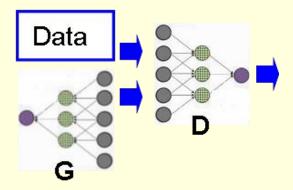




Deep Learning by Example on Biowulf

Class #4: Generative Adversarial Networks and their application to bioimage synthesis

Gennady Denisov, PhD

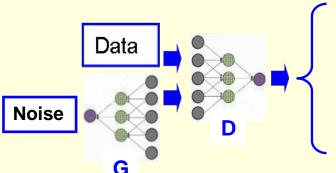


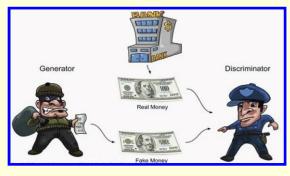
Intro and goals

I.Goodfellow et al., Generative Adversarial Nets. NIPS Proc. 2014

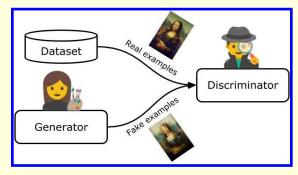
What is a GAN?

- A composite network comprising 2 subnetworks: Generator and Discriminator
- The G produces fake data from scratch/noise; learns to trick the D
- The D compares fake data against the true data; learns to expose the G









Forger vs art dealer/critique analogy

Features:

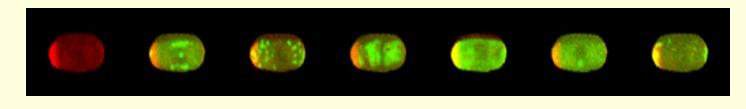
Generative model: the goal is to generate new, **synthetic** instances of data that can pass for real data **G** and **D** are trained by **pitting** one against the other – thus the **adversarial**, i.e. antagonistic, or confrontational "...The most interesting idea in ML in the last 10 years." (Yann LeCun)

Examples:

Generating face images



BioGANs: GANs for biological image synthesis



Examples overview

					_		
Class #	1	2	3	4	5	6	7
Bio app	Bioimage segmentation / fly brain connectome	Genomics / prediction of function of non-coding DNA	Genomics / reduction of dimensionality of cancer transcriptome	Bioimage synthesis / developmental biology	Drug molecule design	Genomics / classification of cancer types	Drug molecule property prediction
Neural network type	Convolutional	Recurrent or 1D- Convolutional	Autoencoder	Generative Adversarial	Reinforcement Learning	Graph Convolutional	Message Passing
ML type	Supervised	Supervised	Unsupervised	Unsupervised	Reinforcement	Supervised	Supervised
 unsupervised ML generative model, functionally similar to VAE composite network comprising two subnetworks the subnetworks are trained interactively, by playing a minimax game GAN flavors: GAN, DCGAN, WGAN, WGAN-GP 				GAN Data	RLN G •••••••••••••••••••••••••••••••••••	GCN	MPN

Deep Convolutional GAN (DCGAN): a simple example

tensors, units, layers, parameters, hyperparameters, convolution

A.Radford et al, arXiv:1511.06434v2 (2016)



RNN/1D CNN prototype example from class #2:

Input: a set of training sequences of 0's and 1's with binary labels assigned to each sequence depending on whether or not a certain (unknown) motif is present in the sequence

Example: 010<mark>111</mark>00101

<u>Task:</u> predict the label, or the occurrence of the **unknown** motif, in new, previously unseen sequences.

DCGAN prototype example:

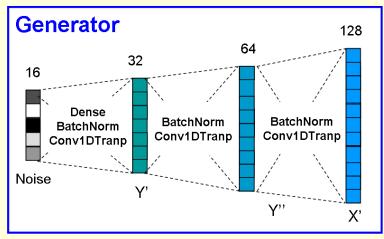
Input: a training set of only "good" sequences of 0's and 1's, i.e. **all** of them contain a certain motif

Example: 01011<mark>0011001100110011</mark>11

<u>Task:</u> learn what makes all of the training sequences "good" and then generate new "good" sequences from scratch.

Challenge: only positive examples, no labels

Discriminator Z=A(\(\sum_i\)\cdot Y_i+b) Conv1D Dense Z A



Architecture guidelines for stable DCGANs:

- Use convolutions (D) and transposed convolutions (G) instead of MaxPooling / Upsampling layers
- Use **BatchNormalization** in both the G and the D.
- Avoid Dense/Fully Connected hidden layers

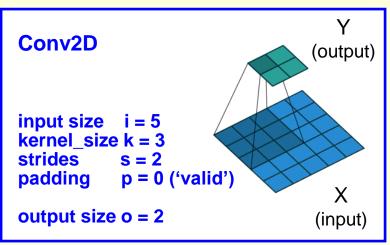
- ...<mark>.</mark>

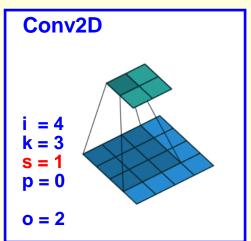
The Transposed Convolution (a.k.a. deconvolution, or fractional-strided convolution)

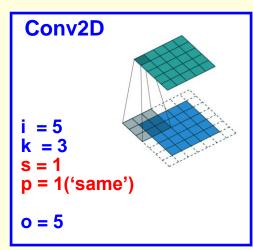
convolution, transposed convolution, stride, kernel size, padding

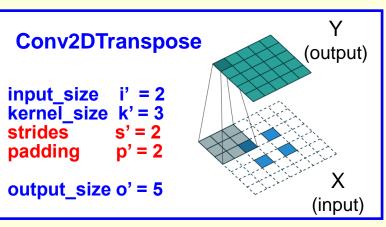
V.Dumoulin, F.Visin - A guide to convolution arithmetic for deep learning (2018)











Conv2D:

$$i + 2*p = k + s*(o - 1)$$

'valid' padding: p = 0'same' padding: o = round(i / s)

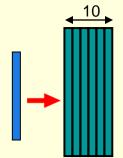
num. of filter / filters / kernel kernels size

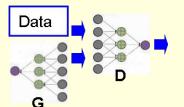
Conv2DTranspose(10, **3**, padding = 'same', ...)

Conv2DTranspose:

$$o' = i' + (i'-1)*(s'-1) + 2*p' - k'+1)$$

'valid' padding: p' = k' - 1 'same' padding: o' = i' * s'





The simple GAN code: (1) header and (2) defining a model

generator, discriminator, GAN, compile, loss, optimizer, trainable

(1) Header:

- general Python imports
- Numpy imports
- Keras library imports

(2) Define a model

- discriminator (D)
- generator (G)
- combined model (GAN)
- Conv1DTranspose
- BatchNormalization

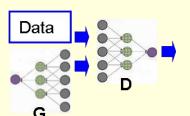
GAN <

```
@ denisovga@biowulf:/data/denisovga/1_DL_Course/0_Intro
                                                              BatchNormalization layer
 mport os, re, random, collections
 mport numpy as np, tensorflow as tf
  om tensorflow.keras.optimizers import RMSprop
 rom tensorflow.keras.layers import Conv1D, Flatten, Dense, Reshape, BatchNormalization, Activation,
     Conv1DTranspose
n_chan,f_size,seq_len,noise_len,init_len,seed,lr = 10,16,128,50,16,2,0.01
np.random.seed(seed); random.seed(seed); <u>tf.random.set_seed(seed)</u>
D = tf.keras.models.Sequential()
D.add(Conv1D(n_chan, f_size,
                                                               D outputs the probability
      activation='relu', input_shape=(seq_len,1)))
                                                               that the input data is "good"
D.add(Flatten())
D.add(Dense(1, activation=
D.compile(loss='mse', optimizer= RMSprop(learning_rate=lr))
G = tf.keras.models.Sequential()
G.add(Dense(init_len*n_chan, input_shape=(noise_len,)))
G.add(Reshape((init_len, n_chan)))
G.add(BatchNormalization(momentum=0.1, epsilon=1.e-5))
for i in range(0, 2):
    G.add(Conv1DTranspose(n_chan,f_size, strides=2, padding="same"))
    G.add(BatchNormalization(momentum=0.8, epsilon=1.e-5))
G.add(Conv1DTranspose(1, f_size, strides=2, padding="same"))
G.add(Activation('sigmoid'))
GAN = Sequential()
GAN.add(G)
                                       GAN = D(G(z))
D.trainable = False
GAN.add(D)
GAN.compile(loss='mse', optimizer=RMSprop(learning_rate=lr))
                             1)
                                 like D. GAN outputs a probability
```

like G, GAN takes noise as input

only G weights are adjustable when training GAN

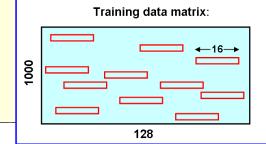
2)



The simple GAN code (cont.): getting data and training the model



motif, train_on_batch, epoch, batch size, predict



(3) Get data

- motif

(4) Run the model

- train_on_batch
- num. of epochs
- batch size

```
Select denisovga@biowulf:/usr/local/apps/DLBio/class4/bin
n_data.motif =
x_str = [''.join([random.choice('01')
                                              for i in range(seq_len)])
                                              for i in range(n_data)1
for j in range(n_data):
    rint = np.random.randint(0, high=seq_len-len(motif))
x_str[j]= x_str[j][:rint] + motif + x_str[j][(rint+len(motif)):]
x_train = np.reshape(np.array([[int(c) for c in x_str[j]] \
            for j in range(n_data)]), [n_data,seq_len,1])
epochs, b_{size}, GAN_{loss} = 500, 10, 1
    epoch in range(epochs+1):
    n_{iterD,n_{iterG=[5,0]}} if epoch <= 300 else [0,1]
    real_data = np.array(x_train[np.random.randint(0,x_train.shape[0],b_size)])
real_data = np.reshape(real_data,(real_data.shape[0],real_data.shape[1],1))
                 = np.random.normal(0, 1, (b_size, noise_len))
    fake_data = G.predict(noise)
           in range(n iterD):
                    = D.train_on_batch(real_data, np.ones(( b_size,1))
                  = D.train_on_batch(fake_data, np.zeros((b_size,1
     for i in range(n iterG):
         GAN_loss = GAN.train_on_batch(noise.
                                                         np.ones((b_size,1)))
        epoch%50 ==
         print(f
```

train_on_batch:

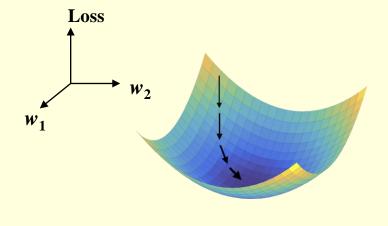
- train D: D (real data) → 1
- train D: D (fake data) \rightarrow 0 (G weights frozen)
- train GAN: GAN (fake_data) → 1 (D weights frozen)

The GAN optimization objective

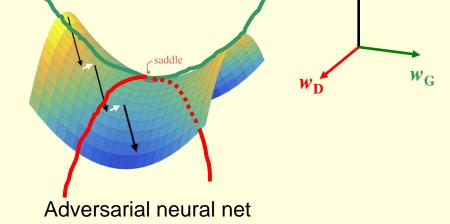
A. Yadav, S.Shah et al., ICLR 2018

The minimax optimization objective:

$$J_{\text{minimax}} = \min_{\mathbf{W}_{G}} \max_{\mathbf{W}_{D}} E_{\text{data}} \{ \ln \mathbf{D}(\mathbf{x}; \mathbf{W}_{D}) \} + E_{\text{noise}} \{ \ln (1 - \mathbf{D}(\mathbf{G}(\mathbf{z}; \mathbf{W}_{G}); \mathbf{W}_{D}) \}$$



Standard neural net



 $J_{minimax}$

Mode collapse

What is mode collapse?

- an issue that often occurs in GANs due to problems in training when training/real data comprise >= 2 types/"modes"
- generator can only produce a single type of output or a small subset of types

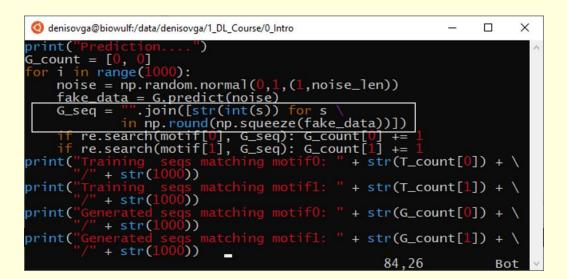
The mode collapse prototype example:

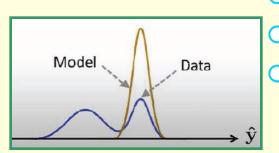
<u>Input:</u> a training set of "good" sequences of 2 types ("modes"), each sequence containing a motif of one type

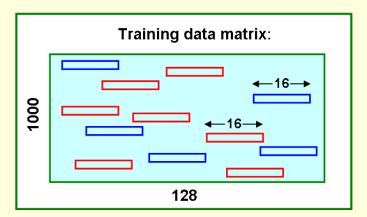
Example: 01011<mark>0011001100111</mark>11, 00<mark>010101010101011</mark>11010

<u>Task:</u> train a GAN on these data and then count the sequences of the two types in the data generated by model after training.

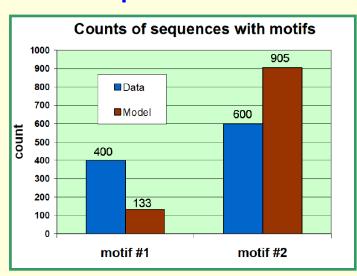
Predictions from the model:







Computed results:



How to run the simple GAN examples on Biowulf?



```
Executables
```

Data with single motif

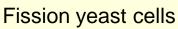
Data with two motifs

```
denisovga@biowulf:/data/denisovga/1_DL_Course/0_Intro
                                                                             ×
 sinteractive --gres=gpu:p100:1 --mem=4g
 module load DLBio/class4
$ ls $DLBIO_BIN
simple_gan.py mode_collapse.py
$ simple_gan.py
Training...
                                         0.366844356060
   0: Dt_loss= 0.058466792107
                                                          Df_loss=
   50: Dt_loss= 0.000000028773
                                Df loss= 0.002305581467
                                                          GAN loss= 1.0000000000000
 100: Dt_loss= 0.000000000129
                                         0.000038872400
                                                          GAN_loss= 1.000000000000
                                Df_loss=
500: Dt_loss= 0.000000000005
                              Df_loss= 0.000000004494
                                                        GAN_loss= 0.0000000000000
Prediction...
Generated seqs matching motif: 999/1000
Random
        segs matching motif: 0/1000
$ mode_collapse.py
Training...
   0: Dt_loss= 0.057551991194
                                Df_loss= 0.501274228096
                                                          Dt_loss= 0.00000001346
                                         0.003325915430
                                Df loss=
                                                          GAN loss= 1.0000000000000
                                         0.000045182696
       Dt_loss= 0.000000000943
                                Df_loss=
                                                          500: Dt_loss= 0.000000000002
                                Df_loss=
                                         0.000000004260
                                                          GAN_loss= 0.000000000000
Prediction.
Training seqs matching motif0: 400/1000
Training segs matching motif1: 600/1000
Generated seqs matching motif0: 133/1000
Generated segs matching motif1: 905/1000
                                                                  16,1
                                                                               A11
```

Example 4. BioGANs: GANs for Biological Image Synthesis

A.Osokin e.a. IEEE Int. Conf. on Computer Vision (ICCV), 2017 https://github.com/aosokin/biogans https://hpc.nih.gov/apps/biogans.html





			(13)			
Bgs4	Bgs4 +	Bgs4 +	Bgs4 +	Bgs4 +	Bgs4	Bgs4
	Alp14	Arp3	Cki2	Mkh1	Sid2	Twa1

Proteins: growth marker Bgs4 and polarity factors Alp14, Arp3, Cki2, ...

Biological task: investigate how different polarity factors interact with one another

Computational task: train a GAN on available data and generate synthetic images that show localization of multiple polarity factors, together with Bgs4, at the same stage of cell growth cycle (i.e. the images that cannot be produced experimentally)

Data: the Localization Interdependency network (LIN) dataset

The BioGANs pipeline (reimplemented in Keras from PyTorch):

train.py predict.py visualize.py

The Keras source code:

train.py, predict.py, visualize.py, gans.py, models.py, dataloader.py, options.py,

Header

- import statements
- parsing the command line options

Getting data

- LIN dataset

Define a (network) model

models available:
 DCGAN,
 DCGAN-separable,
 DCGAN-starshaped

Run the model

- GAN algorithms: (traditional) GAN WGAN
 WGAN-GP
- optimizer: RMSProp

An overview of the BioGANs training code

https://hpc.nih.gov/apps/biogans.html



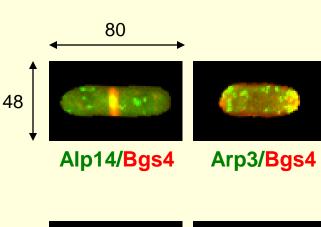
```
    denisovga@biowulf:/data/denisovga/1_DL_Course/4_GANs

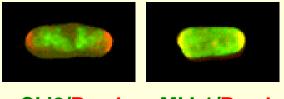
 ort os, sys, random
  ort numpy as np
    dataloader import get_data
    options import parse_training_arguments, process_options
   models import get_network_models
 port tensorflow as tf
 om tensorflow.keras.optimizers import Adam, RMSprop
  __name__ == '__main__':
   opt = parse_training_arguments()
   opt, DCGAN_model, gan_algorithm, optimizer = process_options("train", opt)
  dataset, opt.n_classes = get_data(opt, "train")
                 UDA_VISIBLE_DEVICES'] = "0"
   os.environ[
   if opt.num_apus > 1:
       for j in range(1, opt.num_gpus):
                                       EVICES'] += "," + str(j)
   with tf.device(')
       random.seed(opt.random seed)
      netG, netD = get_network_models(DCGAN_model, opt, opt.red_portion)
      gan_algorithm == "GAN":
                    netG, netD, opt).train(dataset, opt)
       gans. GAN (
   elif gan_algorithm ==
                     netG, netD, opt).train(dataset, opt)
       gans.WGAN(
   elif gan_algorithm ==
                         netG, netD, opt).train(dataset, opt)
       gans. WGAN_GP(
       sys.exit("Undefined gan_algorithm: " + gan_algorithm + "\n")
                                                                  39.9
```

BioGANs data: the Localization Interdependency Network (LIN) dataset

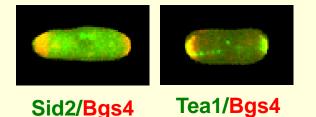


J.Dodgson et al, https://www.biorxiv.org/content/10.1101/116749v1.full





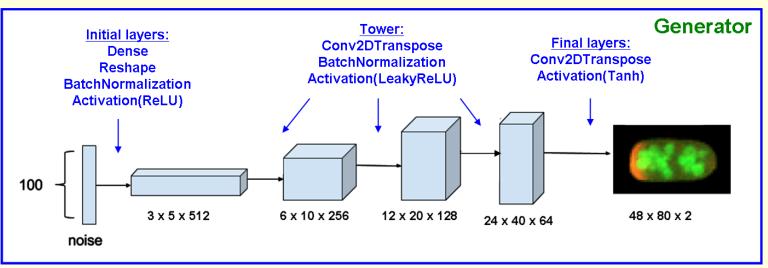
Cki2/Bgs4 Mkh1/Bgs4

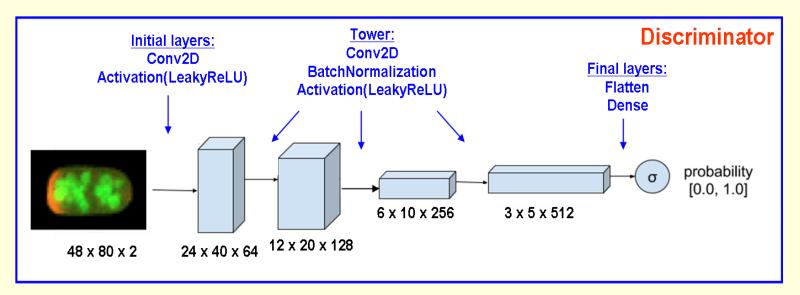


Features:

- **2D fluorescence microscopy images** of Fission yeast cells, each (7 ÷14) x 4 μm
- 2-channel images of size is 48 x 80 pixels
 (1 pixel = 100 nm)
- red channel = protein Bgs4, localizes in the area of active growth
- green channel = any of 41 different polarity factors
 that define a cell geometry
- 170,000 images for 41 polarity factors available in the in the LIN dataset.
- the BioGANs application focuses on Bgs4 and
 6 polarity factors Alp14, Arp3, Cki2, Mkh1, Sid2
 and Tea1, totaling to 26,909 images

The DCGAN model of the BioGANs application





Features of the DCGAN architecture:

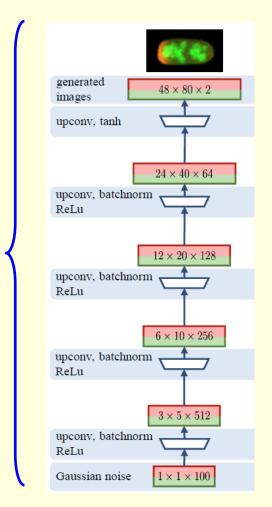
- the most basic model implemented as a part of the BioGANs application
- due to the mode collapse, can only generate green channels for a subset of polarity factors



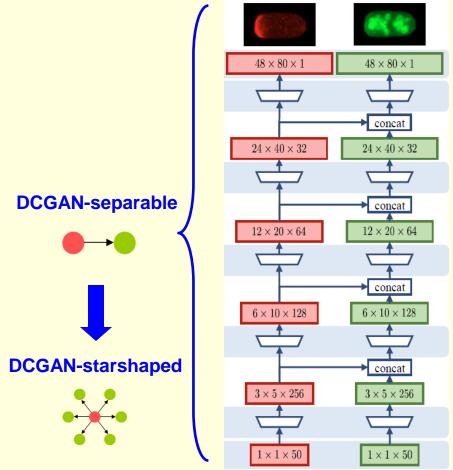
BioGANs generator architrectures: DCGAN, DCGAN-separable and DCGAN-starshaped

A.Osokin e.a. IEEE Int. Conf. on Computer Vision (ICCV), 2017





DCGAN



Two shortcomings of the DCGAN Generator:

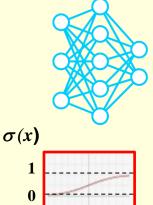
- the signal in the green channel is not dependent on / influenced by the red channel
- cannot generate multiple green channels

The Wasserstein GAN (WGAN)

M.Arjovsky et al, Wasserstein GAN – arXiv: 1701.07875 (2017)

Problem with training vanilla GAN: vanishing gradients (discussed in class #2) due to the last/sigmoid layer in the Discriminator:

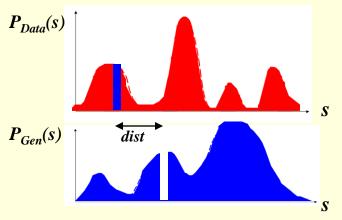
$$D(I, w) = \sigma(F(I, w)) = \nabla_w D = \sigma' \cdot \nabla_w F \rightarrow 0$$
 at saturation



WGAN ideas:

- get rid of the σ layer => can no longer use the BCE loss
- replace D with F; rename F to critic and its output to score s
- as a new loss function, use the Earth Mover's distance (EMD) between the distributions of the critic scores $P_{Data}(s)$ and $P_{Gen}(s)$

EMD, a.k.a. Wasserstein loss = minimum amount of work to transform one distribution to another



Work = dist * mass (=area of the piece)

Binary cross entropy loss:

$$BCE = -\frac{1}{N} \sum_{i=1}^{N} y_i \cdot log(p_i(w)) + (1 - y_i) \cdot log(1 - p_i(w))$$

The approx. Wasserstein loss when the two distributions are similar/close:

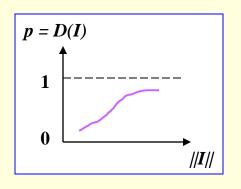
$$EMD \approx -E \left[s^{Data} \cdot s^{Gen} \right]$$

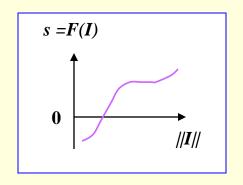
EMD → minforces the two distributionsto have maximaat the same locations

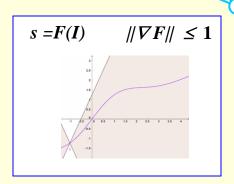
WGAN with gradient penalty (WGAN-GP)

Gulrajani et al., Improved Training of Wasserstein GANs - arXiv:1704.00028v3 (2017)

How can we limit the growth of critic F to avoid exploding gradients / instability?







(Vanilla) GAN:

use sigmoid activation: $D(I) = \sigma(F(I))$

WGAN:

clip the F weights that are beyond [-c, c]

Data transform. by one layer: $\mathbf{Z} = \mathbf{A}(\sum \mathbf{w_i} \cdot \mathbf{X_i} + \mathbf{b})$

WGAN features:

- (1) rename Discriminator *D* to Critic *F*
- (2) use EMD loss
- (3) clip <u>all weights</u> after <u>each epoch</u> (c = 0.01)
- (4) use RMSProp optimizer with Ir = 0.00005

WGAN-GP:

penalize the loss to force $||\nabla F||$ be close to 1

 $WGAN-GP \ loss = EMD + \lambda \cdot E[(//\nabla F//-1)^2]$

WGAN-GP features:

- (1) same as for WGAN
- (3) penalize the loss using ∇F ; $\lambda \approx 10$
- (4) use either RMSProp or Adam optimizer

Training of WGAN(-GP) on data with || *I*|| ≈ 1:

train_on_batch:

- train F: F (real data) → -1
- train F: F (fake data) → 1 (G weights frozen)
- train WGAN(-GP): WGAN(-GP) (fake data) → -1 (F weights frozen)

The Root Mean Squared Propagation (RMSProp) optimizer

Slides: http://www.cs.toronto.edu/~tijmen/csc321/slides/lecture_slides_lec6.pdf Video: https://goo.gl/XUblyJ

Basic gradient descent formula for updating weights:

$$\boldsymbol{w}_{t+1} - \boldsymbol{w}_t = - \boldsymbol{\gamma} \cdot \nabla_{\!\!\!\boldsymbol{w}} \boldsymbol{J}(\boldsymbol{w}_t)$$

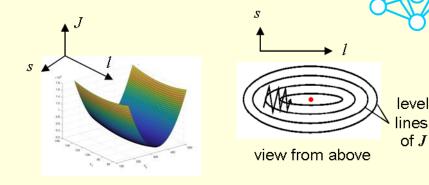
w = vector of weights

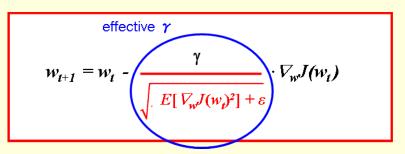
y = learning rate

t = update #

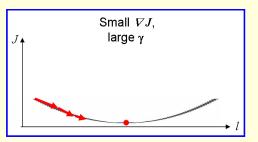
 $\nabla_{w} J$ = gradient of the loss

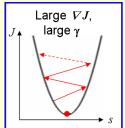
The RMSprop gradient descent formula:

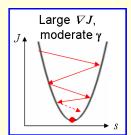




E[...] = running average of the magnitudes of recent gradient squares
 ε = small parameter







Effective γ :

- large when moving in the l-direction (with small ∇J)
- moderate or small when moving in the s-direction (with large ${f
 abla} {f J}$)

$$E[\nabla_{w}J(w)^{2}]_{t} = \rho \cdot E[\nabla_{w}J(w)^{2}]_{t-1} + (1 - \rho) \cdot \nabla_{w}J(w_{t})^{2}$$

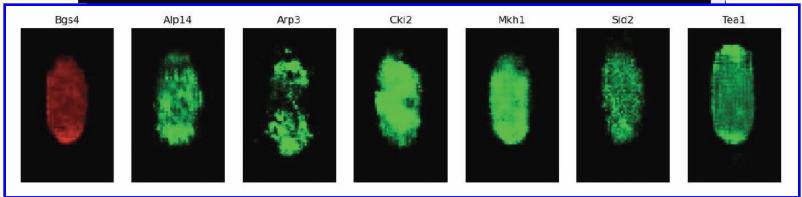
Computing the running average of $(\nabla J)^2$, $\rho \sim 0.9$

keras.optimizers.RMSprop(learning_rate=0.001, rho=0.9, epsilon=1e-07, ...)

How to run the BioGANs application on Biowulf?

https://hpc.nih.gov/apps/biogans.html

```
Odenisovga@biowulf:/data/denisovga/1_DL_Course/4_GANs
                                                                                           X
sinteractive --mem=40g --gres=gpu:p100:1,lscratch:10
module load biogans
cp $BIOGANS_DATA/* .
ls $BIOGANS_SRC
predict.py
             visualize.py gans.py
dataloader.py mo
                                       options.py utils.
models.py __pycache__
train.pv
train.py -d <data_folder> [-m <network_model>] [-a <gan_algorithm>]
# network_model = DCGAN, DCGAN-separable or DCGAN-starshaped (default)
# gan_algorithm = GAN, WGAN or WGAN-GP (default)
Example:
train.py -d data
predict.py -i <checkpoint_file> [ other options ]
Example:
predict.py -i checkpoints/weights.generator.data.DCGAN-starshaped.wGAN-GP.6.h5
visualize.py -i <image_stack>
Example:
visualize.py -i images/stack7.DCGAN-starshaped.wGAN-GP.h5
```





Summary



- 1) Intro using a simple example
 - simple GAN that can generate sequences containing certain motif(s):
 Discriminator network is the same a model from class #2
 Generator network produces a sequence from random noise
 - the Conv2DTranspose (transposed convolution, a.k.a. deconvolution) layer
 - the BatchNormalization layer
 - the train on batch method
 - the mode collapse issue
- 2) The BioGANs application:
 - BioGANs data: the LIN dataset
 - generator architectures: DCGAN, DCGAN-separable and DCGAN-starshaped
 - discriminator/critic architectures: (vanilla) GAN, WGAN and WGAN-GP
 - the Earth Mover's distance (EMD) loss and the gradient penalty
 - the gradient descent-based optimization algorithm RMSprop