CLAIMS

[Claim 1]. A computer-implemented method of base calling clusters, including:

processing input data through a neural network and producing an alternative representation of the input data, wherein the input data includes

(i) per-cycle data for each of one or more sequencing cycles of a sequencing run that comprises pixels that depict intensity emissions indicative of the one or more clusters at a respective one of the sequencing cycles, and

(ii) supplemental distance information that identifies distances between the pixels of the per-cycle data;

wherein, during the processing of the pixels of the per-cycle data by the neural network, the supplemental distance information accompanies the per-cycle data and conveys to the neural network which of the pixels of the per-cycle data contain centers of the clusters and which of the pixels of the per-cycle data are farther away from the centers of the clusters;

processing the alternative representation through an output layer and producing an output; and

base calling one or more of the clusters at one or more of the sequencing cycles from values of the output.

[Claim 2]. The computer-implemented method of claim 1, wherein the per-cycle data is indicative of a surrounding background at the respective one of the sequencing cycles.

[Claim 3]. The computer-implemented method of any of claims 1-2, wherein the supplemental distance information improves accuracy of the base calling.

[Claim 4]. The computer-implemented method of claim 3, wherein the neural network uses the supplemental distance information to assign a sequencing signal to its proper source cluster by attending to central cluster pixels, their neighboring pixels, and alternative representations derived from them more than perimeter cluster pixels, background pixels, and alternative representations derived from them.

[Claim 5]. The computer-implemented method of claim 1, further including accompanying the per-cycle data with supplemental scaling information that assigns scaling values to the pixels of the per-cycle data.

[Claim 6]. The computer-implemented method 1, wherein the per-cycle data is indicative of a voltage change detected at the respective sequencing cycle.

[Claim 7]. The computer-implemented method of claim 1, wherein the per-cycle data is indicative of an electric current signal measured at the respective sequencing cycle.

[Claim 8]. A neural network-implemented method of base calling clusters synthesized during a sequencing run comprising a plurality of sequencing cycles, the method including:

convolving input data through a convolutional neural network to generate a convolved representation of the input data,

wherein the input data convolved for a current sequencing cycle includes image patches extracted from one or more images in each of a current image set generated at the current sequencing cycle of the sequencing run, one or more preceding image sets respectively generated at one or more sequencing cycles of the sequencing run preceding the current sequencing cycle, and of one or more succeeding image sets respectively generated at one or more sequencing cycles of the sequencing run succeeding the current sequencing cycle,

wherein each of the image patches depicts intensity emissions of a target cluster being base called, and

wherein the input data further includes distance information indicating respective distances of pixels of the image patch from a center pixel of the image patch;

processing the convolved representation through an output layer to produce an output; and

base calling the target cluster at the current sequencing cycle based on the output.

[Claim 9]. The neural network-implemented method of claim 8, further including:

providing as input to the convolutional neural network position coordinates of centers of image regions representing respective clusters,

wherein the input is provided to a first layer of the convolutional neural network,

wherein the input is provided to one or more intermediate layers of the convolutional neural network, and

wherein the input is provided to a final layer of the convolutional neural network.

[Claim 10]. The neural network-implemented method of any of claims 8-9, further including:

providing as input to the convolutional neural network an intensity scaling channel that has scaling values corresponding to pixels of the image patches, and

wherein the scaling values are based on a mean intensity of center pixels of the image patches that each contain a particular target cluster.

[Claim 11]. The neural network-implemented method of any of claims 8-10, wherein the intensity scaling channel pixel-wise includes a same scaling value for all the pixels of the image patches.

[Claim 12]. The neural network-implemented method of claim 8, wherein each image patch further comprises pixel distance data indicating a distance between respective pixels and a nearest one of the plurality of clusters, the nearest one of the plurality of clusters selected based on center-to-center distances between the pixel and each of the clusters.

[Claim 13]. The neural network-implemented method of claim 8, wherein each image patch further comprises cluster distance data that identifies a distance of each cluster pixel from an assigned one of the plurality of clusters selected based on classifying each cluster pixel to only one of the clusters.

[Claim 14]. The neural network-implemented method of any of claims 8-13, wherein convolving the input data through the convolutional neural network to generate the convolved representation of the input data comprises:

separately processing each per-cycle image patch set through a first convolutional subnetwork of the convolutional neural network to produce an intermediate convolved representation for each sequencing cycle, including applying convolutions that combine the intensity and distance information and combine resulting convolved representations only within a sequencing cycle and not between sequencing cycles;

groupwise processing intermediate convolved representations for successive sequencing cycles in the series through a second convolutional subnetwork of the convolutional neural network to produce a final convolved representation for the series, including applying convolutions that combine the intermediate convolved representations and combine resulting convolved representations between the sequencing cycles;

and wherein processing the convolved representation through the output layer to produce the output comprises processing the final convolved representation through the output layer.

[Claim 15]. The neural network-implemented method of any of claims 8-14, further including:

reframing the pixels of each image patch to center a center of the target cluster in a center pixel to generate reframed image patches; and

wherein convolving the input data through the convolutional neural network to generate the convolved representation of the input data comprises convolving the reframed image patches through the convolutional neural network to generate the convolved representation.

[Claim 16]. The neural network-implemented method of claim 15, wherein the reframing further includes intensity interpolation of the pixels of each image patch to compensate for the reframing.

[Claim 17]. A neural network-implemented method of base calling, the method including:

separately processing each per-cycle input data in a sequence of per-cycle input data through a cascade of convolution layers of the convolutional neural network, wherein

the sequence of per-cycle input data is generated for a series of sequencing cycles of a sequencing run, and

each per-cycle input data includes image channels that depict intensity emissions of one or more clusters and their surrounding background captured at a respective sequencing cycle;

for each sequencing cycle,

based on the separate processing, producing a convolved representation at each of the convolution layers, thereby producing a sequence of convolved representations,

mixing its per-cycle input data with its corresponding sequence of convolved representations and producing a mixed representation, and

flattening its mixed representation and producing a flattened mixed representation;

arranging flattened mixed representations of successive sequencing cycles as a stack;

processing the stack in forward and backward directions through a recurrent neural network that

convolves over a subset of the flattened mixed representations in the stack on a sliding window basis, with each sliding window corresponding to a respective sequencing cycle, and

successively produces a current hidden state representation at each time step for each sequencing cycle based on (i) the subset of the flattened mixed representations in a current sliding window over the stack and (ii) a previous hidden state representation; and

base calling each of the clusters at each of the sequencing cycles based on results of processing the stack in forward and backward directions.

[Claim 18]. The neural network-implemented method of claim 17, further including:

base calling each of the clusters at a given sequencing cycle by:

combining forward and backward current hidden state representations of the given sequencing cycle on a time step-basis and producing a combined hidden state representation, wherein the combining includes concatenation or summation or averaging;

processing the combined hidden state representation through one or more fully-connected networks and producing a dense representation;

processing the dense representation through a softmax layer to produce likelihoods of bases incorporated in each of the clusters at the given sequencing cycle being A, C, T, and G; and

classifying the bases as A, C, T, or G based on the likelihoods.

[Claim 19]. A neural network-based system for base calling, the system comprising:

a hybrid neural network with a recurrent module and a convolution module, wherein the recurrent module uses inputs from the convolution module;

the convolution module processing image data for a series of sequencing cycles of a sequencing run through one or more convolution layers and producing one or more convolved representations of the image data, wherein the image data depicts intensity emissions of one or more clusters and their surrounding background;

the recurrent module producing current hidden state representations based on convolving the convolved representations and previous hidden state representations; and

an output module producing a base call for at least one of the clusters and for at least one of the sequencing cycles based on the current hidden state representations.