Deep Molecular Programming: 
A Natural Implementation of Binary-Weight ReLU Neural Networks

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Abstract
Embedding computation in molecular contexts incompatible with traditional electronics is expected to have wide ranging impact in synthetic biology, medicine, nanofabrication and other fields. A key remaining challenge lies in developing programming paradigms for molecular computation that are well-aligned with the underlying chemical hardware and do not attempt to shoehorn ill-fitting electronics paradigms. We discover a surprisingly tight connection between a popular class of neural networks (Binary-weight ReLU aka BinaryConnect) and a class of coupled chemical reactions that are absolutely robust to reaction rates. The robustness of rate-independent chemical computation makes it a promising target for bioengineering implementation. We show how a BinaryConnect neural network trained in silico using well-founded deep learning optimization techniques, can be compiled to an equivalent chemical reaction network, providing a novel molecular programming paradigm. We illustrate such translation on the paradigmatic IRIS and MNIST datasets. Toward intended applications of chemical computation, we further use our method to generate a CRN that can discriminate between different virus types based on gene expression levels. Our work sets the stage for rich knowledge transfer between neural network and molecular programming communities.

1. Introduction
Although molecular computation cannot compete with electronics based on speed, the goal is to enable computation in contexts where traditional electronics cannot go. Chemical control modules compatible with the chemical environments within natural or synthetic cells, bioreactors, and in-the-field diagnostics, are all envisioned applications for such technology. Such computation could, for example, recognize disease state based on chemical inputs and actuate drug delivery to the affected cell. The extensive information processing that occurs in natural cellular regulatory networks underlying all complex life, is a strong proof-of-principle that chemical computation is possible and useful.

Networks of coupled chemical reactions (Chemical Reaction Networks, CRNs) are known to be Turing universal (Fages et al., 2017; Soloveichik et al., 2008), but the resulting systematic ways of programming their behavior can result in extremely large reaction networks and exceedingly inefficient computation. Reasoning in chemical reaction space is difficult: even a very small CRN can be difficult to analyze. Thus, there were many previous attempts in building intuitive, yet more efficient programming approaches for CRNs. For example, (Senum & Riedel, 2011) describe a number of computational modules including arithmetic modules and control flow. Another example is CRN++ (Vasic et al., 2018), an imperative programming language that compiles to CRNs. Here, we present a drastically different programming paradigm, one that allows translation of neural networks into chemical reactions. In a similar way that writing an image classifier in an imperative language is prohibitively complex, writing a classifier in molecular programming language such as CRN++ is practically impossible. However, the technique of programming using neural networks that we demonstrate in this paper opens doors for such applications in molecular programming community.

We focus on a class of neural networks called BinaryConnect. These networks have binarized weights \{+1, −1\}, and were originally popularized due to their computational efficiency in electronics hardware (Courbariaux et al., 2015). We show that BinaryConnect networks have a tight correspondence to a class of rate-independent CRNs (Chen et al., 2014a;b). In rate-independent CRNs, computation arises solely from the stoichiometric exchange of reactants for products and the equilibrium is completely independent of reaction rates. The absolute robustness to reaction rates makes rate-independent CRNs a promising implementation target for bioengineering.

We first demonstrate our approach by training classifiers
on the widely used machine learning datasets IRIS and MNIST. A promising envisioned application of molecular computation lies in medical diagnostics and so called “smart drugs” which activate in response to specific molecular cues. Thus, we next trained a classifier to differentiate between four viral infections using chemical information as input (gene expression levels). In all cases, we translate neural networks into CRNs, and simulate CRN behavior in a chemical kinetics simulation framework. The chemical reaction networks exhibit the same output as their corresponding neural networks.

2. Background

In this section we provide a brief description of CRNs and BinaryConnect networks.

2.1. CRNs

Chemical reaction networks (CRNs) formally model the time evolution of chemical concentrations in a solution undergoing chemical reactions. CRNs are typically used to abstract the behavior of existing biological regulatory networks. Towards engineering synthetic CRNs, a technique called DNA strand displacement can in principle (and, to some extent, experimentally (Chen et al., 2013; Srivivas et al., 2017)) implement arbitrary, rationally designed chemical reactions (Soloveichik et al., 2010). The CRN formalism thus provides a standardized way to specify the interaction rules that we expect interacting chemicals to obey in order to perform computation. Closely related models from distributed computation include population protocols (Angluin et al., 2006), Petri nets (Petri, 1966), and vector addition systems (Karp & Miller, 1969).

A CRN is formally modeled by a set of species $A$ (typically finite) and a set of reactions (also typically finite). Each reaction is formally a pair $(r, p) \in \mathbb{N}^A \times \mathbb{N}^A$ specifying the stoichiometry, but reactions are better illustrated by example:

$$A + B \rightarrow C + D.$$

Intuitively, this reaction increases concentrations of $C$ and $D$ while reducing concentrations of $A$ and $B$ over time. Further, the reaction must obey stoichiometry, meaning that if $A$ is reduced by $\delta$, then $B$ is also reduced by $\delta$, and $C$ and $D$ are increased by $\delta$. Lastly, species concentrations must stay nonnegative. Typically reactions have associated rates, which determine how much change occurs over time, but we will not formalize them, and instead argue that our systems work independent of rates. We let $a(t)$ denote the concentration of species $A$ at time $t$. The inputs for our model of CRN computation are the concentrations of some input species $X_i$ at time 0 (written $x_i(0)$), and the output is the concentration of a species $Y$ as time approaches infinity ($\lim_{t \to \infty} y(t)$, or we simply write $y$).

Many CRN computations work under strong assumptions about the rates of the reactions, but engineering reactions with precise rates is difficult, and small changes in the environment can further disturb these rates. Instead, computation can be achieved by stoichiometry (Chen et al., 2014a;b). The essential example is the following reaction:

$$X_1 + X_2 \rightarrow Y.$$

The concentration of $Y$ as time approaches infinity is the $\min$ of the initial concentrations of $X_1$ and $X_2$, since the reaction can fire as long as both $X_1$ and $X_2$ are present. Thus we say this CRN computes the $\min$ function: $y = \min(x_1(0), x_2(0))$, and does so independently of the rate of the reaction.

Although concentrations of species must be nonnegative, to imitate the computation done by a neural network we need to store and process negative numbers. To do so, we represent negative logical values by the dual-rail convention: a logical value $x$ is represented not by the concentration of one species $X$, but by the difference in concentration between two species $X^+$ and $X^-$. More precisely, at time $t$, $x(t) = x^+(t) - x^-(t)$.

We will use the following CRN to compute the ReLU function, proposed in (Vasic et al., 2019) (it is also shown that it is the smallest CRN computing ReLU):

$$X^+ \rightarrow M + Y^+ \quad (1)$$
$$M + X^- \rightarrow Y^- \quad (2)$$

In order to understand why the above CRN computes ReLU, imagine we start with $x^+(0)$ amount of $X^+$ and $x^-(0)$ amount of $X^-$ and no other species. These concentrations represent the input value $x(0) = x^+(0) - x^-(0)$ in dual-rail form. Although the two reactions will be happening in parallel, eventually the first reaction converges to producing $x^+(0)$ amount of $M$ and $Y^+$. Therefore, the second reaction converges to producing $\min(x^+(0), x^-(0))$ of $Y^-$. This implies that the system converges to the dual-rail value of the output $y = y^+(t) - y^-(t) = x^+(0) - \min(x^+(0), x^-(0)) = (x^+(0) - x^-(0)) - \min(x^+(0) - x^-(0), x^-(0) - x^-(0)) = x - \min(x, 0) = \max(x, 0)$. Note that this CRN is likewise rate-independent because the computation will be correct no matter what the rates of the individual reactions are.

2.2. Binary-Weight ReLU (BinaryConnect)

There is a rich body of work in building more optimized, i.e., computationally efficient neural networks (Courbariaux et al., 2015; Hubara et al., 2016; Li et al., 2016; Simons & Lee, 2019). One of the initial works in the area introduces BinaryConnect networks (Courbariaux et al.,...
These networks restrict weights of neural networks to values ±1, thus allowing drastic reduction of computational expenses. Multipliers are the most space and power hungry components of specialized deep learning hardware, and BinaryConnect networks enable replacement of most of the multiply units by simple accumulators, thus allowing for significant optimization of hardware.

BinaryConnect discretizes weights stochastically, i.e., given a real-valued weight \( w \), binarized value is +1 with probability \( \sigma(w) \) and −1 with probability \( 1 - p \); where \( \sigma \) is hard sigmoid function: \( \sigma(x) = \text{clip}(\frac{x+1}{2}, 0, 1) = \max(0, \min(1, \frac{x+1}{2})) \). While forward and backward propagation passes are computed using the binarized weights, parameter updates are done on the real-valued weights. Even though weights are severely restricted, the authors show that BinaryConnect networks can achieve near state-of-the-art performance.

3. Technique

First we describe the technique for compiling Binary-Weight ReLU networks to CRNs. Then we show how to optimize the CRN to reduce the total number of reactions. Ultimately, there will be one reaction per ReLU node.

3.1. Compiling Binary-Weight ReLU networks

Figure 1 shows an example Binary-Weight ReLU network. This network consists of an input layer, a single hidden layer with ReLU activation function, and an output layer without activation function. The output of the network is defined by: \( y = \text{ReLU}(x^T \cdot W_1) \cdot w_2 \), where \( x \in \mathbb{R}^2 \) is an input vector, \( W_1 \in \{-1, 1\}^{2 \times 3} \) is a weight matrix into the hidden layer, \( w_2 \in \{-1, 1\}^3 \) is a weight vector into the output layer, and \( y \in \mathbb{R} \) is the output (we ignore the bias terms for now).\(^1\) The Figure 1 neural network weight values are:

\[
W_1 = \begin{bmatrix} 1 & 1 & 1 \\ -1 & -1 & -1 \end{bmatrix}, \quad w_2 = [1 \quad 1 \quad -1]^T
\]

We now convert this Binary-Weight ReLU network into a CRN. Initially, for each input \( x_i \) in the input vector, species \( X_i^+ \) and \( X_i^- \) will be present such that \( x_i^+(0) - x_i^-(0) = x_i \). We multiply the input vector by the weights \( W_1 \) by the following set of reactions:

\[
\begin{align*}
X_i^+ &\rightarrow I_{i,1}^+ + I_{i,2}^+ + I_{i,3}^+ \quad (3) \\
X_i^- &\rightarrow I_{i,1}^- + I_{i,2}^- + I_{i,3}^- \quad (4) \\
X_2^+ &\rightarrow I_{1,1}^- + I_{1,2}^- + I_{1,3}^- \quad (5) \\
X_2^- &\rightarrow I_{1,1}^+ + I_{1,2}^+ + I_{1,3}^+ \quad (6)
\end{align*}
\]

Species \( I_{i,l} \) represents the \( i \)th intermediate (before applying nonlinearity) species of the layer \( l \). For a weight with value 1 we include a reaction with a positive input species as a reactant and positive output species as a product, as that has the effect of addition to the product’s logical values. For a weight with value −1 we include a reaction with a positive input species as a reactant and negative output species as a product, as that has the effect of subtraction from the product’s logical values. Due to the dual-rail convention we also include a reaction which contains all the same species with signs flipped. Next, to implement ReLU nonlinearity we use the module discussed above (reactions 1–2), with the appropriate renaming of species: and obtain the following system of reactions:

\[
\begin{align*}
I_{1,1}^+ &\rightarrow M_{1,1} + H_{1,1}^+ \quad (7) \\
M_{1,1} + I_{1,1}^- &\rightarrow H_{1,1}^- \quad (8) \\
I_{1,2}^+ &\rightarrow M_{1,2} + H_{1,2}^+ \quad (9) \\
M_{1,2} + I_{1,2}^- &\rightarrow H_{1,2}^- \quad (10) \\
I_{1,3}^+ &\rightarrow M_{1,3} + H_{1,3}^+ \quad (11) \\
M_{1,3} + I_{1,3}^- &\rightarrow H_{1,3}^- \quad (12)
\end{align*}
\]

Each intermediate species \( I_{1,l} \) of the hidden layer \( l \) is a part of a separate ReLU module producing output species \( H_{1,l} \). Finally, to multiply by the weight vector \( w_2 \) we use the following set of reactions (similar to the multiplication by...
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Algorithm 1 NNCompiler(neural network: nn)

1: crn = {}
2: for l = 1 to nn.numLayers() - 1 do
3:   layer = nn.getLayer(l)
4:   W, b, a = layer.params()
5:   pName = ‘H’ if a.linear() else ‘I’
6:   for i = 1 to W.dimsX do
7:     rxn = newReaction()
8:     rxn.reactants = {X_i^l if l == 1 else H_{l-1,i}^+}
9:     rxn.products = {}
10:    for j = 1 to W.dimsY do
11:      if W[i, j] == 1 then
12:        rxn.products.add(pName_{i,j}^{pSign})
13:      else
14:        crn.add(rxn)
15:        crn.add(reverse(rxn.reversedSigns()))
16:    end for
17:    if b[j] > 0 then
18:      crn.setConc(pName_{i,j}, b[j])
19:    else
20:      crn.setConc(pName_{i,j}, -b[j])
21:    end if
22:    if a.nonlinear() then
23:      crn.add(M_{i,j}^+ \rightarrow I_{i,j}^+ + H_{i,j}^+)
24:      crn.add(M_{i,j}^- \rightarrow I_{i,j}^- + H_{i,j}^-)
25:    end if
26:  end for
27: return crn

Algorithm 2 SetInputs(CRN: crn, Input vector: x)

1: for i = 1 to N do
2:   if x[i] > 0 then
3:     crn.setConc(X_i^+, x[i])
4:   else
5:     crn.setConc(X_i^-, -x[i])
6: end if
7: end for

The input of the algorithm is a Binary-Weight ReLU network (nn), and the output is its CRN equivalent. First, we iterate through all the layers of nn starting from the first hidden layer and including the output layer, where layer 0 is the input layer. If a layer does not contain the nonlinear activation (ReLU) we include reactions directly producing the layer output species (named H), otherwise intermediate species are produced first (named I); the name of the appropriate product species is stored in pName – line 5. We iterate through the rows of the weight matrix (W), creating one reaction per row, where the reactant is $H_{i-1,i}^+$ (ith unit of the previous layer), or $X_i^+$ in the case where the previous layer is the input layer – line 8. To construct products of the reaction we iterate through all the columns of W, adding pName species with positive sign (when weight is +1) or negative sign (when weight is −1) – lines 11-12. We include such reactions to the CRN, and considering dual-rail implementation we also include its reverse (where signs of all the species present in the reaction are flipped) – lines 14-15. Next, we set the initial concentrations of pName species to correspond to the bias terms – if bias term is positive, we set the positive species to b[j], otherwise we set the negative species to −b[j] – lines 18-22. Finally, if the layer contains a ReLU activation, we include the ReLU CRN taking as inputs layer intermediate (I) species and producing layer output (H) species. Previous operations are done for all the layers of the nn returning the resulting CRN in the end. Note that unlike in the previous example, the network output species will be denoted by $H_{N-1,j}$ (where N is the number of layers in the network).

Algorithm 2 shows how in the previously constructed CRN input species concentrations should be set for a given input.

3.2. Optimization: Reducing the compiled CRN

We find that unimolecular reactions, such as the first reactions of ReLU modules, can be eliminated from the CRN by altering the bimolecular reactions and the initial concentrations of the CRN species, a process which we describe next. Unimolecular reactions are those with exactly one reactant like $A \rightarrow B + C$. Whenever A is produced in another reaction, we can replace it with $B + C$. For exam-
ple, if there is another reaction $X \rightarrow A + B$, we replace the reaction with $X \rightarrow 2B + C$. Further, we adjust the initial concentrations of the product species ($B$ and $C$) by increasing them by the initial concentrations of the reactant ($A$). Importantly, this transformation works only if $A$ is not a reactant in any other reaction; for example, if there were another reaction like $X + A \rightarrow Y$, it is not clear what to replace instances of $A$ with, and indeed it is not possible to remove the unimolecular reaction in that case. Luckily, our construction has the property that any species occurs as a reactant in at most one reaction.

We will now illustrate the aforementioned elimination procedure on the neural network CRN presented in Section 3.1, characterized by the reactions 13-18. We start by removing the downstream-most unimolecular reactions (reactions 13-18), although the order does not matter. Removing these reactions results in the following CRN:

$$
\begin{align*}
X_1^+ & \rightarrow I_{1,1}^+ + I_{1,2}^+ + I_{1,3}^+ & (19) \\
X_1^- & \rightarrow I_{1,1}^- + I_{1,2}^- + I_{1,3}^- & (20) \\
X_2^+ & \rightarrow I_{1,1}^+ + I_{1,2}^- + I_{1,3}^- & (21) \\
X_2^- & \rightarrow I_{1,1}^+ + I_{1,2}^+ + I_{1,3}^- & (22) \\
I_{1,1}^- & \rightarrow M_{1,1} + Y^+ & (23) \\
M_{1,1} + I_{1,1}^- & \rightarrow Y^- & (24) \\
I_{1,2}^- & \rightarrow M_{1,2} + Y^+ & (25) \\
M_{1,2} + I_{1,2}^- & \rightarrow Y^- & (26) \\
I_{1,3}^- & \rightarrow M_{1,3} + Y^- & (27) \\
M_{1,3} + I_{1,3}^- & \rightarrow Y^+ & (28)
\end{align*}
$$

Note that the initial concentrations of $Y$ species are unaffected as species $H_{1,i}$ are set to 0 initial concentration. Next, we remove the following downstream-most unimolecular reactions (reactions 23,25,27) and obtain the following CRN:

$$
\begin{align*}
X_1^+ & \rightarrow M_{1,1} + M_{1,2} + M_{1,3} + 2Y^+ + Y^- & (29) \\
X_1^- & \rightarrow I_{1,1}^- + I_{1,2}^+ + I_{1,3}^- & (30) \\
X_2^- & \rightarrow I_{1,1}^- + I_{1,2}^+ + I_{1,3}^- & (31) \\
X_2^- & \rightarrow M_{1,1} + M_{1,2} + M_{1,3} + 2Y^+ + Y^- & (32) \\
M_{1,1} + I_{1,1}^- & \rightarrow Y^- & (33) \\
M_{1,2} + I_{1,2}^- & \rightarrow Y^- & (34) \\
M_{1,3} + I_{1,3}^- & \rightarrow Y^+ & (35)
\end{align*}
$$

Initial concentrations of $M_{1,1}$, $M_{1,2}$, $M_{1,3}$, $Y^+$ and $Y^-$ are also affected:

$$
\begin{align*}
m_{1,i}(0) &= + i_{1,i}^-(0), \forall i \in \{1, 2, 3\} \\
y^+(0) &= + i_{1,1}^+(0) + i_{1,2}^+(0) \\
y^-(0) &= + i_{1,3}^-(0)
\end{align*}
$$

Finally, we remove the last unimolecular reactions (reactions 29-32) (there are no other reactions producing the reactants) and obtain the following CRN:

$$
\begin{align*}
M_{1,1} + I_{1,1}^- & \rightarrow Y^- & (36) \\
M_{1,2} + I_{1,2}^- & \rightarrow Y^- & (37) \\
M_{1,3} + I_{1,3}^- & \rightarrow Y^+ & (38)
\end{align*}
$$

The initial concentrations are modified in a following way:

$$
\begin{align*}
m_{1,i}(0) &= + x_i^0(0) + x_i^0(0), \forall i \in \{1, 2, 3\} \\
i_{1,i}^-(0) &= + x_i^0(0) + x_i^0(0), \forall i \in \{1, 2, 3\} \\
y^+(0) &= + 2x_i^0(0) + 2x_2(0) \\
y^-(0) &= + x_i^0(0) + x_2(0)
\end{align*}
$$

Note that previously we needed 16 reactions (3-18) to implement the neural network, while with the proposed optimizations it takes only 3 reactions. Indeed, it takes one bimolecular reaction per each ReLU unit of the neural network.

The Algorithm 3 summarizes the reduction procedure. The algorithm iterates in a loop as long as there are unimolecular reactions left in the CRN. For each unimolecular reaction ($R \rightarrow \sum_i P_i$) following steps are done: (a) for every reaction in the CRN producing $R$ a list of products is altered by removing product $R$ and adding products $P_i$ (lines 5-10); (b) initial concentrations of species $P_i$ are increased for amount of the initial concentration of $R$ (line 12); and (c) the unimolecular reaction is removed from the crn (line 14).

4. Experiments

In this section we describe experiments showcasing compilation from neural networks to CRNs. We train BinaryConnect networks on IRIS (Anderson, 1936; Fisher,
1936), MNIST (LeCun et al., 1998), and virus infection datasets (GSE73072). We translate trained neural networks to CRNs following our compilation technique (Section 3), and simulate the reactions’ behavior using an ODE simulator (CRNSimulator). Our main goal is to show the equivalence of a trained neural network and compiled CRN, and not to improve accuracy of ML models, which is orthogonal to our work.

4.1. Datasets

**IRIS.** IRIS dataset consists of 150 examples of 3 classes of flowers (Setosa, Versicolor or Virginica), and 4 features per example (sepal length and width, and petal length and width). Considering the small dataset size and our main goal being to show the equivalence of a neural network and translated CRN, we use the whole dataset for both training and evaluation.

**MNIST.** MNIST dataset consists of labeled handwritten digits, where features are image pixels, and labels are digits (0 to 9). We split the original MNIST training set consisting of 60,000 images into 50,000 for the training set, and 10,000 for the validation set. We use the original test set consisted of 10,000 images. In a preprocessing stage we center the images (as done in the BinaryConnect work), and additionally we scale them from $28 \times 28$ to $14 \times 14$.²

**Virus Infection.** For the virus infection classifier, we used data from NCBI GSE73072 (GSE73072). The dataset contains microarray data capturing gene expression profiles of humans, with the goal of studying four viral infections: H1N1, H3N2, RSV, and HRV (labels). There are 148 patients in the dataset, each with about 20 separate profiles taken at different times during their infection period, for a total of 2,886 samples. The dataset contains information about which patient was infected and during which point of time. We filter the samples leaving only those that correspond to an active infection, and thus make the data suitable for classification of the four viruses. Finally, we have in total 698 examples, split in 558 for training, 34 for validation, and 104 for test. Each sample measures expression of 12,023 different genes (features); we use the 10 most relevant genes as features which are selected using GEO2R tool (GEO2R) from the NCBI GEO.

4.2. Results

**IRIS.** We train a neural network with a single hidden layer consisting of 8 units, 4 input units (capturing the features of IRIS flowers), and 3 output units where the unit with the highest value determines the output class. Considering a small dataset size (150 examples), and that our primary goal is to show the equivalence of a neural network and compiled CRN we train and evaluate on the whole dataset in a case of IRIS. We achieve accuracy of 94% (141 out of 150 examples correctly classified) with a trained BinaryConnect neural network. We translate the network to equivalent CRN consisting of 40 chemical reactions (unoptimized compilation), and 8 chemical reactions (optimized compilation). We simulate both versions of CRNs and confirm that their outputs (labels) match the one of the neural network in all of the 150 examples. Figure 2 shows simulation results of IRIS CRNs (unoptimized and optimized version) on an example. For this concrete example outputs of the neural network are $6.0779$, $-6.4697$, and $-7.5785$ (rounded on four decimals) for $y_0$, $y_1$, and $y_2$, respectively; thus the example is classified with label 0. In both CRNs the final simulation value of $y_0$, $y_1$ and $y_2$ matches the output value of the neural network, thus not only the CRN has the same output species at the highest value (which is enough to predict the correct class), but also values of the individual output species match the outputs of the neural network. Regarding the CRN convergence, value of $y_0$ in the unoptimized CRN overshoots value $6$ at $t = 9$ and reaches the final $6.0779$ at $t = 19$, while in the optimized CRN value $6$ is overshoot at $t = 2$ and the final value is reached at $t = 5$. As expected, the reduced CRN converges significantly faster.

**MNIST.** We train a neural network with 3 hidden layers and 256 units per each hidden layer. We downscale MNIST images from original $28 \times 28$ resolution to $14 \times 14$; thus the neural network has $14^2$ input units (one per pixel). We use 10 output units (for digits 0 to 9), and train the neural network to maximize the output unit corresponding to the correct digit. Our trained model achieves accuracy of 92.28% on the test set. Note that we did not focus on achieving high accuracy, BinaryConnect in original paper achieves accuracy of over 98%, but uses more units per layer (1024 compared to 256 in our work) – we use less units in order to produce a smaller CRN. We translate the network to an equivalent CRN consisting of 3464 chemical reactions (unoptimized compilation), and 768 chemical reactions (optimized compilation). The CRN consists of $2 \cdot 14^2$ input species (two species per input unit encoding positive and negative parts), and similarly 2·10 output species. We simulate the CRN on 100 randomly chosen examples from the test set, and confirm that output matches that of the neural network in all of the cases. Figure 3 shows simulation results on an example input image (unoptimized CRN). The output species exhibiting the highest value is the output of the classification, 4 for the given example.

**Virus Infection.** We train a neural network with 1 hidden layer with 32 units, 10 input units capturing expression of different genes, and 4 output units classifying between virus infections. We achieve test set accuracy of 95.20%.

²Scaling is not necessary but we aimed at creating smaller CRNs.
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**Figure 2.** Simulation of IRIS CRN (left) and IRIS CRN in reduced form (right) on the same example. Plots show concentrations of the output species over time, i.e., the difference between positive and negative output species ($y_i(t) = y^+_i(t) - y^-_i(t)$). Networks classify given input with label 0. The reduced CRN converges significantly faster.

**Figure 3.** Simulation of the MNIST CRN (part b) on an input image (part a). The image is encoded via the input species concentrations: e.g., value 0.54 of the 65th pixel (4th row, 9th column) is represented via initial concentrations of $x^+_65$ and $x^-_65$ species. Simulation shows concentrations of the output species over time, i.e., the difference between positive and negative output species ($y_i = y^+_i - y^-_i$). The CRN classifies the input image as a number 4 (as $y_4$ has the highest value).

**Figure 4.** Simulation of Virus Infection CRN on an example (misclassified example). Example is classified as HRV virus, while the true label is H1N1.

We translate the network to equivalent CRN consisting of 148 chemical reactions (unoptimized compilation), and 32 chemical reactions (optimized compilation). We simulate the CRN on 100 randomly chosen examples from the test set, and confirm that output matches that one of the neural network in all of the cases. Figure 4 shows simulation of unoptimized CRN on an example that is misclassified. Performed experiments empirically confirm soundness of our compilation technique.

**4.3. Training Specifics**

We use the implementation of BinaryConnect networks published by the authors of the original work (Courbariaux et al., 2015), and follow the same training procedure except for the following points: (1) We focus solely on the ReLU activation function since other activation functions such as sigmoid, hyperbolic tangent, and softmax are not continuous piecewise linear and thus cannot be implemented with rate-independent CRNs (Chen et al., 2014b). (2) We do not use Batch Normalization (Ioffe & Szegedy, 2015). The reason for not using Batch Normalization is that it would incur multiplication and division operations at inference stage (training stage is not a problem) that would be hard to efficiently implement in CRNs. Instead, we rely on Dropout (Srivastava et al., 2014) (stochastically dropping out units in a neural network during training) as a regularization technique. In all our experiments we use the square hinge loss (as used in BinaryConnect) with ADAM optimizer.
We train on MNIST dataset for 250 epochs, measuring the validation accuracy at each epoch, and returning the model that achieved the best validation accuracy during training. We train on IRIS dataset for 10,000 epochs, and return the best performing epoch. We train on the Virus Infection dataset for 200 epochs, and return the model that achieved the best validation set accuracy. We use an exponentially decaying learning rate. The rate constants of all reactions are set to 1, and all chemical simulations are performed for 50 arbitrary time units in the CRNSimulator package (CRNSimulator).

5. Related Work

It has long been observed that biological regulatory networks arguably behave in manner analogous to neural networks. For example, both phosphorylation protein-protein interactions (Bray, 1995; Hellingwerf et al., 1995) and transcriptional networks (Buchler et al., 2003) can be viewed as performing neural network computation.

The challenge of implementing neural networks in chemical reaction networks also has a long history. For example, Hjelmfelt et al (Hjelmfelt et al., 1991) propose a binary-valued chemical neuron, whose switch-like behavior relies on competition between excitation and inhibition. Recently, Moorman et al (Moorman et al., 2019) proposed an implementation of ReLU units based on a fast bimolecular sequestration reaction which competes with unimolecular production and degradation reactions. In contrast to the prior work, our implementation relies solely on the stochiometric exchange of reactants for products, and is thus completely independent of the reaction rates. Our CRN is also significantly more compact, using only a single bimolecular reaction per neuron, with two species per every connection (without any additional species for the neuron itself). Finally, in contrast to the prior schemes, our CRN converges to a static rather than a dynamic equilibrium, which means that all reactions cease firing. This implies that our implementation does not waste energy to maintain state.

We use neural networks as a way to program chemistry. The programming is done offline in the sense that neural networks are trained in silico. However, there is a body of work on creating chemical systems that are capable of learning in chemistry (Blount et al., 2017; Chiang et al., 2015). Although these constructions are much more complex than ours, and arguably difficult to realize, they demonstrate the proof-of-principle that chemical interactions such as those within a single cell are capable of brain-like behavior.

Besides the above mentioned theoretical work on chemical neural networks, wet-lab demonstration of synthetic chemical neural computation argues that the theory is not vapid and that neural networks could be realized in chemistry. A chemical linear classifier reading gene expression levels could perform basic disease diagnostics (Lopez et al., 2018). Larger systems based on strand displacement cascades were used to implement Hopfield associative memory (Qian et al., 2011), and winner-take-all units to classify MNIST digits (Cherry & Qian, 2018). Interestingly, the direct strand displacement implementation of a neuron by our construction is significantly simpler (in terms of the number of components needed) than the previous laboratory implementations, arguing for its feasibility.

6. Conclusion

We demonstrate how BinaryConnect (weight \{+1, −1\}) neural networks could be implemented in chemistry using rate-independent chemical reaction networks. Our construction is surprisingly compact in the sense that we use exactly one reaction per ReLU node. This compactness argues that neural networks may be a fitting paradigm for programming chemical computation.

As proof of principle, we demonstrate our scheme with numerical simulations of resulting CRNs classifying the MNIST and IRIS datasets. We further simulate a CRN constructed from a ReLU network trained to classify a virus gene expression dataset. Since this network relies on chemically available information for input, this example argues for the potential biological and medical utility of programming chemical computation via a translation from neural networks.

Although in principle arbitrary CRNs can be implemented using DNA strand displacement reactions, current laboratory demonstrations have been limited to small systems (Srinivas et al., 2017), and many challenges remain in constructing large CRNs in the laboratory. Rate independent CRNs possibly offer an attractive implementation target due to their absolute robustness to reaction rates.

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