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Research Article

Advanced Process Control for Production of Influenza Vaccine Shariah Compliance using Acutase in Batch Reactor

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Abstract: Influenza viruses cause significant worldwide morbidity and mortality every year. Muslims all over the world are debating whether the vaccine qualifies as halal. When this topic is brought up again, some of them even took the chance of forgoing the vaccine. Muslim reluctance and rejection of vaccination is founded on presumptions and convictions that such a procedure and the substances employed are "doubtful (mashbooh)". Process control for the production of shariah compliance vaccine mainly focused on bioreactor to produce hemagglutinin (HA) using Acutase. The process control is carried out via artificial intelligence approach. Artificial neural network (ANN) was employed to create a shallow neural network to predict the HA yield using experimentation data sourced from a relatable journal, whereby the inputs were pH, temperature (°C), pressure (bar), reaction time (day) and oxygen level. A performance comparison and evaluation was carried out to analyse and validate the Levenberg-Marquardt (LM) & Bayesian Regularisation (BR) based-ANN models by altering the number of neurons. Overall, LM generalised better than BR algorithm as all of LMANNs' MSE values were kept low. It was determined that LMANN is suitable for the experimental database used to build the ANN models.

Keywords: Neural networks, Acutase, Batch Reactor, Vaccine, Process Control.

1. Introduction

Influenza viruses cause significant worldwide morbidity and mortality every year [1], [2]. Vaccines are the best tools available to prevent the disease burden [3]. A vaccine is a biopharmaceutical product that is utilised all over the world to prevent infection for a communicable disease. It has antigenic components that can stimulate the body's immune system to fortify defences against a certain disease. As part of a community immunisation programme, vaccination, which was first introduced in England, started to be implemented globally in the 1800s [4], [5]. The acceptance of vaccination around the world, however, has shown a declining trend recently due to vaccine hesitancy, particularly in Muslim countries like Malaysia, Afghanistan, Saudi Arabia, and Pakistan [6], [7]. Muslim reluctance and rejection of vaccination is founded on presumptions and convictions that such a procedure and the substances employed are "doubtful (mashbooh)", and they would prefer to forego it to preserve their sanctity [1]. Halal vaccinations represent one of the major business prospects in the field of Halal pharmaceuticals. Currently, only a small number of vaccinations with Halal certification have been created by businesses aiming at the Muslim consumer market. According to data, by 2028, the worldwide vaccination market is expected to reach US$103.57 billion. Due to Muslim consumers' impressions of the current vaccinations on the market and their religious beliefs, there is a need for the development of various types of Halal vaccines [8]. Ros et al. also explained that by using a bioreactor to culture the cell in a large quantity is more convenient. [9].

There are many types of vaccine which is inactivated virus, using live but attenuated virus, specified nuclei or polysaccharides and inactivated toxin that produced by certain bacteria. Influenza is responsible for about 17,000 to 51,000 deaths annually in the United States and global pandemic death tolls reach the millions [10]. Influenza virus comes from Orthomyxoviridae family and can be classifies into three types which are Influenza A, Influenza B and Influenza C. The most dangerous influenza is A that causes pandemic and infects humans and animals such as pigs, birds and horses. The virus always undergoes genetic changes and form new types of viruses that cannot be recognized by humans' immune system. Hence, the production of influenza virus must be done annually and compatible to the new viruses [11]. Milian and Kamen (2015) found that there are numerous ways to make a vaccine, including egg-based, cell-based, and cell culture approaches. For instance, Madin Darby Canine Kidney (MCDK) cells were used in the cell culture that produced the vaccines Optaflu and Flucelvax [10]. The influenza is then purified from the supernatant through several process which is filtration, centrifugation and chromatography to separate the impurities or cell debris within the virus. After that, the virus will be inactivated by using a chemicals such as B-propiolactone (B-PL) and cetyltrimethyl ammonium bromide (CTAB) and will be send to be tested [12].

The impact of the pandemic made it impossible to carry out the study endeavour as intended, which calls for experimentation. Therefore, using artificial intelligence (AI) was a viable solution to finish the project. In recent years, it has become increasingly common to use AI methods like response surface methodology (RSM) and artificial neural networks (ANN) to forecast the results of biological processes. Artificial neural networks (ANNs), for example, have the capacity to learn and generalise the behaviour of complicated non-linear data while calculating the link between input and output [13]. A neural network processes information similarly to the human brain. The neurons that make up a human brain are connected, with the neuron serving as the processing unit. The neural network's nodes, which are connected by weights, represent the neurons in the human brain. Each input element of the relevant neuron is associated with a weight, as shown in Figure 1, which is used as a guide for explanation. Each neuron has a bias component that affects how information is stored. The information of a neural network is stored in weights and biases to make it simpler.

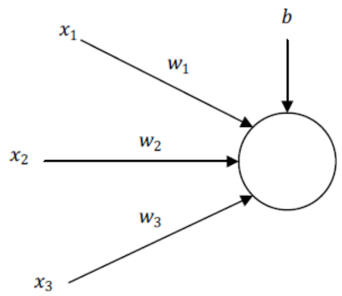


Figure 1: Neuron Structure [14]

Transfer functions link the network's inputs and outputs together. Based on the inputs, transfer functions model the desired result. Sigmoid function, hyperbolic tangent function, sine function, linear and saturated linear transfer functions are some examples of transfer function types [14]. The neurons are normally grouped into subsets which are categorised as layers. The layers are input layer, hidden layer and output layer. An ANN architecture with those three layers are described as multi-layer neural network as illustrated in Figure 2.

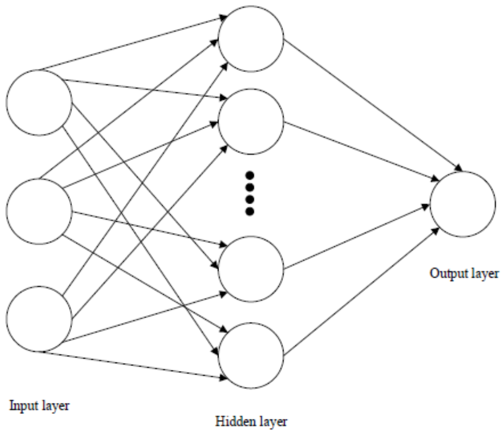


Figure 2: Architecture of a Feed-Forward ANN Model [14]

Multi-layer neural networks come in two types: shallow neural networks and deep neural networks. Deep neural networks have two or more hidden layers, whereas shallow neural networks only have one hidden layer. A typical prediction model is a shallow neural network. The multi-layer feed-forward with back propagation learning algorithm (FFBP) is one of the well-liked topologies suggested for ANN. As a systematic way to find flaws in the hidden layers, the back-propagation technique is used. In essence, it means that the algorithm passes between the hidden layer and the input layer before propagating output faults backwards. Thus, based on the inaccuracy, the weights and biases are adjusted throughout the training phase. The selection of training method is a key element in determining the accuracy of an ANN model. Levenberg-Marquardt (LM) and Bayesian Regularisation (BR) are suggested for complicated non-linear systems as they process the model quickly and minimise overfitting issues [14].

Hence, this study proposed a conventional process control for the unit operation which is PID controller and developed a shallow neural networks to predict the hemagglutinin (HA) yield using experimentation data sourced from a relatable journal. The inputs were pH, temperature (°C), pressure (bar) and reaction time (day). The output was HA yield (%). A performance comparison and evaluation was carried out between Levenberg-Marquardt (LM) and Bayesian Regularisation (BR) based-ANN models by altering the number of neurons. This was done to obtain the most accurate and reliable predictive network.

2. Methodology

2.1. Construction of Piping and Instrumentation Diagram (P&ID)

To construct a piping and instrumentation diagram (P&ID), a process flow diagram (PFD) of the unit operation or the process is necessary. PFD is a graphical way of describing a process, its constituent tasks and their sequence. A PFD helps with the brainstorming and communication of the process design [15]. After thorough literature review on the production of vaccine using Acutase, a PFD of this process is constructed. Building a P&ID is an important stage in developing a process control system because it enables you to see how components of the pipeline, instrumentation, and system equipment are connected functionally [16]. Hence, flow diagram is the most effective method to deliver information about a process [17]. The P&ID is developed after a literature review is carried out on the process.

2.2 Simulation of Conventional PID Control System

Proportional (P), integral (I), derivative (D), proportional-plus-integral (PI), and proportional-plus-integral-plus-derivative (PID) are well-known examples of typical process control systems. When selecting a controller, one must ensure that it has a quick response time, a low steady state error, and a minimum amount of overshoot for a certain process unit [18]. Figure 3 below illustrates the procedures for simulating the traditional controller of unit operation.

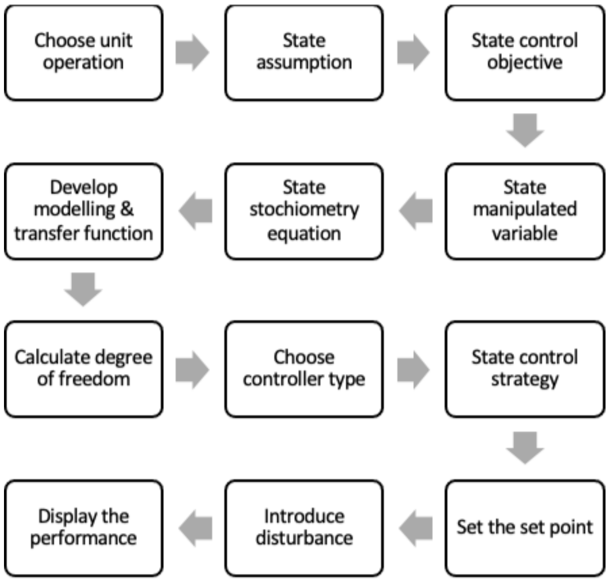


Figure 3: Steps in conventional process control system
Source: [19]

First step, the bioreactor is chosen as the unit operation while PID controller as the conventional controller. Figure 4 shows the extension steps in Figure 3 that can be followed to construct the conventional controller by using MATLAB SIMULINK R2023a software. A block diagram of process control system is developed with and without conventional PID controller by using the software to compare the output response.

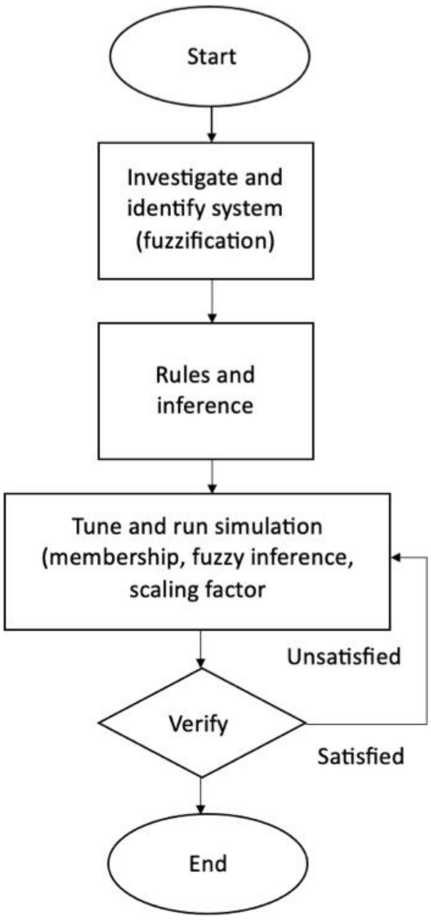


Figure 3: Steps in simulation of conventional process control system [19]

2.3 Methodology of Artificial Neural Network

For this study, experimental data sourced from a related journal was fitted using the neural network toolbox in MATLAB R2023a. A multi-layer feed forward back propagation (FFBP) shallow neural network was developed using sigmoid function and linear function as activation functions for the hidden layer and output layer respectively. The data set used in the training phase has 27 experimental points where 70 % is taken up for training, 15 % for testing and another 15 % for validation of ANN model.

The training algorithms chosen to develop the ANN models were altered between training algorithm LM and BR. Using Figure 2 as a guidance, the ANN parameter was optimised by varying the number of neurons in the hidden layer for both training algorithm. The performance of ANN is validated based on the calculation of mean square error (MSE) and correlation coefficient (R^2) using Equation 1 and 2 respectively [20].

$$\text{MSE} = \frac{1}{\ }\sum^{n} (y_i - y_{di})^2 \quad (1)$$

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - y_{di})}{\sum_{i=1}^{n}(y_{di} - y_m)^2} \quad (2)$$

n is the number of points, is the predicted HA yield, is the experimental HA yield and is the mean of experimental HA yield. Lower values of MSE indicates that the model is suitable. On the other hand, R2 has to be more than 0.90 for both training algorithms as this shows how well the outcomes are to be predicted by the models developed. So, the training phase for each network is stopped until low MSE and high R2 values were obtained. The properties of the ANN model developed in this study is as described in Table 1.

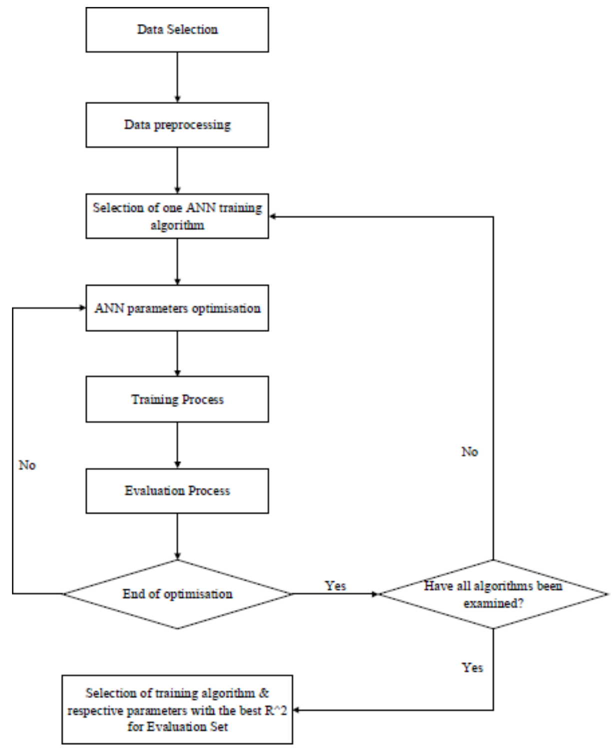


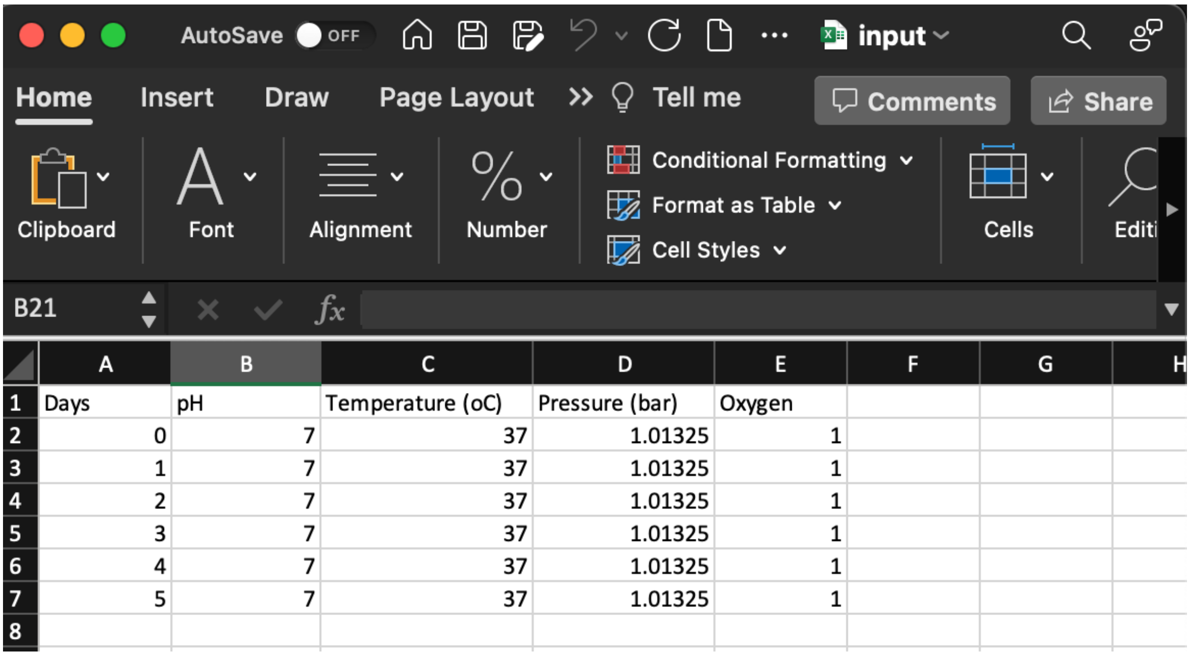
Figure 4: Methodology of training the ANN model

Table 1: Properties Of Ann Model

ANN model	
Shallow neural Network type	
Activation function network	
(hidden)	hyperbolic tangent Activation function
(output) linear	
Number of neurons (input)	5
Number of neurons (hidden layer)	10
Number of neurons (outputs)	1
Learning algorithm	Back-propagation
Training algorithm	LM and BR

2.2. Development of Artificial Neural Network in MATLAB

Input and output tabs were created in Excel then the respective tabs were filled with the dataset obtained from external journal. The software by default create the decimal number up to five places.



	A	B	C	D	E
1	Days	pH	Temperature (oC)	Pressure (bar)	Oxygen
2	0	7	37	1.01325	1
3	1	7	37	1.01325	1
4	2	7	37	1.01325	1
5	3	7	37	1.01325	1
6	4	7	37	1.01325	1
7	5	7	37	1.01325	1

Figure 5: Data key-in in Excel

Started the neural network fitting toolbox by keying 'nftool' in Matlab command window.

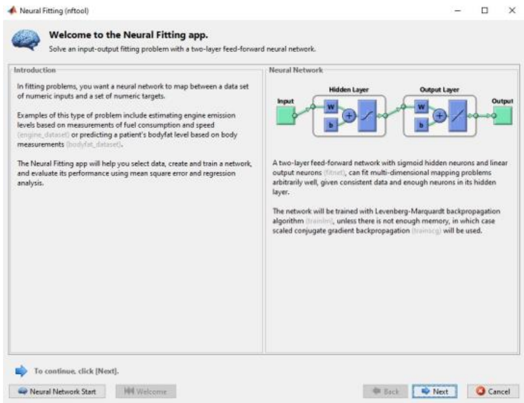


Figure 6: Neural net fitting tool in MATLAB

Selected the respective input and output variables

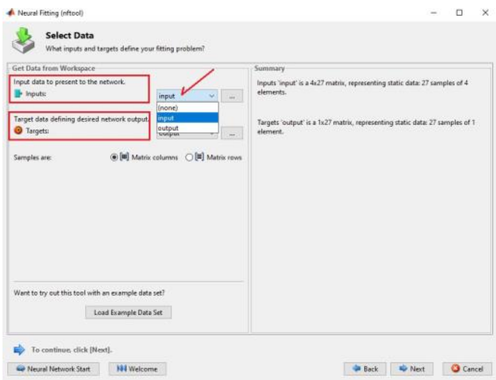


Figure 7: Data selection in neural net fitting tool

Select a specific number of neurons in the hidden layer within the range of 3 to 25 neurons for network training:

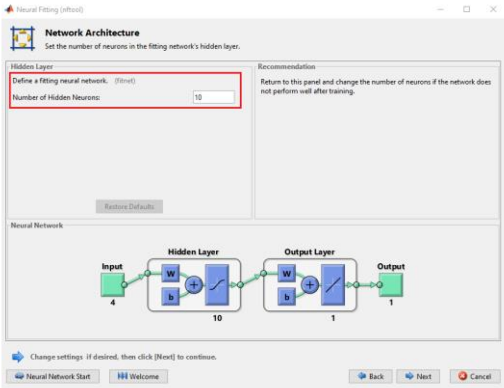


Figure 8: Network architecture in neural net fitting tool

Select either Levenberg-Marquardt or Bayesian Regularization training algorithm and then network was trained:

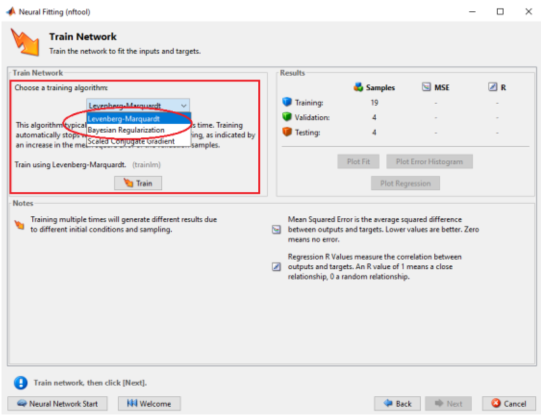


Figure 9: Training network in neural net fitting tool

Extract the 'Performance' and 'Regression' plots to get the MSE and values:

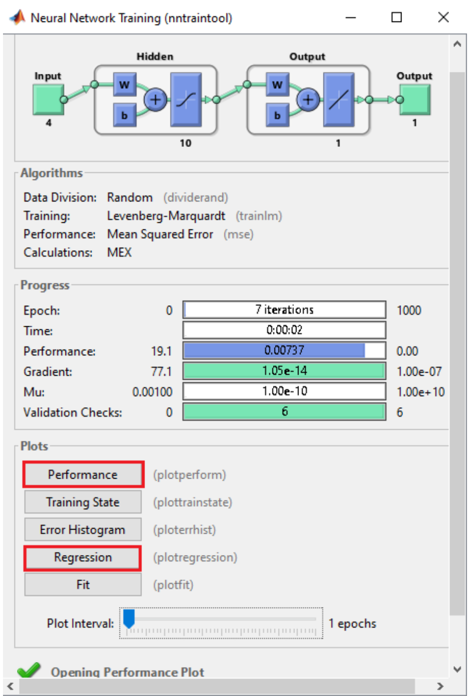


Figure 10: Neural net fitting app

If satisfactory MSE and R^2 values were obtained, then the MATLAB script for the neural network architecture developed was generated by clicking onto 'Simple Script'. The results of the predicted outputs as well the errors were saved:

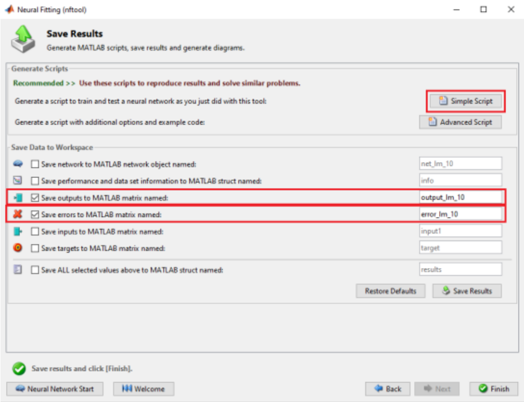


Figure 11: Results in neural net fitting tool

If the results achieved are not desirable, then the network was retrained until satisfactory MSE and values were obtained for that particular architecture. Once that network architecture has produced desirable results, the number of neurons are changed to get the optimum network architecture:

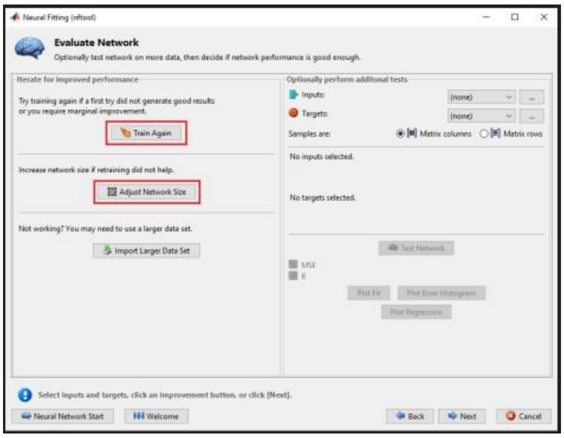


Figure 12: Network evaluation in neural net fitting tool.

3. Results and Discussion

3.1. Piping and Instrumentation Diagram (P&ID)

The P&ID of the bioreactor is constructed as shown in Figure 13. Three feedback controller was done on the bioreactor which are temperature, pH and level. The control strategies on the bioreactor can be seen as in Table 2.

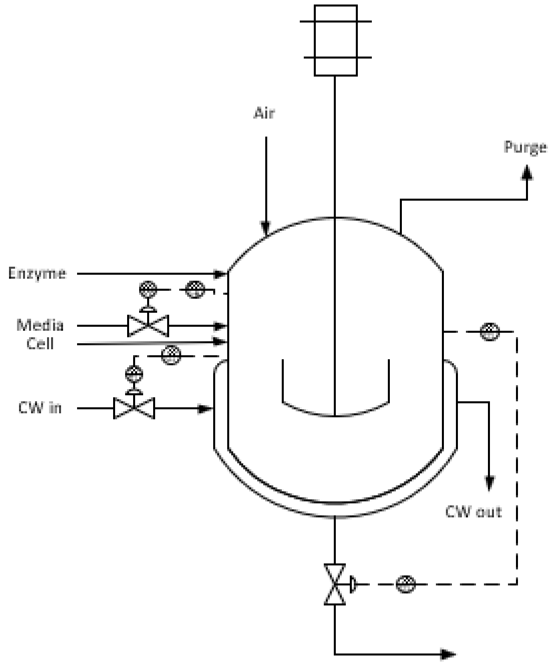


Figure 13: P&ID for vaccine production via batch bioreactor

Table 2: Control strategies on batch bioreactor

Type of controller	Temperature controller	pH controller	Level controller
Control objective	To avoid overheating and maintain temperature within setpoint 37°C	Maintaining pH in the bioreactor	Maintaining the level of the bioreactor
Control variable	Temperature in batch bioreactor	pH of bioreactor (setpoint = pH 7)	Level of bioreactor
Manipulated variable	Inlet cooling water flowrate of the jacket	Inlet flowrate of media	Flowrate of bottom product
Control action	Temperature transmitter (TT) sense the temperature changes in the bioreactor and send signal to temperature controller (TC). TC will manipulate the valve opening of cooling water inlet of jacket. When T>SP, valve opening increase. When T<SP valve opening decrease.	pH Transmitter (PHT) sense the pH changes in the bioreactor. If deviation occurs, PHT will send signal as error to pH Controller (PHIC). PHIC accept signal from PHT and it will manipulate the valve opening of the inlet media. For instance, if the pH is lower	Level Transmitter (LT) measure the level inside the bioreactor and send signal to LC if level deviates from desired set point. LC receive signal from LT and manipulate the valve opening at outlet of product. As the level of the medium inside the bioreactor is increased, the valve will open to increase the flow rate of the product to reduce the level. As the level of the

		than the set point, the valve will be controlled to open wider to supply more media to stabilize back the bioreactor pH. When the pH is higher the set point, the valve opening is decreased to achieve the desired pH.	medium inside the fermenter is decreased, the valve will close to reduce the flow rate of the product to increased the level.
Types of valve	Diaphragm valve	Diaphragm valve	Diaphragm valve

3.2 Conventional PID control system

A batch bioreactor had been chosen as the unit operation in this study for vaccine production from Acutase. The assumption of this unit operation is it is a steady state process. The control objectives are to control the temperature and pH of the bioreactor. The setpoint for the temperature is set at 37°C and at pH 7. From literature review, the transfer function for temperature [21] is as below:

$$TF_{Temperature} = \frac{0.50077}{20.20s + 1}$$

The transfer function for pH [22] is as below:

$$TF_{pH} = \frac{0.609}{1.218s + 1}$$

Figure 14 shows the Simulink block, where the simulation is done with and without PID controller.

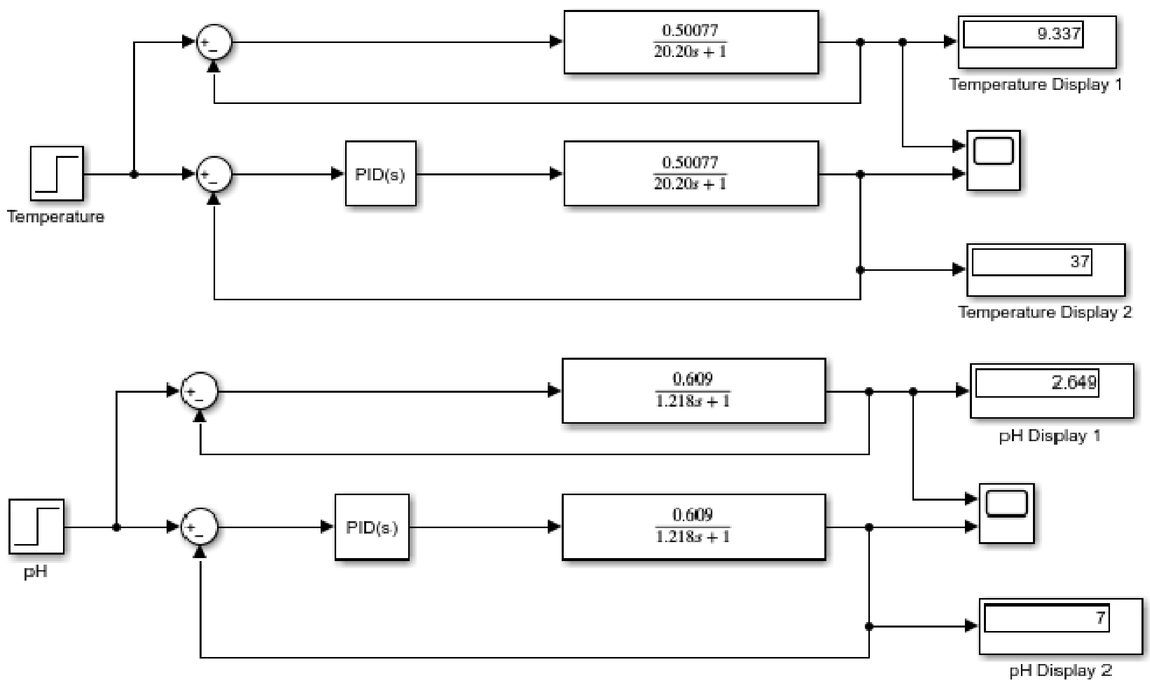


Figure 14: SIMULINK block with and without PID controller

The response for the PID controller for both temperature and pH with and without PID controller are shown in Figure 15. Without any controller, the temperature cannot reach to the setpoint of 37°C, and it can only be maintained at 9.337°C. When PID controller is used, it able to reach the setpoint value at 1s. For the pH parameter, same goes with the temperature where when no controller is used, it is not able to reach the desired value of pH at 7. By using PID controller, it can reach the pH of 7 at 6s. Based on the results, the conventional method of process control by using PID controller can give good results, however the conventional controller is much more complicated and take time to set up the control [23], [24].

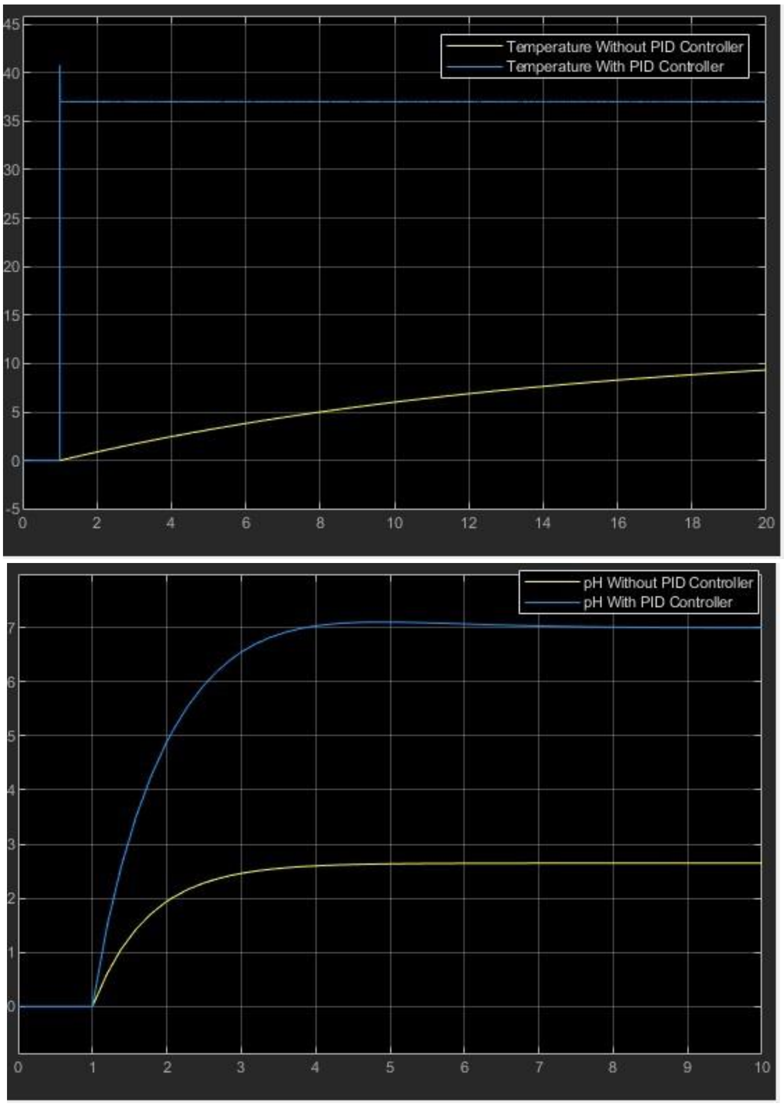


Figure 15: Temperature and pH output response in batch bioreactor

3.3 *Database for Experimental Results of Hemagglutinin (HA) Yield*

Due to the current exceptional situation caused by the COVID-19 pandemic, the experimentation was impossible to be carried out as planned. Hence, a similar experimentation data sourced from another journal was used in this experiment. The data proposed for the simulation of artificial neural network (ANN) is obtained from a journal from Ros et al. [10]. In this research journal, the authors produced HA using Trypsin and Acutase in batch reactor.

The parameters studied in this experiment was pH, temperature (°C), pressure (bar), reaction time (day) and oxygen level. The synthesis of HA was carried out in a batch bioreactor. Table 3 is the data used as inputs and output for the ANN models developed in this study in the nomenclature.

Table 3: Experimental Data Extracted From External Journal [10]

	Variables				**Response**
Days	Temperature (°C)	pH	Pressure (bar)	Oxygen	Cell concentration
0	37	6	1.01325	1	0
1	37	6	1.01325	1	200000
2	37	6	1.01325	1	3.80000
3	37	6	1.01325	1	1.170000
4	37	6	1.01325	1	800000

5	37	6	1.01325	1	600000
0	37	7	1.01325	1	19.2
1	37	7	1.01325	1	23.7
2	37	7	1.01325	1	17.2
3	37	7	1.01325	1	22.3
4	37	7	1.01325	1	21.8
5	37	7	1.01325	1	20.1
0	37	8	1.01325	1	23.7
1	37	8	1.01325	1	21.3
2	37	8	1.01325	1	21.8
3	37	8	1.01325	1	23.7
4	37	8	1.01325	1	16.8
5	37	8	1.01325	1	25.3

3.2. *Development Performance Evaluation of Levenberg-Marquardt & Bayesian Regularization Based-ANN Models*

A feed-forward multi-layer ANNs were developed using neural network fitting tool (nftool) in MATLAB R2023a. The input layer has five neurons corresponding to temperature (37°C), reaction time (0-5 days), pH (6-8), pressure (1.01325 bar) and oxygen (1) while the output has one neuron that corresponds to HA concentration. The training function of the developed ANN updates the weights and biases according to the selected training algorithm. For this study, the training algorithm is back-propagation. Back-propagation algorithm adjusts the weights in the network by following negative direction of the gradient from sum of squared errors (SSEs) with respects to the weight variables [25].

The optimum performance results for each network was selected when minimum MSE and maximum was achieved. MSE is the average squared difference between output and target data. Lower values of MSE indicate higher accuracy of network. Correlation coefficient (R^2) is a measure of the relationship between output and target. A value close to 1 shows that output has a stronger relationship to the target data [26]. The performances for each network developed are as in Figure 16.

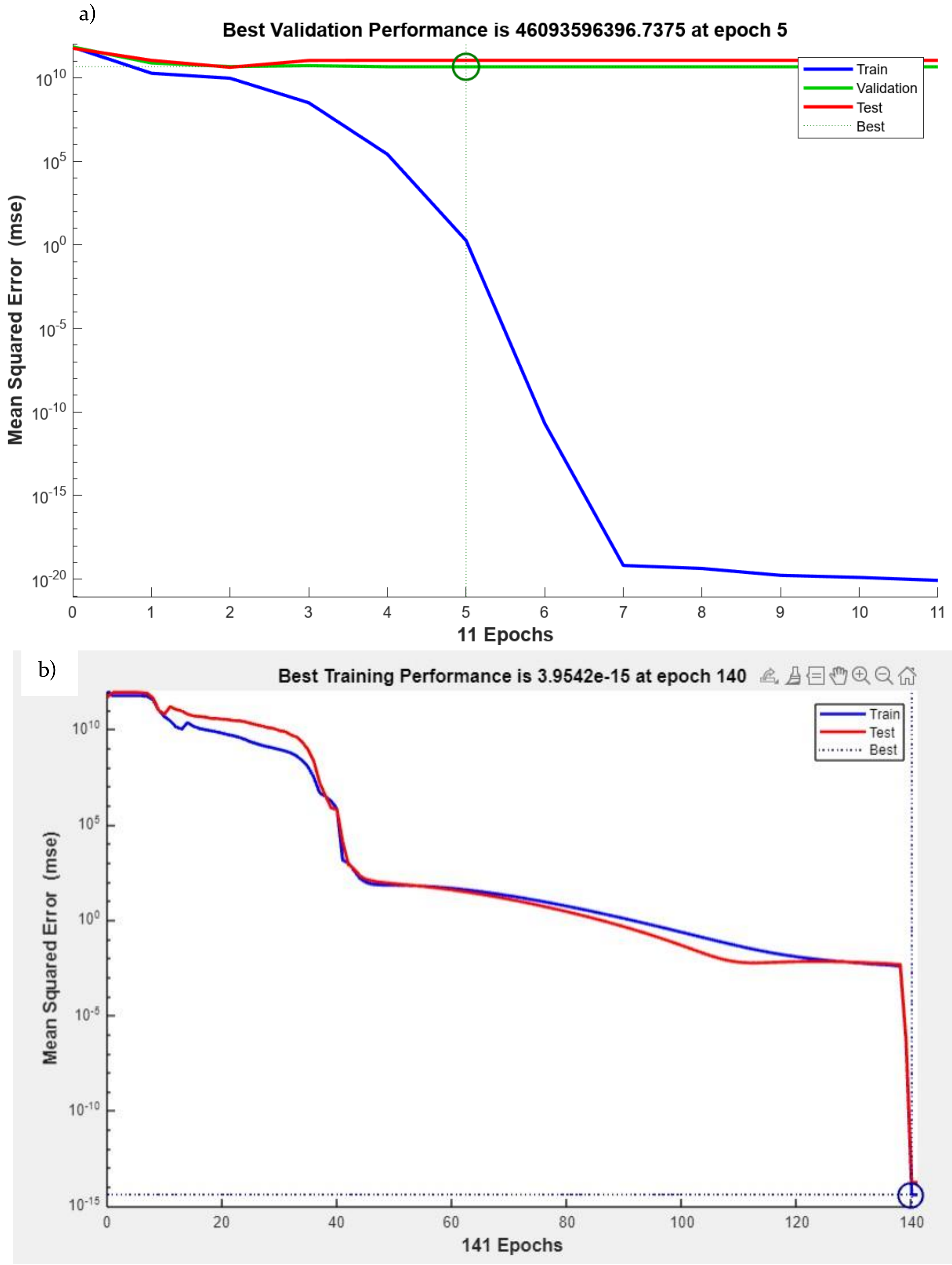


Figure 16: Performance for: a) Levenberg-Marquadt model; b) Bayesian regularization model

Levenberg-Marquadt (LM) algorithm is an efficient algorithm used in deep learning and it is vastly employed in neural network. LM is essentially an iterative method that locates local minimum of multivariate function which is expressed in the SSEs of non-linear, real-valued functions [27]. LM's curve-fitting method is a combination of Gauss-Newton and gradient descent method (GDM). So, when the solution is far from local minimum, the algorithm behaves like gradient descent method; slow convergence. In contrast, when the solution is close to local minimum, algorithm behaves like Gauss-Newton; fast convergence.

Figure 17 shows the training, testing and validation regression plots for LMANN structure.

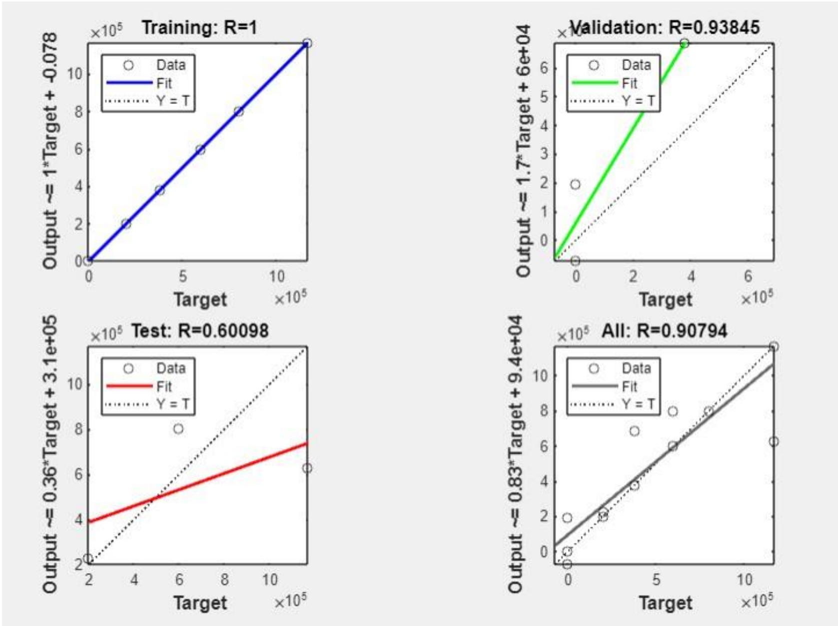


Figure 17: LMANN regression plots

Bayesian regularization (BR) algorithm is a method that performs shrinkage to estimate the model with the least number of weights. A BRANN penalises large weights to prevent overfitting and to get a smoother mapping of the datasets. Thus, BRANN takes a much longer prediction time and it also performs more iterations (epochs) than other training algorithms [20]. The datasets plugged in as inputs and target variables in BRANN is divided into three parts; training, testing and validation. However, this may not be the case if the datasets are small. Instead, the data will be segregated for training and testing only. Figure 18 illustrates the training and testing regression plots for BRANN structure.

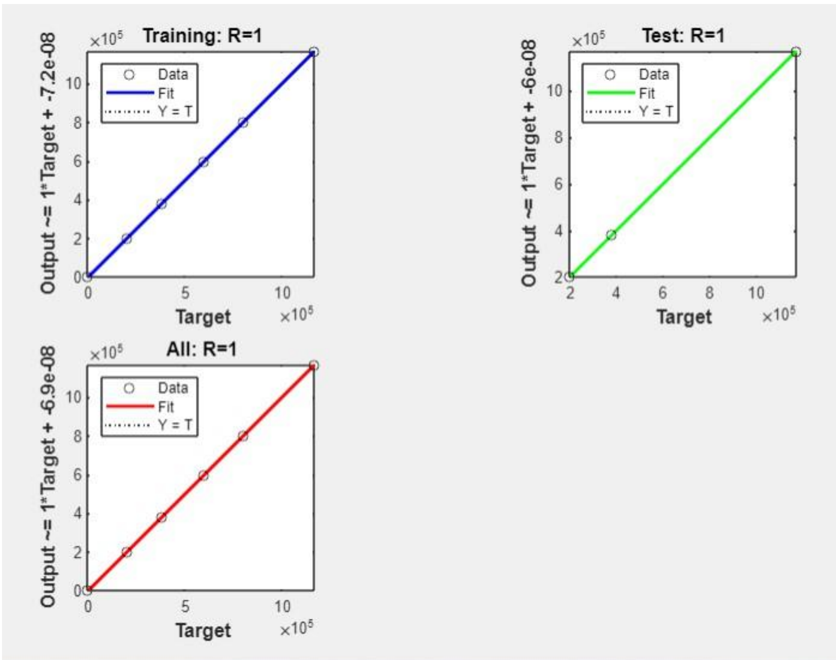


Figure 18: BRANN regression plots

3.4. *Conclusion of study*

In this study, LMANN model has proven to have the most accurate prediction and stronger relationship with the experimental data. Since BR method has the ability to remove large weights using the penalty term, it is supposed to deliver better prediction results than LM algorithm. However, it has proven to be otherwise in this study. All of the BRANNs architecture were giving high MSEs and low R^2 values except for the last two architectures. Overall, the relationship between BRANNs predicted data and experimental data were rather random and has large deviation from each other.

LM's method focusses on minimising the sum of squared errors (SSEs) and produce a network with fast convergence [28] It can be concluded that LM algorithm is suitable for the datasets. Despite LMANN demonstrated high prediction accuracy, the deviation rates were possibly caused by insufficient data. To reduce the deviation rates and to build a much more stable network, more datasets should be employed to build a reliable predictive network.

4. Conclusion

Vaccines are the best tools available to prevent the disease burden. The acceptance of vaccination around the world, however, has shown a declining trend recently due to vaccine hesitancy, particularly in Muslim countries like Malaysia, Afghanistan, Saudi Arabia, and Pakistan. The impact of the pandemic made it impossible to carry out the study endeavour as intended, which calls for experimentation. Therefore, using artificial intelligence (AI) was a viable solution to finish the project. Artificial neural networks (ANNs), for example, have the capacity to learn and generalise the behaviour of complicated non-linear data while calculating the link between input and output. Transfer functions link the network's inputs and outputs together. Based on the inputs, transfer functions model the desired result. The study had successfully proposed a conventional process control for the unit operation which is PID controller and developed a shallow neural networks to predict the hemagglutinin (HA) yield using experimentation data sourced from a relatable journal. The inputs were pH, temperature (oC), pressure (bar) and reaction time (day). The output was HA yield (%).

The type of training algorithm selected determines the accuracy and relationship of network with the experimental data. The suitable training algorithm along with the optimum number of hidden neurons can produce an efficient and accurate ANN model. For this study, Levenberg-Marquardt (LM) and Bayesian regularisation (BR) were assessed. The LMANN and BRANN models were analysed statistically based on MSE and R^2. For a non-linear and small dataset, LMANN has a better predictive ability than BRANN. Therefore, it can be concluded that the predicted HA concentration or yield from LMANN is accurate and have a stronger relationship to the experimental data. To conclude the finding in this study, LM algorithm is suitable for small datasets and ANN is an excellent prediction tool for non-linear and simple datasets.

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