requires more exploration and is outside the scope of the present research.

QLT Model development

The QLT has been utilized with the package in MATLAB to calibrate a local model by waiting for a query instance Raman spectrum. After collecting fresh Raman spectra, this was running through the library to find the best appropriate set of local measurements. A pertinent specimen was chosen based here based on the query's Euclidean distance location as well as the library's spectral scanning - entries nearest in response to the inquiry instance (Euclidean distance) was regarded to develop into the extra pertinent. Its 100 best entries from the library were used to set up a local calibration. During local model calibration, the Quick Learning Technique system was outfitted with Partial Least Squares & GPs. Remember that when utilizing PLS as local models, the client has complete control over the number of elements to include in the model (either arbitrarily / based on optimization); whereas, no such adjustable parameters are available for GPs. The Partial Least Squares & GPs were investigated for purposes of comparison. The local calibration group as well as the local model both were destroyed after estimating the important parameters for the provided query instance, as well as the platform, was returned toward its initial state configuration of another point of query.

Outcomes and Conversations

A verification study was conducted to assess the effectiveness of global & Quick Learning Technique-based generic

systems. The goal of this research was to figure out which general modeling strategy - global or Quick Learning Technique – made the most of given calibration information. For just a valid comparison, both global & Quick Learning Technique models were given the same library to choose their calibration sets of data. A global model has included a full library in its calibration set as an information-pooling method, but the Quick Learning Technique only comprised the part for the library (2.5s). A global system then was measured utilizing the six-element Partial Least Squares system optimized using Sartorius-Stedim, Sweden & the six-element Partial Least Squares local system of online measurement on the Quick Learning Technique. These were done to make sure that the only difference between the global & Quick Learning Technique models that's how the calibration information is utilized by every model. The global & Quick Learning Technique models were referred to as Global- Partial Least Squares & Quick Learning Technique - Partial Least Squares generic models in this research as they both utilize Partial Least Squares.

The RMSE was used to evaluate the reliability of the Global-Partial Least Squares & Quick Learning Technique - PLS. A popular metric of the disparity among model predictions & real or reference survey information is the root mean square error. The above formula was used to determine the root mean square error for the model (Global-PLS / Quick Learning Technique - Partial Least Squares).

$$Root\ Mean\ Square\ Error = \sqrt{\frac{1}{Time}\sum_{s=1}^{Time}(b_s - b_s{}^*)^2} \quad (1)$$

In MATLAB, Global-Partial Least Squares & Quick Learning Technique - Partial Least Squares were utilized to forecast crucial parameters in actual time in an experiment described earlier inside the library. In another word, the calibration set of data already included the verification test. For such validation dataset, highlights the effectiveness of Global-PLS & Quick Learning Technique - Partial Least Squares in estimating glucose, ammonium, as well as viable cell density level. Analytic measurements from the Nova Bio-Profile Flex Analyzer also are offered for reference shown in **Figure 1**.

Variations in glucose levels were monitored by the Global-PLS & Quick Learning Technique -PLS, with RMSEs of 0.0105 & 0.009, respectively, while ammonium levels were monitored by the Global-PLS & Quick Learning Technique - Partial Least Squares, include RMSEs of 0.0167 & 0.006, correspondingly. In

comparison to Quick Learning Technique - Partial Least Squares, Global- Partial Least Squares systems for glucose & ammonium struggled to adjust to freq concentration variations, resulting in large offsets. This is owing to Global-Partial Least Squares models' inflexible architecture, which prevents them from reacting to quick process variations. Quick Learning Technique -PLS models for glucose & ammonium, on either hand, displayed agility in adjusting to frequent process modifications. In comparison to Global-PLS, Quick Learning Technique - Partial Least Squares glucose & ammonium designs improved their RMSE by 14.56 percent & 64.11 percent, correspondingly. Accordingly, including an RMSE of 0.0080 & 0.0045, the QLTPLS viable cell density system beat the Global- Partial Least Squares viable cell density system. In this verification research, Quick Learning Technique - Partial Least Squares surpassed Global- Partial Least Squares on each significant metric **(Table 1)**.

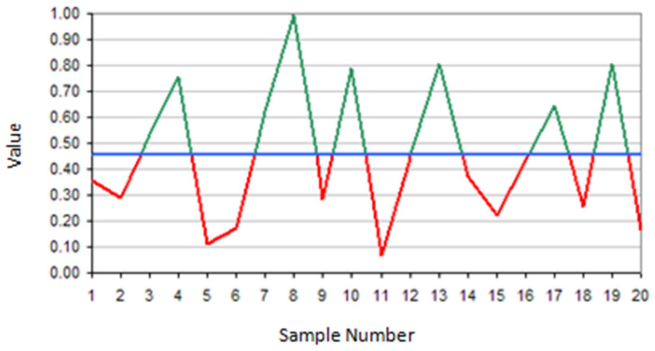

Figure 2: Sample number Vs Value for the Model predictions

Table 1: RMSE values are calculated based on Equation.

Module	RMSE value for Global-PLS	RMSE value for JITL-PLS	Enhancement in Percentage
Glucose	0.05	0.09	7.25
Glutamate	0.02	0.03	15.3
Glutamine	0.01	0.04	15.2
Lactate	0.05	0.08	14.3
Sodium	0.01	0.06	4.3
Ammonium	0.03	0.04	32.2
Calcium	0.04	0.02	12.3
VCD	0.04	0.02	21.2
Viability	0.02	0.05	20.3

Table 2: RMSE values are calculated based on Equation and independent experiment

Module	RMSE value for Global-PLS	RMSE value for JITL-PLS	Enhancement in Percentage
Glucose	0.02	0.04	8.32
Glutamate	0.04	0.06	5.6
Glutamine	0.03	0.05	5.32
Lactate	0.05	0.02	16.3
Sodium	0.05	0.05	5.5
Ammonium	0.06	0.03	22.46
Calcium	0.01	0.08	6.74

VCD	**0.06**	**0.03**	**7.45**
Viability	**0.05**	**0.03**	**18.10**

Table 3: RMSE values are calculated based on Equation

Module	RMSE value for JITL-PLS	RMSE value for JITL-GP	Enhancement in Percentage
Glucose	**0.04**	**4.36e**	**89**
Glutamate	**0.03**	**0.08**	**91**
Glutamine	**0.02**	**0.03**	**68**
Lactate	**0.04**	**0.05**	**82**
Sodium	**0.08**	**0.04**	**61**
Ammonium	**0.03**	**0.02**	**65.3**
Calcium	**0.05**	**0.07**	**10.3**
VCD	**0.06**	**2.7e**	**85**
Viability	**0.02**	**4.65e**	**89**

Table 4: RMSE values are calculated based on Equation and independent validation experiment

Module	RMSE value for JITL-PLS	RMSE value for JITL-GP	Enhancement in Percentage
Glucose	**0.03**	**0.02**	**24.12**
Glutamate	**0.08**	**0.04**	**16.78**
Glutamine	**0.09**	**0.02**	**12.06**
Lactate	**0.04**	**0.03**	**19.46**
Sodium	**0.08**	**0.05**	**16.65**
Ammonium	**0.05**	**0.06**	**54.26**
Calcium	**0.03**	**0.03**	**10.2**
VCD	**0.06**	**0.04**	**9.65**
Viability	**0.04**	**0.08**	**16.02**

Figure 2: Global- Partial Least Squares & Quick Learning Technique PLS model predictions compared. For 3 basic parameters, especially glucose (a & b), ammonium c and d, & viable cell density, the accuracy of the model is illustrated (e and f). Its findings are from an operation that was discussed previously inside the library.

An external validation exercise was used to assess the Global- Partial Least Squares & Quick Learning Technique - Partial Least Squares. In forecasting essential cultured cells performance characteristics, **Table 2** compares the root mean square error values of Global- Partial Least Squares & Quick Learning Technique - Partial Least Squares. **Table 2** shows that Quick Learning Technique - Partial Least Squares outperforms Global- Partial Least Squares in forecasting glucose, ammonium, & survivability by 44:89 percent, 44:89 percent, & 36:20 percent, correspondingly. On all of the essential metrics studied, Quick Learning Technique -PLS outperformed Global- Partial Least Squares, as shown in **Table 2**.

It would be instructive to note that modern pre-processing filters, like as derivative or Savitzky-Golay _lters, could increase the reliability of Global- PLS; but, such _lters also had no influence based on the reasonable reality of Global- Partial Least Squares & Quick Learning Technique - Partial Least Squares, as pre-processing improves a reality for Quick

Learning Technique - Partial Least Squares. Moreover, the findings emphasize the advantages of utilizing the local strategy to the measurement process rather than the worldwide approaches. Furthermore, the research reveals that Quick Learning Technique makes effective use of existing information for a particular calibration data & performs significantly better than global models.

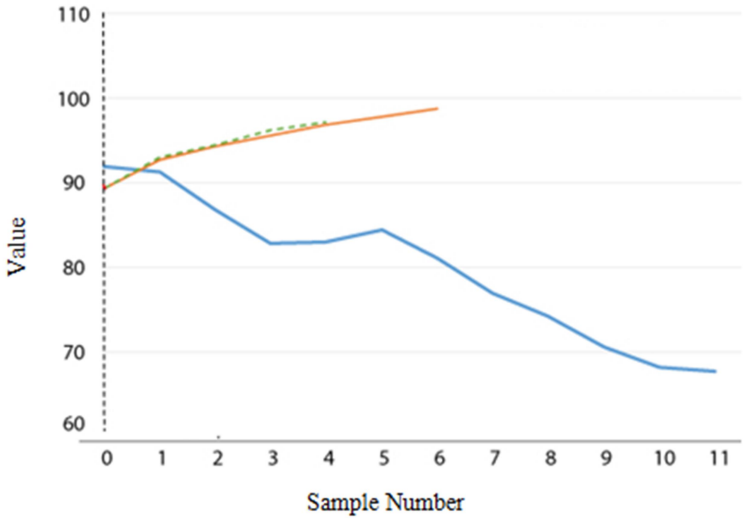

Figure 3: Model Accuracy of the experiment

Scalability of QLT Models of Generic

The verification research was considered to examine the performance of Quick Learning Technique-based models during process scalability. Actual period projections of vital variables of the protein secreting for fusion altered Chinese Hamster Ovary-based line of cell cultivated in a 2,000 L industrial bio-reactor were used in this investigation. All of the earlier research on this line of the cell was carried out in lab-scale / pilot-scale bio-reactors. The effectiveness of Quick Learning Technique-based systems was assessed based upon how they predicted a line of the cell at a processing scale that had never been examined previously.

In an industrial bio-reactor, **Figure 3** shows the reliability of the Quick Learning Technique-Gaussian process in forecasting glucose, ammonium, & viable cell density contents. With a root mean square error of 0.01 of glucose, the predictive model accurately monitored variations in glucose levels. A Quick Learning Technique-Gaussian process glucose model was capable of monitoring both high & low glucose readings. Since the Quick Learning Technique - Gaussian process was calibrated on relevant samples from the library, the calibration group only contained samples with similar glucose levels at higher glucose levels.

With a root mean square error of 0.019, the Quick Learning Technique -

Gaussian process ammonium system monitored variations in ammonium levels across different operational situations. The ammonium forecasts were shown to be rather noisy, despite the tiny root mean square error. This could be because Quick Learning Technique- Gaussian process was calibrated using a limited calibration set of 100 samples. A larger sample size is one way to obtain smoother predictions; although, caution should be taken because just a larger sample size leads to the choice of the less relevant samples inside the calibration group. As a result, determining the best sample group is a difficult challenge that is currently being researched. Gaussian processes, on the other hand, contain several techniques variable which could be a good strain to produce infinitely flattened estimates.

With an RMSE of 0.0237, the Quick Learning Technique-Gaussian process system for viable cell density likewise produced reliable forecasts of viable cell density concentrations (Figs 6e & 6f). All through the test, there was a modest under-prediction of viable cell density concentrations that could have been related to instrument from object variation, which out from across locations owing to the age as well as upkeep of various analysis tools.

Because the Quick Learning Technique-Gaussian process was found to be more accurate than Global-PLS (Tab. 1) / QLT-PLS (Tab. 3), only the Quick Learning Technique-Gaussian process was studied in depth. Despite this, Quick Learning Technique-Gaussian process systems for glucose, ammonium, & viable cell density lowered root mean square error by 30.29 percent, 67.36 percent, & 65.26 percent, correspondingly, when comparison to Global-Partial Least Squares. Additionally, this research shows that without a priori exposure to past information from the at-scale processes, the suggested Quick Learning Technique calibration systems could adjust to a new scale in actual time.

CONCLUSIONS

To evaluate universal Raman spectroscopic systems, they suggested a unique Quick Learning Technique architecture. Our suggested methodology was flexible, but it may be often used to forecast actual results for the variety of modality, patient-derived, medium growth, as well as operational but also working variables. In contrast to current methodologies, the Quick Learning Technique process made the maximum use of resources measurement results, as seen in the assertions. Moreover, especially the part of the scene system growth or perhaps

the arrival of a new medium, a suggested Quick Learning Technique presentation template system is designed which are both precise and accurate. The routing protocol model conceptualizes a fundamental change in the way design corrections were generally carried out like in medical production, also with the ability to drastically reduce the cost of materials. Given the success of the Quick Learning Technique beyond typical Raman calibration procedures described before, it is unknown whether Quick Learning Technique could be used in GMP situations, which necessitates further research.

REFERENCES

[1] Loh DR, Yong WX, Yapeter J, Subburaj K, Chandramohanadas R. A deep learning approach to the screening of malaria infection: Automated and rapid cell counting, object detection and instance segmentation using Mask R-CNN. Computerized Medical Imaging and Graphics. 2021 Mar 1;88:101845.

[2] Kumar R, Sharma K, Sharma V. Bloodstain age estimation through infrared spectroscopy and Chemometric models. Science & Justice. 2020 Nov 1;60(6):538-46.

[3] Radtke J, Kleinebudde P. Real-time monitoring of multi-layered film coating processes using Raman spectroscopy. European Journal of Pharmaceutics and Biophar-maceutics. 2020 Aug 1;153:43-51.

[4] McAvan BS, Bowsher LA, Powell T, O'Hara JF, Spitali M, Goodacre R, Doig AJ. Raman spectroscopy to monitor post-translational modific-ations and degradation in monoclonal antibody therapeutics. Analytical chemistry. 2020 Jul 2;92(15):10381-9.

[5] Mayrhofer P, Reinhart D, Castan A, Kunert R. Monitoring of heat-and light exposure of cell culture media by RAMAN spectroscopy: Towards an analytical tool for cell culture media quality control. Biochemical Engineering Journal. 2021 Feb 1;166:107845.

[6] Pernal SP, Liyanaarachchi A, Gatti DL, Formosa B, Pulvender R, Kuhn ER, Ramos R, Naik AR, George K, Arslanturk S, Taatjes DJ. Nanoscale imaging using differential expansion microscopy. Histo-chemistry & Cell Biology. 2020 Jun 1;153(6).

[7] Ezhilarasi, T. P., Dilip, G., Latchoumi, T. P., & Balamurugan, K. (2020). UIP—A Smart Web Application to Manage Network Environments. In *Proceedings of the Third International Conference on Computational Intelligence and Informatics* (pp. 97-108). Springer, Singapore.

[8] Zeid AM, Abdelazim AH, Shahin M. Simultaneous spectro-photometric quantitative analysis of elbasvir and grazoprevir using assisted chemometric

models. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2021 May 5; 252: 119505.

[9] Dr.P.Sivakumar, "Exploring The Trajectory Prediction Using Lstm And Extreme Machine Learing", journal of critical reviews, issn- 2394-5125 vol 7, issue 10, 2020. (Scopus)

[10] Dr.P.Sivakumar, "Design and analysis the performance of real time content delivery network using beam scanning" journal of critical reviews, ISSN- 2394-5125 VOL 7, ISSUE 04, 2020.

[11] Latchoumi, T. P., Balamurugan, K., Dinesh, K., &Ezhilarasi, T. P. (2019). Particle swarm optimization approach for waterjet cavitation peening. Measurement, 141, 184-189.

[12] Jarusintanakorn S, Phechkrajang C, Khongkaew P, Mastrobattista E, Yamabhai M. Determination of Chinese hamster ovary (CHO) cell densities and antibody titers from small volumes of cell culture supernatants using multivariate analysis and partial least squares regression of UV-Vis spectra. Analytical and Bioanalytical Chemistry. 2021 Sep 2:1-1.

[13] Chen G, Hu J, Qin Y, Zhou W. Viable cell density on-line auto-control in perfusion cell culture aided by in-situ Raman spectroscopy. Biochemical Engineering Journal. 2021 Aug 1;172:108063.

[14] Bhattacharyya S, Desir P, Prodinger S, Lobo RF, Vlachos DG. Improved slit-shaped microseparator and its integration with a microreactor for modular biomanufacturing. Green Chemistry. 2021; 23(10): 3700-14.

[15] Zhao Q, Wang M. Electrospinning and Electrospraying with Cells for Applications in Biomanufacturing. Nano LIFE. 2021 Sep 22: 2141003.

[16] Drecksler S, Sen Gupta S, Benvenuti A, Menezes A. Effects of Space Biomanufacturing on Fuel Production Alternatives for Mars Exploration. 2020 International Conference on Environmental Systems.