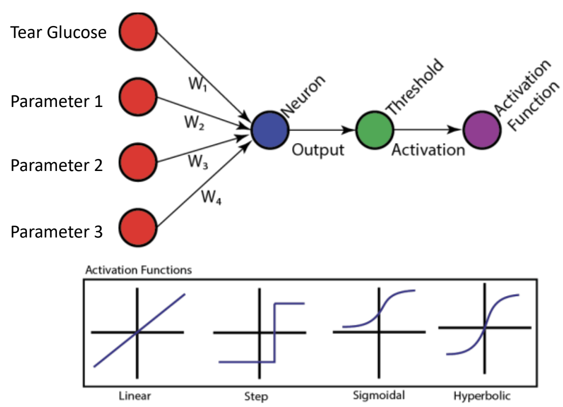
Supplementary Information to

Neural Network:

For calibration a neural network was trained which involved identifying the factors that are suspected to affect the results and providing those factors as well as the input values, in this case, tear glucose data. A subsequent training step for the neural network is performed along with known output values from a subset of data; this is discussed in depth in the supplementary information. The neural network was generated and trained to convert glucose in tears to equivalent blood glucose values and is shown schematically in the supporting information (supporting figure 2).The simple neural network (NN) comprising shallow feed forward single neuron network methodology employed in the development of the algorithm is shown below in Supporting Figure 1. The inputs are weighted and fed into the neuron, which creates an output signal. If that output signal is above a certain threshold, then an activation function is triggered, which leads to an output value. In practice, a network comprises multiple neurons spanning one or more layers. As will be demonstrated later, the neural network generated herein and trained to convert glucose in tears to equivalent blood glucose values consists of 16 neurons in a single hidden layer.

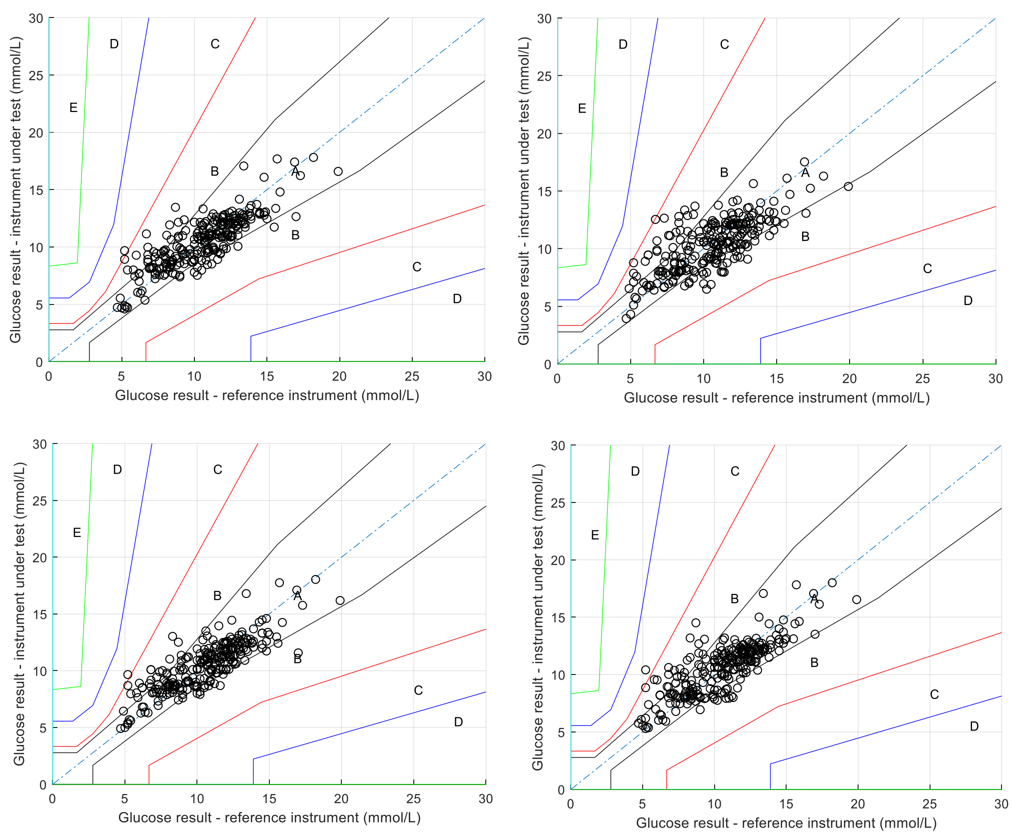


Supporting Figure 1: Schematic presentation of a single neuron feed forward neural network and possible activation functions.

The neural network is generated by selecting the number of neurons, the starting input parameters and selecting the type of training algorithm to use, the network is then built and trained. The parameters are iteratively modified until the optimal performing model is obtained.

The NN model was built using Matlab 2019 and the Neural Network toolbox for regression. To develop the NN regression model the data from 100 min after starting collection for all 21 patients was pooled and each data point was paired with its corresponding blood glucose value (obtained from the Libre device). Using only data following 100 min ensured that the effects due to warm up of the device were minimized and effects relating to the eye to blood transformation play a dominant role. Each data pair was assigned to the device specific calibration factors to generate a set of 5 values for each observation. The data set was randomized by assigning to each observation a computer-generated random number between 1 and the 256 (the total number observations) and then sorted from lowest to highest in excel. The neural network fitting was developed by iteratively varying the number of neurons in the hidden layer until either there was no further reduction or an increase in the mean squared error (MSE) and R values. In order to develop the model the data set was divided into multiple training and testing data sets, initially consisting of 30% of the data in the training data set and 70% of the data in the test data set. The model was built using a Levenburg-Marqardt Regularization which resulted in an R value of 0.87 and an MSE of 2.28. In order to cross validate this model various other models were built from a range of starting points and training states with both Levenburg-Marqart (LM) and Baysean Regularization (BR).

The error grids generated from four of the NN regression models one from each of the regularization and training : test ratios are shown below in Supporting Figure 2. All of the generated models and starting points were consistent and showed very similar spreads of the data.



Supporting Figure 2. Error grids produced from four Neural Network models a) Regularization = LM, training ratio = 70:30, b) Regularization = LM, training ratio = 30:70, c) Regularization = BR, training ratio = 70:30, d) Regularization = BR, training ratio = 30:70.