Application of Machine Learning Methods to Identify Ion Channel Kinetics

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Introduction

Patch-clamp electrophysiology data is vital for understanding ion channel behavior but is laborious to idealize for analysis in research. Previous studies have demonstrated that convolutional neural networks and long short-term memory architecture can automatically idealize complex single-molecule data more quickly and accurately than traditional methods.

In this preliminary study, we attempt to recreate the (1) trained model development and (2) model prediction performance using a new unseen dataset using source code and recordings/data. This methodology may allow researchers to save time and resources by simplifying the data idealization, automatically specifying the number of channels present, and by possibly reducing the number of samples for analyzing patch-clamp electrophysiology data in ion channel research. In this work presented, we train a deep learning model as outlined in the original paper and then utilize the model to analyze previously unseen data using ion channel records provided by Celik et al.[1]

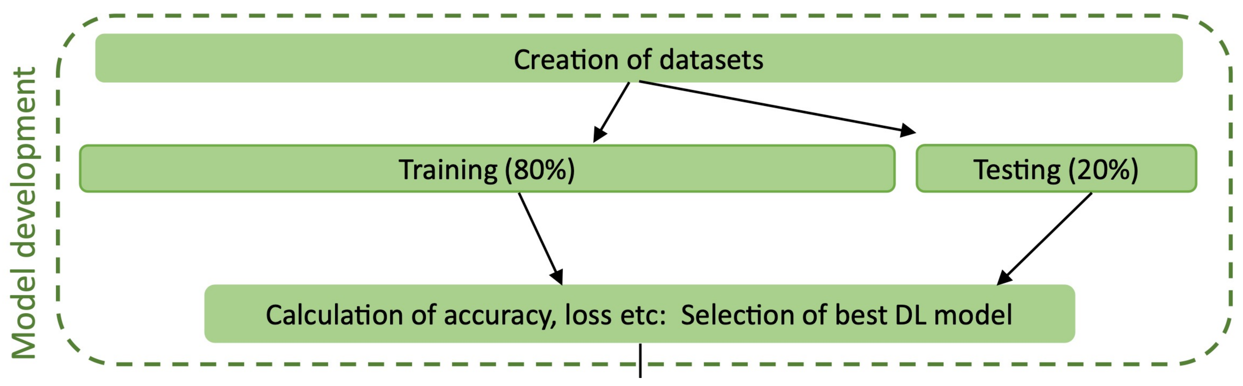

Figure 1. Over-all model design and testing workflow adapted from Celik et al. demonstrating model development. [1]

Here, a hybrid recurrent convolutional neural network (RCNN) model was used to idealize ion channel records. Convolutional neural networks were used in deep learning for learning patterns given complex data and classification problems. Recurrent neural networks were used for time series analyses, but performance degrades on longer time scales in a problem known as the vanishing gradient problem. A long short-term memory (LSTM) network, a type of recurrent neural network, was used in the presented model to address the vanishing gradient problem. In our current study, we attempt to replicate a similar qualitative & performance comparison of a single ion channel and five ion channel data shown by Celik et al. in their original paper, as shown in Fig. 1. In essence, the main goal at this stage is to demonstrate the feasibility of applying Machine learning to identify channel kinetics, specifically that of Piezo Ion Channels, in future works.

Methods

As mentioned previously, long short-term memory (LSTM) network is a type of recurrent neural network (RNN) used to address model degradation on long times scales. Here, a hybrid convolutional neural network model is used. The system used was run on an x64-based processor PC running Windows 10. The PC ran on an 11th Gen Intel® Core™ i7-1165G7 with only 16.0 GB of RAM and no GPU.

For the machine learning architecture, the 1D Convolution layer consists of a 1D-CNN, rectified linear unit (ReLU) layer and max pooling layer. There were 64 filters used and a max pooling layer was added to each output he data was flattened out for use in the LSTM network layer. Stacked LSTM layers consisting of 256 units were used. Finally, the final layer consisted of a Dense output layer with SoftMax activation function. A summary of this model architecture is shown in Fig. 2. This model can account for a maximum of five ion channels. (cont.)

(Methods cont.)

For classification reports of the trained models, the true positive (TP) rate represents the proportion of positive samples that are correctly predicted, and the false positive (FP) rate represents the proportion of actual negatives the model predicted incorrectly. Here the changes in model accuracy are tracked across the entire 50 epochs. The model accuracy is a metric used in evaluating classifications models and is a fraction of predictions that the model made correctly. The metrics used in determining the efficacy and performance of deep learning models include accuracy, precision, recall, and F-score. All of which rely on true positives and false positives. A perfect classifier would have a precision value and recall value of 1. The classification reports for trained models are shown in Table 1 and Table 2. The equations that describe precision, recall, and F-score are shown below.

$$Accuracy = \frac{True\ Positives + True\ Negatives}{True\ Positives + True\ Negatives + False\ Positives + False\ Negatives} \quad (1)$$

$$Precision = \frac{True\ Positives}{True\ Positives - False\ Positives} \quad (2)$$

$$Recall = \frac{True\ Positives}{True\ Positives - False\ Negatives} \quad (3)$$

$$FScore = \frac{2 \times Precision \times Recall}{Precision + Recall} \quad (4)$$

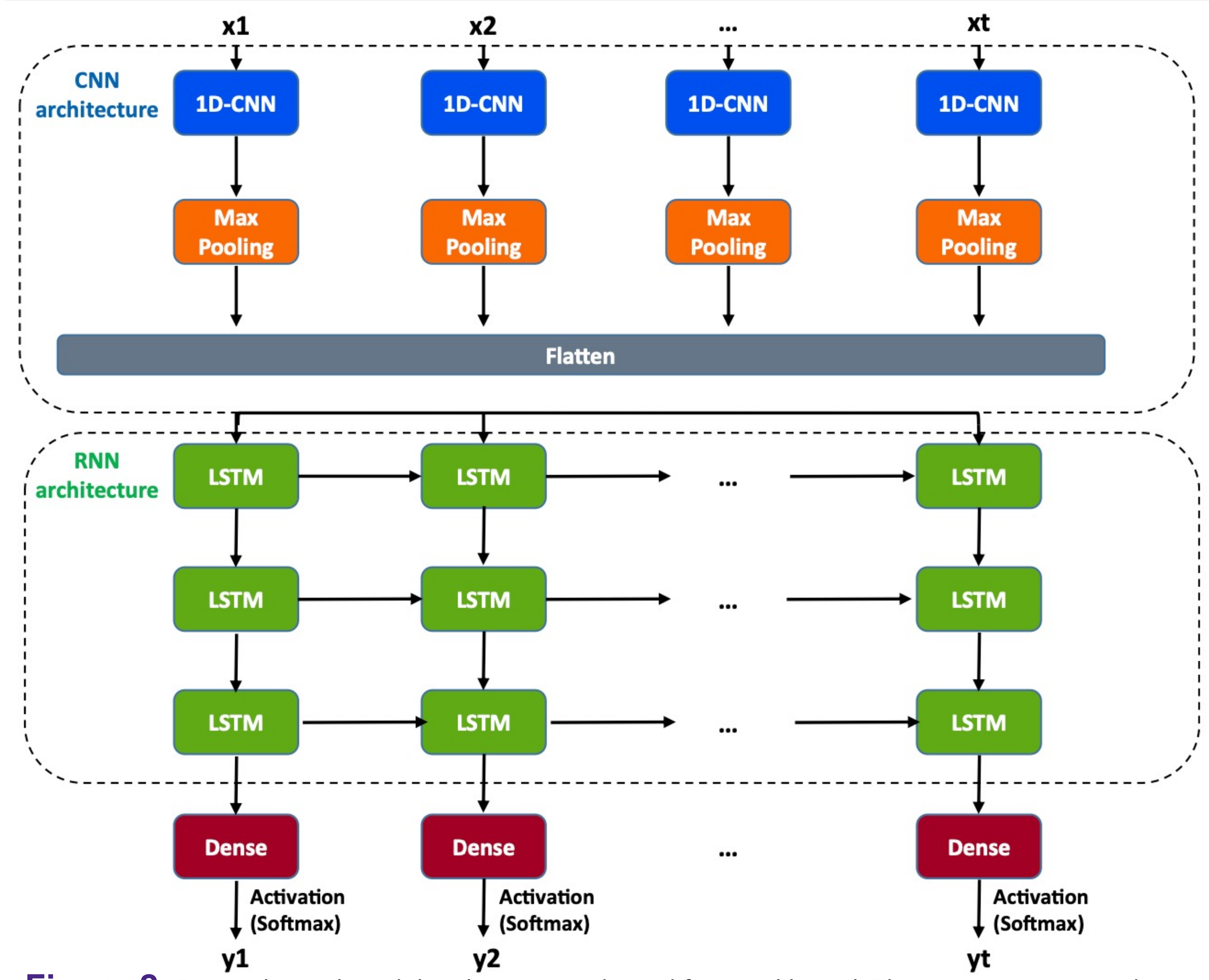

Figure 2. Deep-Channel model architecture adapted from Celik et al. The input time series data were fed to the 1D Convolution layer (1D-CNN) which includes both 1D convolution layers and max pooling layers. After this, data was flattened to the shape of the next network layer, which is an LSTM. Three LSTM layers were stacked and each contains 256 LSTM units. In post-network processing, the most-likely number of channels open at a given time is calculated simply as the class with the highest probability at a given instant (Argmax). [1]

Results

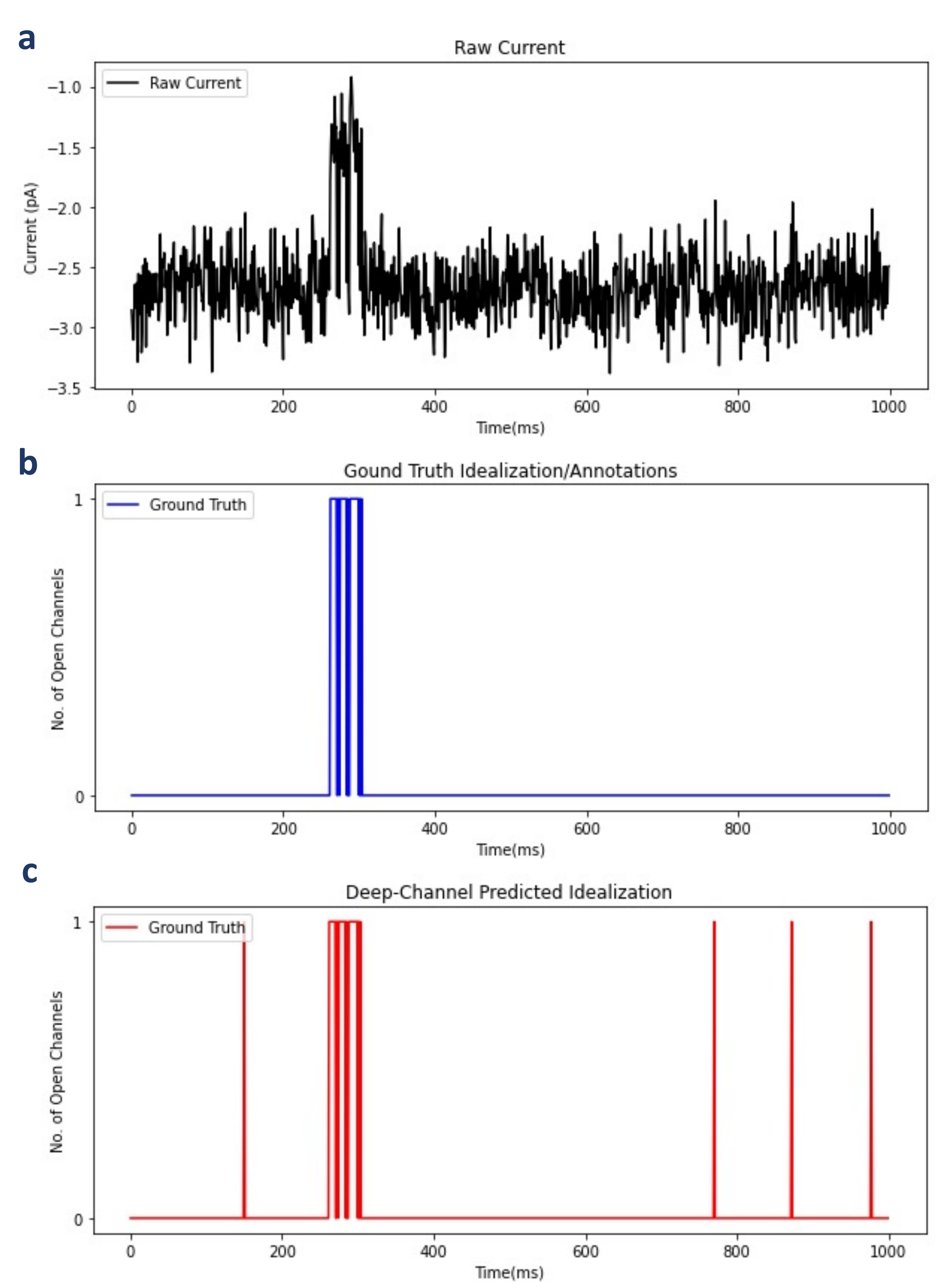

Figure 3. Qualitative performance Deep-Channel with previously unseen data for single ion channel model. a-c Representative example of Deep-Channel performance using single ion channel data training
a The raw semi-simulated ion channel event data (black).
b The ground truth/idealization annotation labels (blue) from the raw data above in (a).
c The Deep-Channel predictions (red) for the raw data above (a).

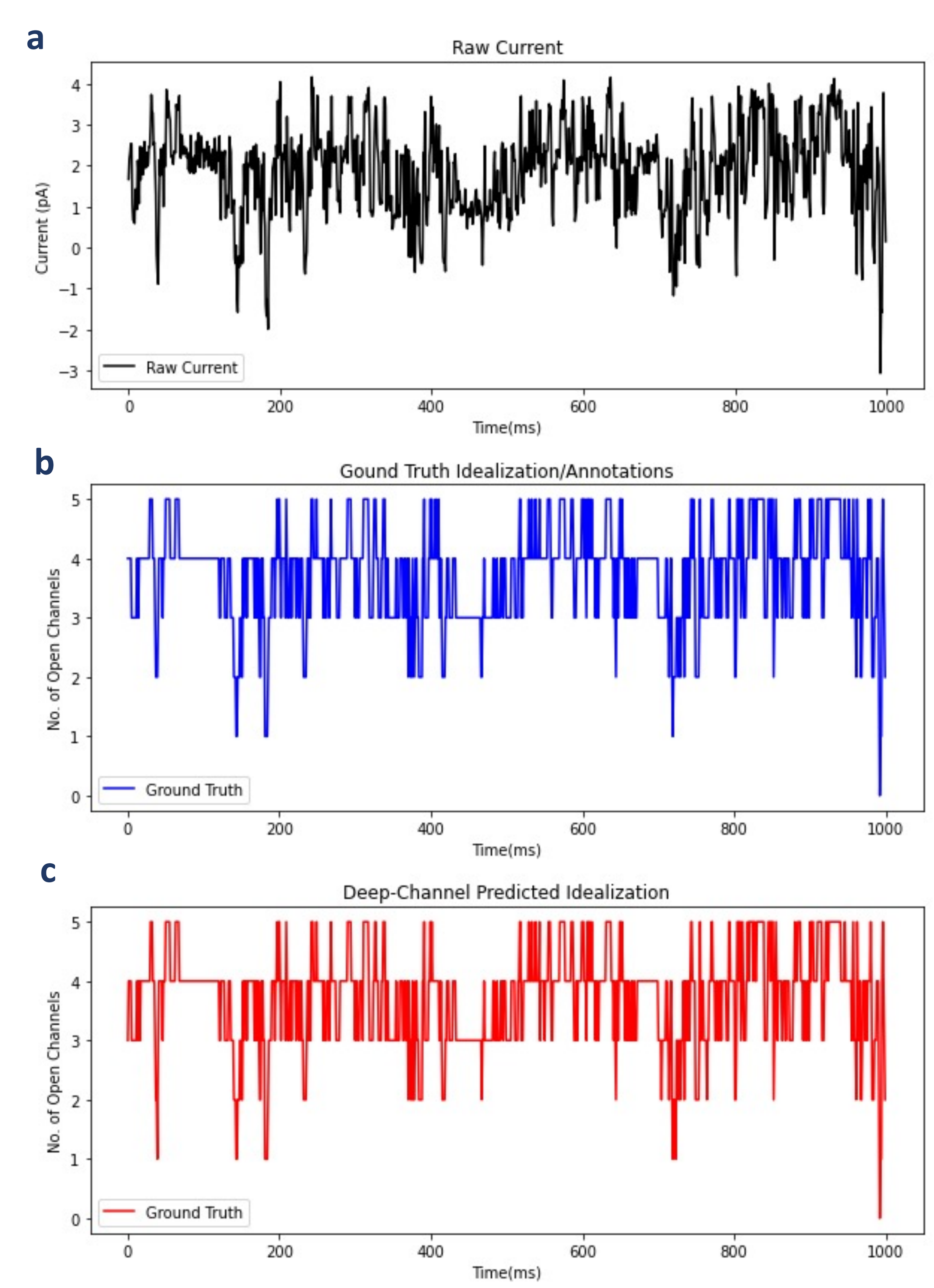

Figure 4. Qualitative performance Deep-Channel with previously unseen data for a five ion channel model. a-c Representative example of Deep-Channel performance using single ion channel data training
a The raw semi-simulated ion channel event data (black).
b The ground truth/idealization annotation labels (blue) from the raw data above in (a).
c The Deep-Channel predictions (red) for the raw data above (a).

Table 1. Classification Reports for Multi-Channel Models on Previously Unseen Data

	Precision	Recall	F1-score
classification report of DC:			
0	0.96	0.95	0.95
1	0.97	0.96	0.96
2	0.95	0.98	0.96
3	0.96	0.97	0.96
4	0.93	0.97	0.95
5	1.00	0.87	0.93
accuracy			0.95
macro avg	0.96	0.95	0.95
weighted avg	0.95	0.95	0.95
classification report of QuB:			
0	1.00	0.57	0.72
1	0.95	0.81	0.88
2	0.95	0.92	0.93
3	0.96	0.96	0.96
4	0.96	0.98	0.97
5	0.98	0.98	0.98
accuracy			0.96
macro avg	0.97	0.87	0.91
weighted avg	0.96	0.96	0.96
classification report of QuB half-amp:			
0	1.00	0.88	0.93
1	0.98	0.90	0.94
2	0.97	0.93	0.95
3	0.96	0.96	0.96
4	0.96	0.97	0.97
5	0.95	0.99	0.97
accuracy			0.96
macro avg	0.97	0.94	0.95
weighted avg	0.96	0.96	0.96

Table 2. Classification Reports for Single Channel Models on Previously Unseen Data

	Precision	Recall	F1-score
classification report of DC:			
0	1.00	1.00	1.00
1	0.94	0.99	0.97
accuracy			1.00
macro avg	0.97	0.99	0.98
weighted avg	1.00	1.00	1.00
classification report of QuB SKM:			
0	1.00	1.00	1.00
1	0.94	0.98	0.96
accuracy			1.00
macro avg	0.97	0.99	0.98
weighted avg	1.00	1.00	1.00
classification report QuB half-amp:			
0	1.00	0.99	1.00
1	0.90	0.99	0.95
accuracy			0.99
macro avg	0.95	0.99	0.97
weighted avg	0.99	0.99	0.99

Conclusion

The results from the model training stage and testing on a previously unseen dataset result are similar to those presented by the original paper. The qualitative performance demonstrates the efficacy of the DC mode. The similarities between the Deep-Channel (DC) predicated idealization and the ground truth idealization are shown in Fig. 3 and Fig. 4. Additionally, the quantifiable comparison between DC, SKM, and half-amp shown in Table 1 and Table 2, demonstrate that the performance of DC is on par with that of QuB models.

Future vision stemming from this current work includes utilizing additional recordings, recreating larger sections of the methodology outlined in the work by Celik et al., and extending use of this the Deep-Channel model with other varieties of ion channels while testing efficacy and performance. Demonstrating the effectiveness and application of this model to other studies may allow researchers to save time by utilizing this more intuitive, easy-to-use model that requires fewer parameters to be set and managed. This investigational study demonstrates similar performance to that outlined by Celik et al. in their original work and provides encouraging results concerning the future application of this model.

References

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