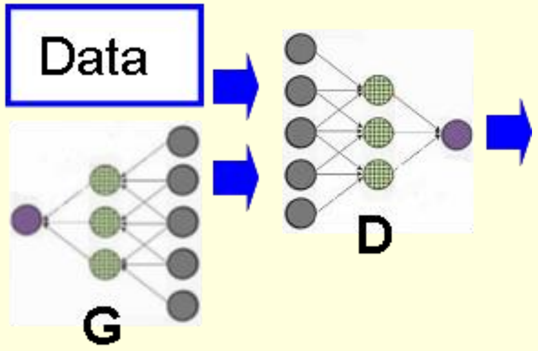
Deep Learning by Example on Biowulf

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

Gennady Denisov, PhD

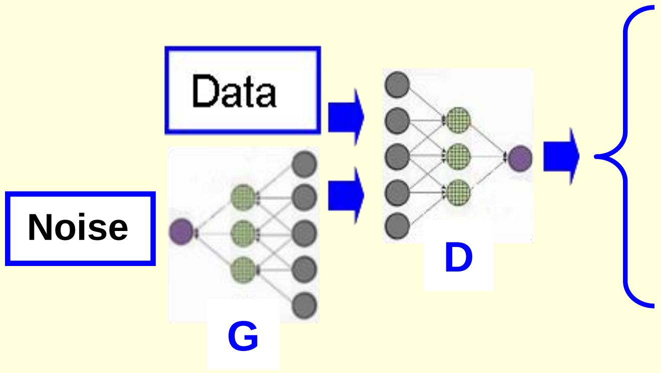


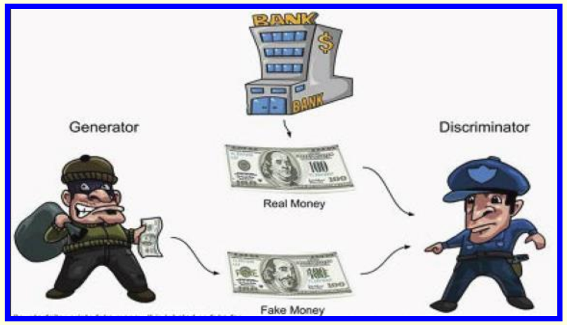
Intro and goals

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

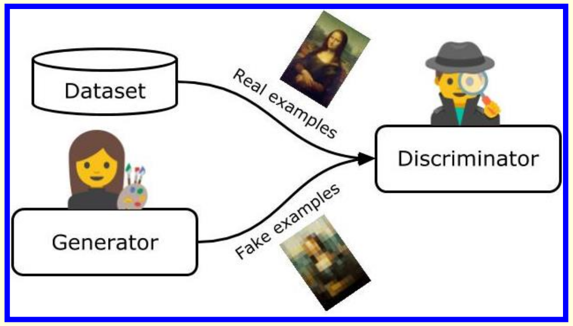
What is a GAN?

- A composite network comprising 2 subnetworks: **G**enerator and **D**iscriminator
- 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**





Counterfeiter vs police analogy



Forger vs art dealer/critique analogy

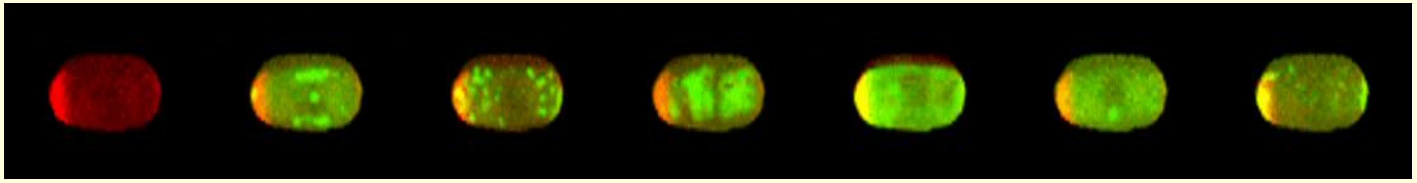
Features:

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

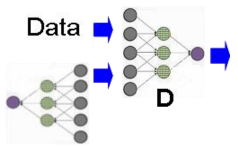


Examples overview

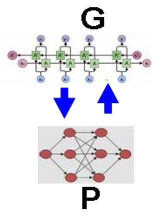
Class #	1	2	3	4	5	6	7
Bio app	Bioimage segmentation / fly brain connectome	Genomics / prediction of function of non-coding DNA	Genomics / reduction of dimensionality of cancer transcriptome	Bioimage synthesis / developmental biology	Drug molecule design	Genomics / classification of cancer types	Drug 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

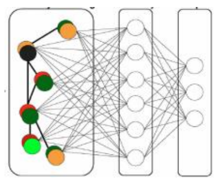
GAN



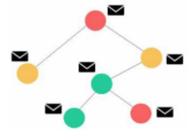
RLN



GCN



MPN



Deep Convolutional GAN (DCGAN): a simple example

tensors, units, layers, parameters, hyperparameters, convolution

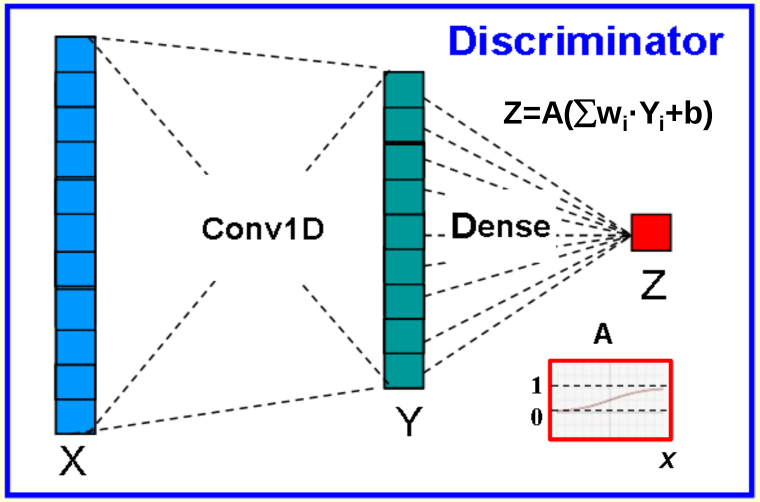
A.Radford et al, arXiv:1511.06434v2 (2016)

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$\boxed{111}$00101

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



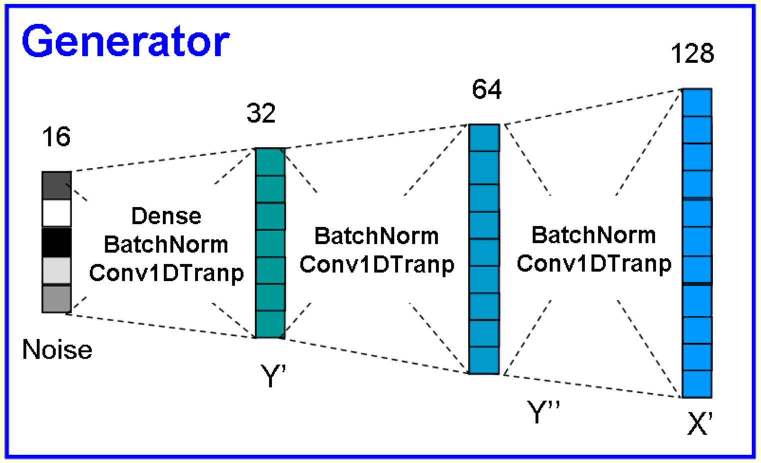
DCGAN prototype example:

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$\boxed{0011001100110011}$11

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

Challenge: only positive examples, no labels



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
- ….

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

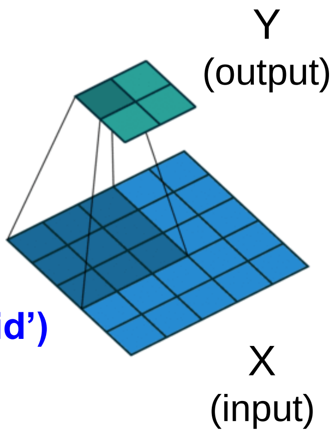
convolution, transposed convolution, stride, kernel size, padding

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

Conv2D

input size i = 5
kernel_size k = 3
strides s = 2
padding p = 0 (‘valid’)

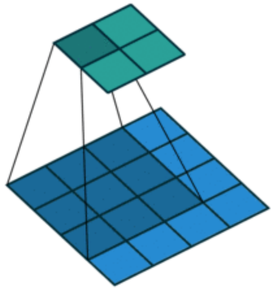
output size o = 2



Conv2D

i = 4
k = 3
s = 1
p = 0

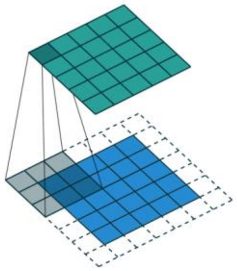
o = 2



Conv2D

i = 5
k = 3
s = 1
p = 1(‘same’)

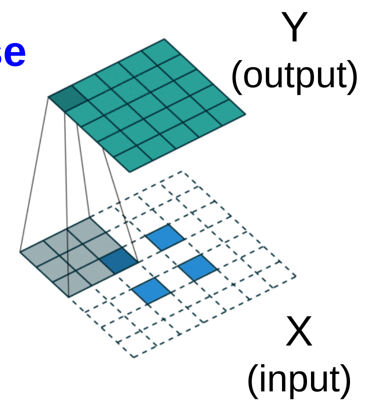
o = 5



Conv2DTranspose

input_size i’ = 2
kernel_size k’ = 3
strides s’ = 2
padding p’ = 2

output_size o’ = 5



Conv2D:

$$\boxed{i + 2*p = k + s*(o - 1)}$$

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

Conv2DTranspose:

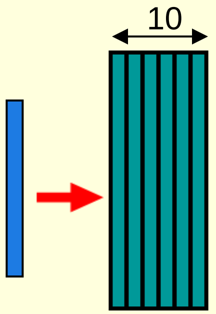
$$\boxed{o' = i' + (i'-1)*(s'-1) + 2*p' - k' + 1}$$

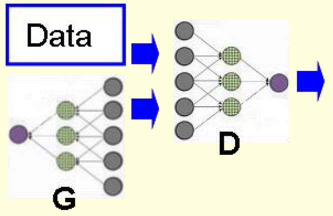
‘valid’ padding: p’ = k’ – 1
‘same’ padding: o’ = i’ * s’

num. of filters / kernels ↓

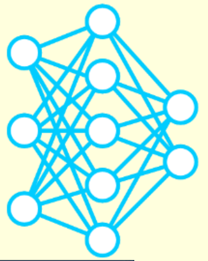
filter / kernel size ↓

Conv2DTranspose(10, 3, padding = ‘same’, …)





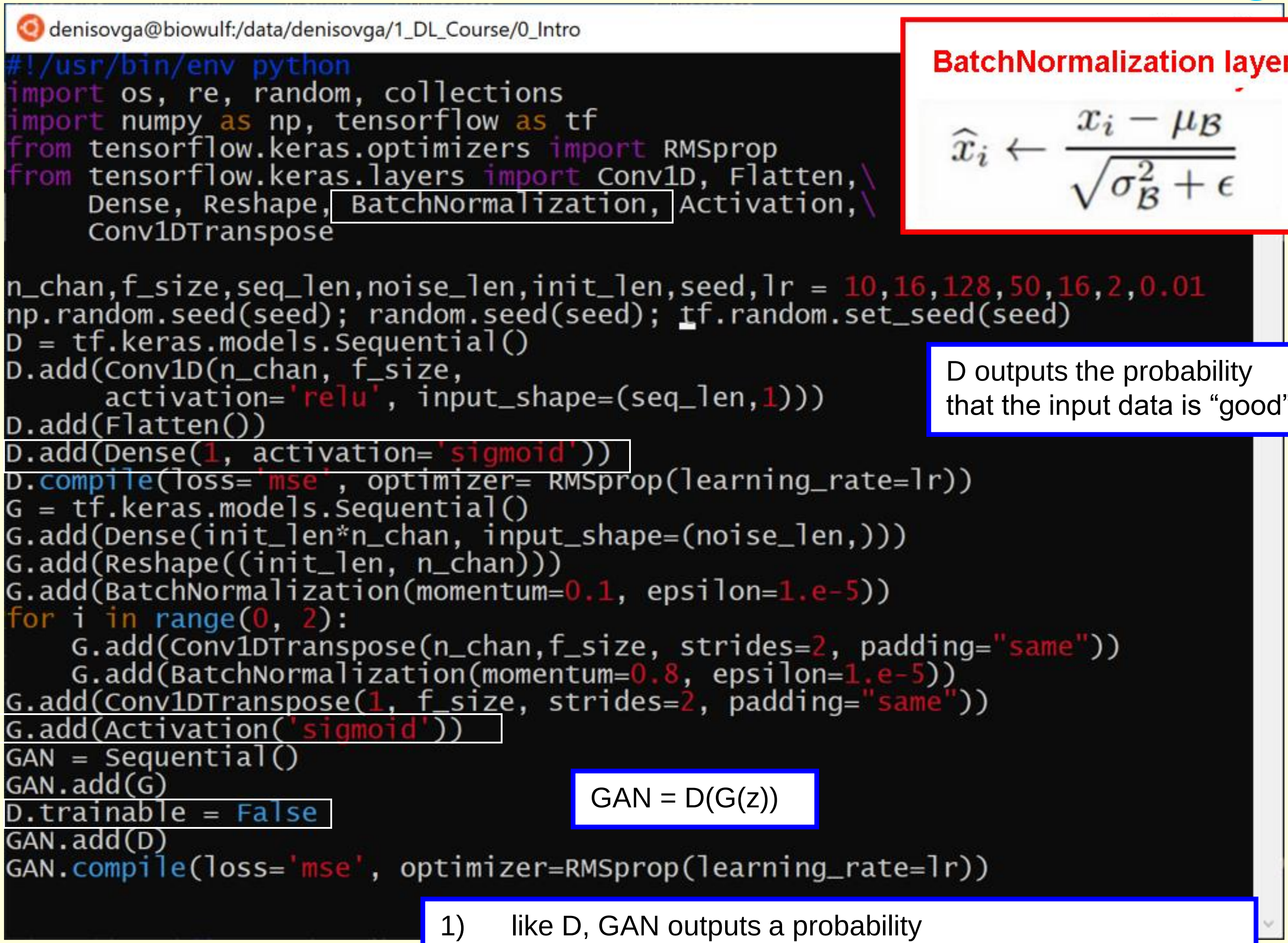
The simple GAN code: (1) header and (2) defining a model



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



denisovga@biowulf:/data/denisovga/1_DL_Course/0_Intro

```
#!/usr/bin/env python
import os, re, random, collections
import numpy as np, tensorflow as tf
from tensorflow.keras.optimizers import RMSprop
from 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); tf.random.set_seed(seed)
D = tf.keras.models.Sequential()
D.add(Conv1D(n_chan, f_size,
      activation='relu', input_shape=(seq_len,1)))
D.add(Flatten())
D.add(Dense(1, activation='sigmoid'))
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)
D.trainable = False
GAN.add(D)
GAN.compile(loss='mse', optimizer=RMSprop(learning_rate=lr))
```

D

G

GAN

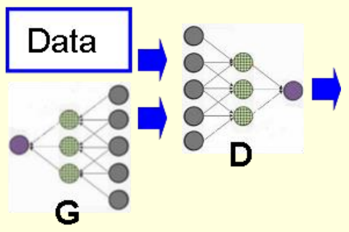
BatchNormalization layer

$$\widehat{x}_i \leftarrow \frac{x_i - \mu_{\mathcal{B}}}{\sqrt{\sigma_{\mathcal{B}}^2 + \epsilon}}$$

D outputs the probability that the input data is "good"

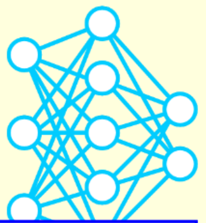
GAN = D(G(z))

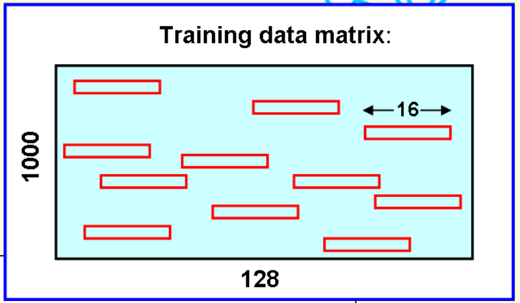
1) like D, GAN outputs a probability
2) like G, GAN takes noise as input
3) only G weights are adjustable when training GAN



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

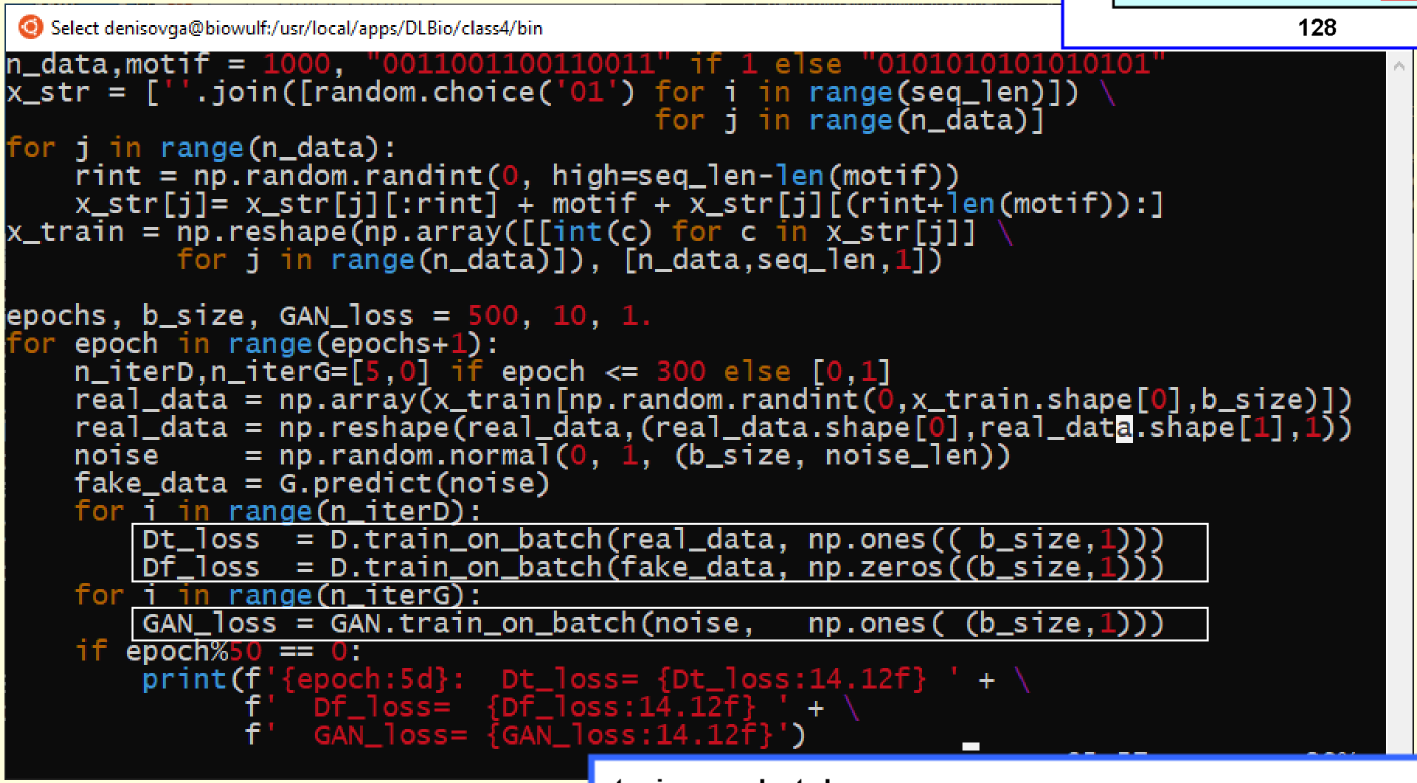
motif, train_on_batch, epoch, batch size, predict





(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 = 1000, "0011001100110011" if 1 else "0101010101010101"
x_str = [''.join([random.choice('01') for i in range(seq_len)]) \
                                      for j in range(n_data)]
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.
for 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))
    noise     = np.random.normal(0, 1, (b_size, noise_len))
    fake_data = G.predict(noise)
    for i in range(n_iterD):
        Dt_loss   = D.train_on_batch(real_data, np.ones(( b_size,1)))
        Df_loss   = 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)))
    if epoch%50 == 0:
        print(f'{epoch:5d}:  Dt_loss= {Dt_loss:14.12f} ' + \
              f'  Df_loss=  {Df_loss:14.12f} ' + \
              f'  GAN_loss= {GAN_loss:14.12f}')
```

train_on_batch:
- train D: D (real data) → 1
- train D: D (fake data) → 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

Re-write from the previous slide

real data $\equiv$ x; fake data $\equiv$ G(z); z $\equiv$ noise

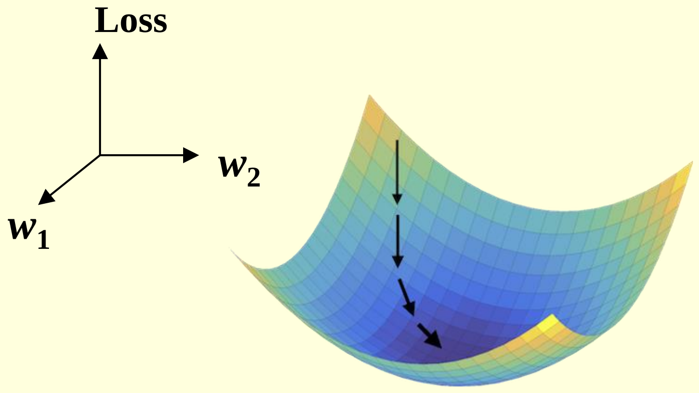
$D(x; w_D) \to 1 \quad \Rightarrow \quad \ln D(x; w_D) \to \max$

$D(G(z; w_G); w_D) \to 0 \quad \Rightarrow \quad \ln(1 - D(G(z; w_G); w_D)) \to \max$

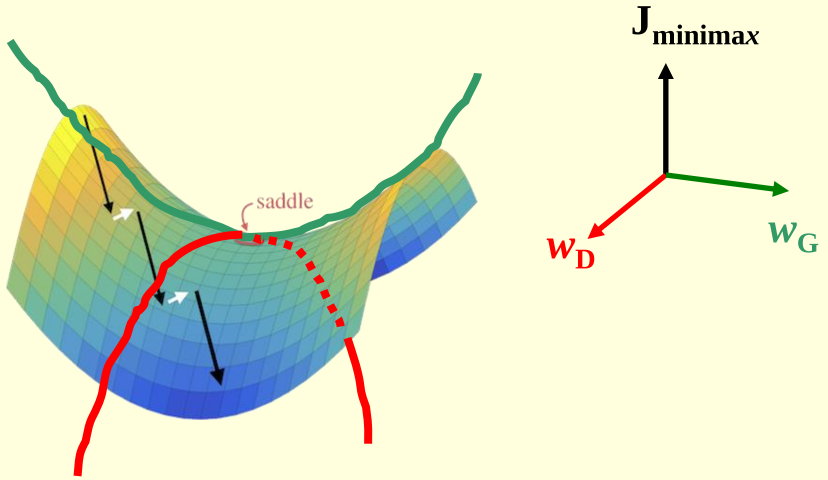
$D(G(z; w_G); w_D) \to 1 \quad \Rightarrow \quad \ln(1 - D(G(z; w_G); w_D)) \to \min$

The minimax optimization objective:

$$\boxed{J_{minimax} = \min_{w_G} \max_{w_D} E_{data}\{\ln D(x; w_D)\} + E_{noise}\{\ln(1 - D(G(z; w_G); w_D))\}}$$



Standard neural net

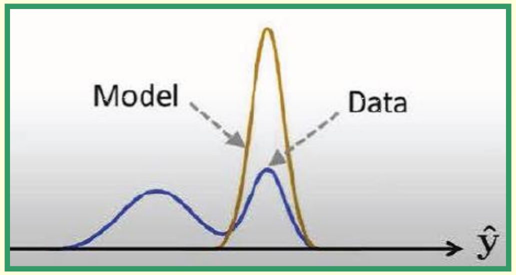


Adversarial neural net

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

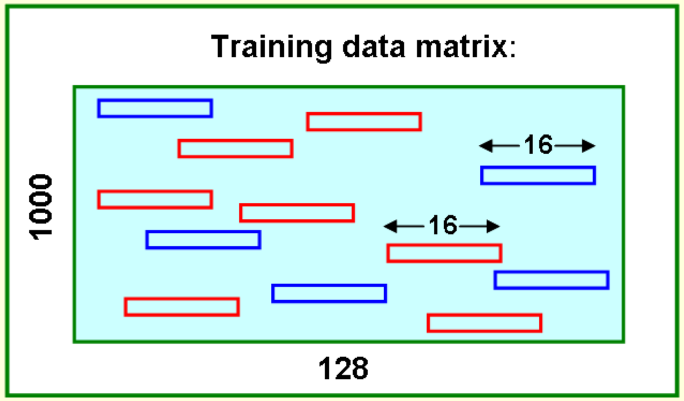


The mode collapse prototype example:

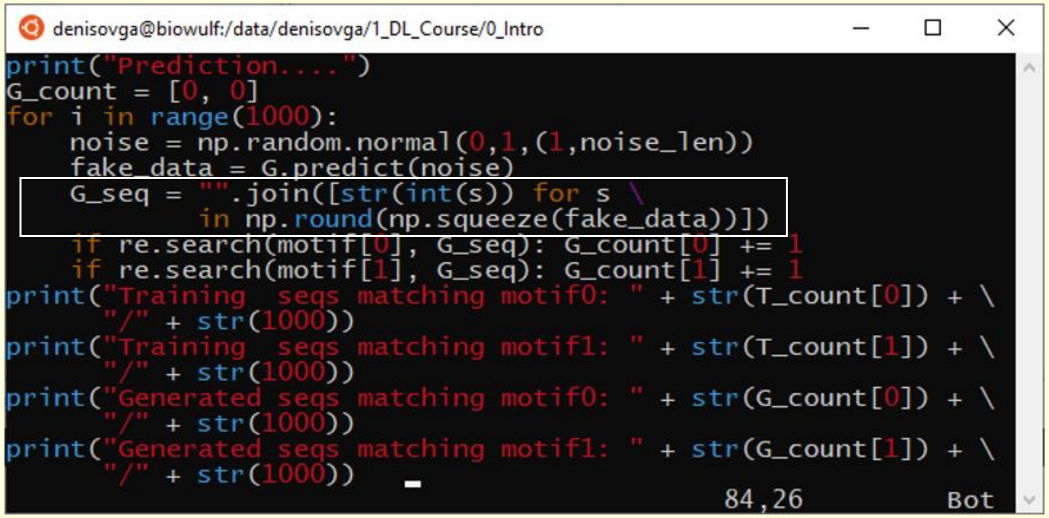
<u>**Input:**</u> a training set of **"good" sequences of 2 types ("modes")**, each sequence containing a motif of one type

<u>**Example**</u>: 01011001100110011001111, 00010101010101010111010

<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.

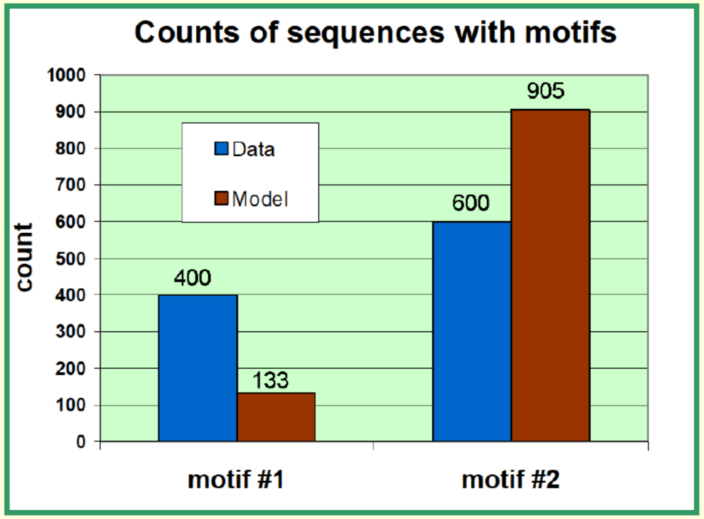


Predictions from the model:



```
denisovga@biowulf:/data/denisovga/1_DL_Course/0_Intro
print("Prediction....")
G_count = [0, 0]
for i in range(1000):
    noise = np.random.normal(0,1,(1,noise_len))
    fake_data = G.predict(noise)
    G_seq = "".join([str(int(s)) for s \
             in np.round(np.squeeze(fake_data))])
    if re.search(motif[0], G_seq): G_count[0] += 1
    if re.search(motif[1], G_seq): G_count[1] += 1
print("Training  seqs matching motif0: " + str(T_count[0]) + \
     "/" + str(1000))
print("Training  seqs matching motif1: " + str(T_count[1]) + \
     "/" + str(1000))
print("Generated seqs matching motif0: " + str(G_count[0]) + \
     "/" + str(1000))
print("Generated seqs matching motif1: " + str(G_count[1]) + \
     "/" + str(1000))
                                              84,26          Bot
```

Computed results:



Counts of sequences with motifs

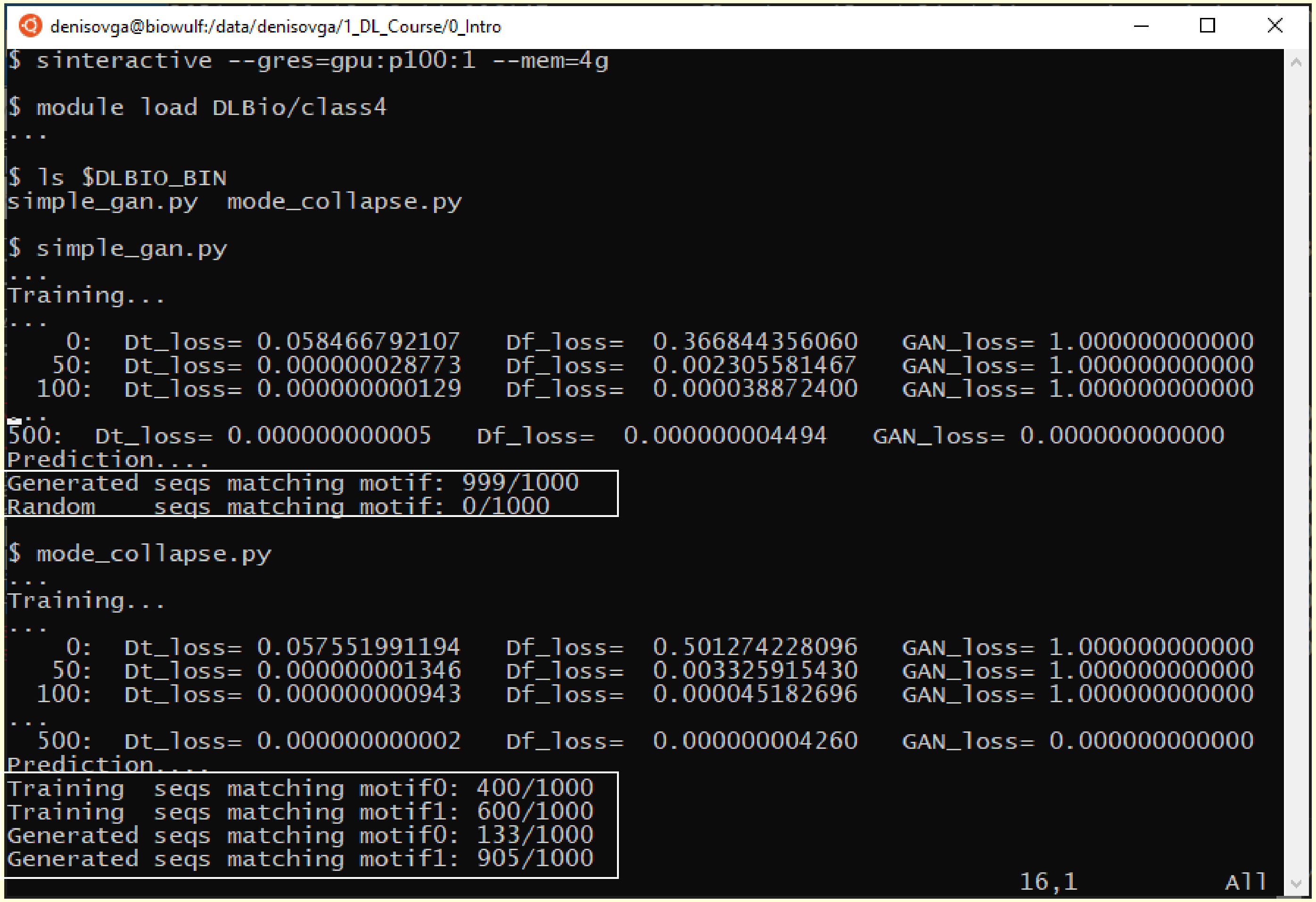
	Data	Model
motif #1	400	133
motif #2	600	905

How to run the simple GAN examples on Biowulf?

Executables

Data with single motif

Data with two motifs

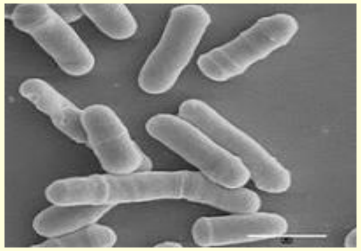


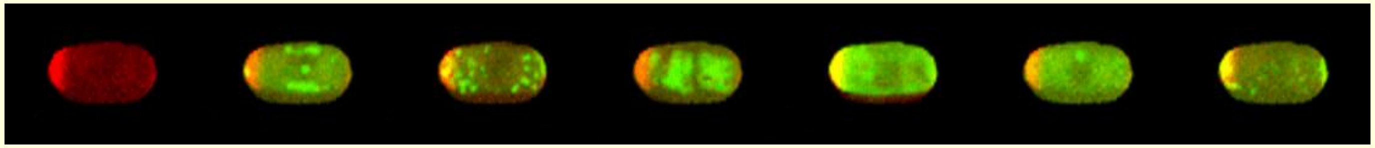
denisovga@biowulf:/data/denisovga/1_DL_Course/0_Intro

```
$ 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:  Dt_loss= 0.058466792107   Df_loss=  0.366844356060   GAN_loss= 1.000000000000
   50:  Dt_loss= 0.000000028773   Df_loss=  0.002305581467   GAN_loss= 1.000000000000
  100:  Dt_loss= 0.000000000129   Df_loss=  0.000038872400   GAN_loss= 1.000000000000
...
500:  Dt_loss= 0.000000000005   Df_loss=  0.000000004494   GAN_loss= 0.000000000000
Prediction....
Generated seqs matching motif: 999/1000
Random    seqs matching motif: 0/1000

$ mode_collapse.py
...
Training...
...
    0:  Dt_loss= 0.057551991194   Df_loss=  0.501274228096   GAN_loss= 1.000000000000
   50:  Dt_loss= 0.000000001346   Df_loss=  0.003325915430   GAN_loss= 1.000000000000
  100:  Dt_loss= 0.000000000943   Df_loss=  0.000045182696   GAN_loss= 1.000000000000
...
  500:  Dt_loss= 0.000000000002   Df_loss=  0.000000004260   GAN_loss= 0.000000000000
Prediction....
Training  seqs matching motif0: 400/1000
Training  seqs matching motif1: 600/1000
Generated seqs matching motif0: 133/1000
Generated seqs matching motif1: 905/1000
                                                                      16,1          All
```

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


Fission yeast cells



Proteins: growth marker Bgs4 and **polarity factors Alp14, Arp3, Cki2, …**
- **- only one polarity factor** per cell can be visualized experimentally
- different cells are at **different stages of the growth cycle** controlled by **Bgs4**

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

Computational task: train a GAN on available data and generate **synthetic images** that visualize localization of **multiple polarity factors,** together with **Bgs4, at the same stage of cell growth cycle**

Data: the Localization Interdependency network (**LIN**) dataset

The BioGANs pipeline (reimplemented in Keras from PyTorch):

$$\boxed{\textbf{train.py}} \rightarrow \boxed{\textbf{predict.py}} \rightarrow \boxed{\textbf{visualize.py}}$$

An overview of the BioGANs training code

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

The Keras source code:

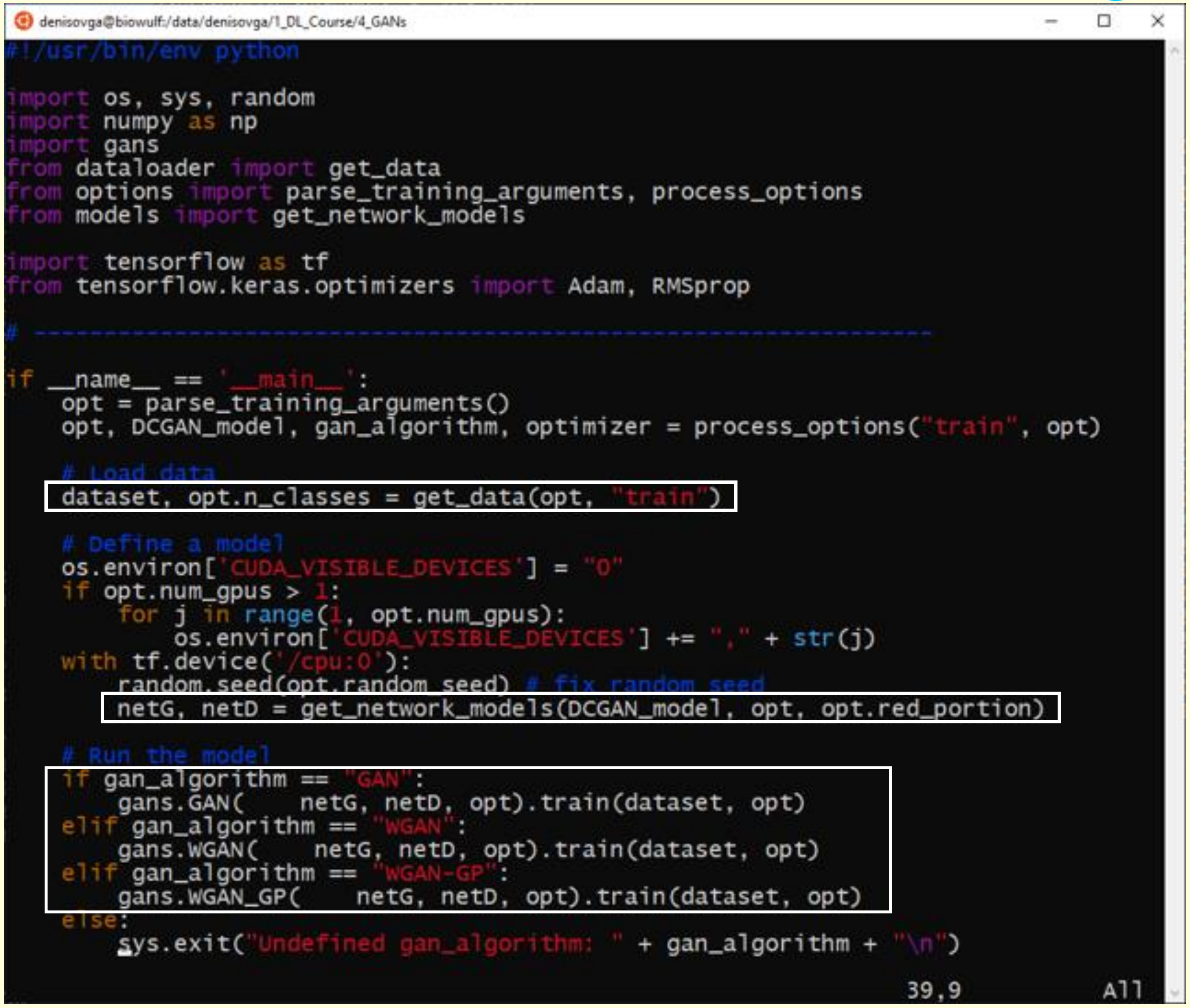
train.py, predict.py, visualize.py, gans.py, models.py, dataloader.py, options.py,

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

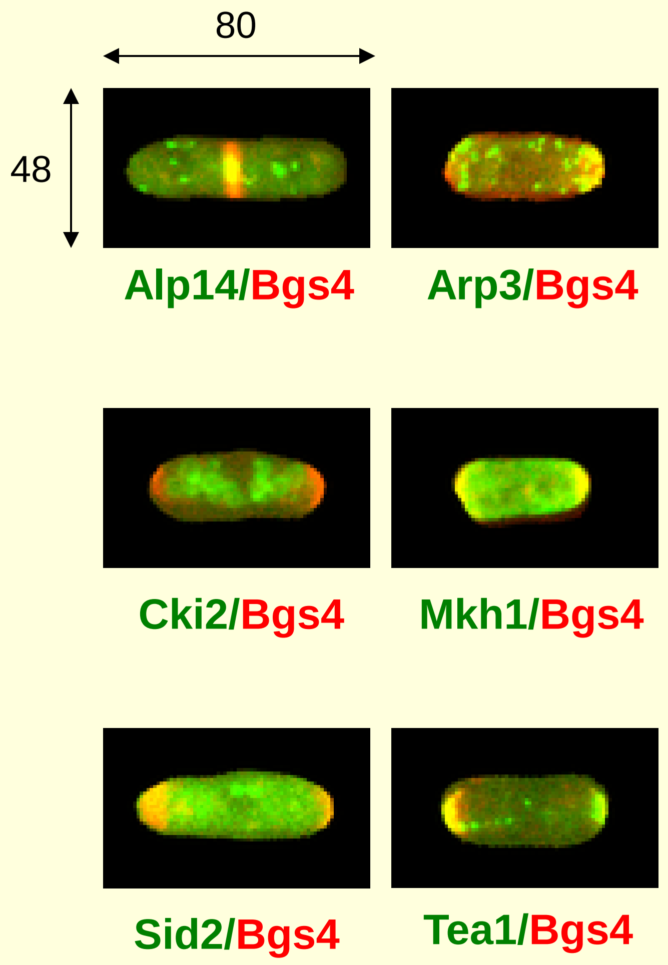


denisovga@biowulf:/data/denisovga/1_DL_Course/4_GANs

```
#!/usr/bin/env python

import os, sys, random
import numpy as np
import gans
from dataloader import get_data
from options import parse_training_arguments, process_options
from models import get_network_models

import tensorflow as tf
from tensorflow.keras.optimizers import Adam, RMSprop

# ----------------------------------------------------------------

if __name__ == '__main__':
    opt = parse_training_arguments()
    opt, DCGAN_model, gan_algorithm, optimizer = process_options("train", opt)

    # Load data
    dataset, opt.n_classes = get_data(opt, "train")

    # Define a model
    os.environ['CUDA_VISIBLE_DEVICES'] = "0"
    if opt.num_gpus > 1:
        for j in range(1, opt.num_gpus):
            os.environ['CUDA_VISIBLE_DEVICES'] += "," + str(j)
    with tf.device('/cpu:0'):
        random.seed(opt.random_seed) # fix random seed
        netG, netD = get_network_models(DCGAN_model, opt, opt.red_portion)

    # Run the model
    if gan_algorithm == "GAN":
        gans.GAN(    netG, netD, opt).train(dataset, opt)
    elif gan_algorithm == "WGAN":
        gans.WGAN(    netG, netD, opt).train(dataset, opt)
    elif gan_algorithm == "WGAN-GP":
        gans.WGAN_GP(    netG, netD, opt).train(dataset, opt)
    else:
        sys.exit("Undefined gan_algorithm: " + gan_algorithm + "\n")
                                                              39,9          All
```

BioGANs data: the Localization Interdependency Network (LIN) dataset

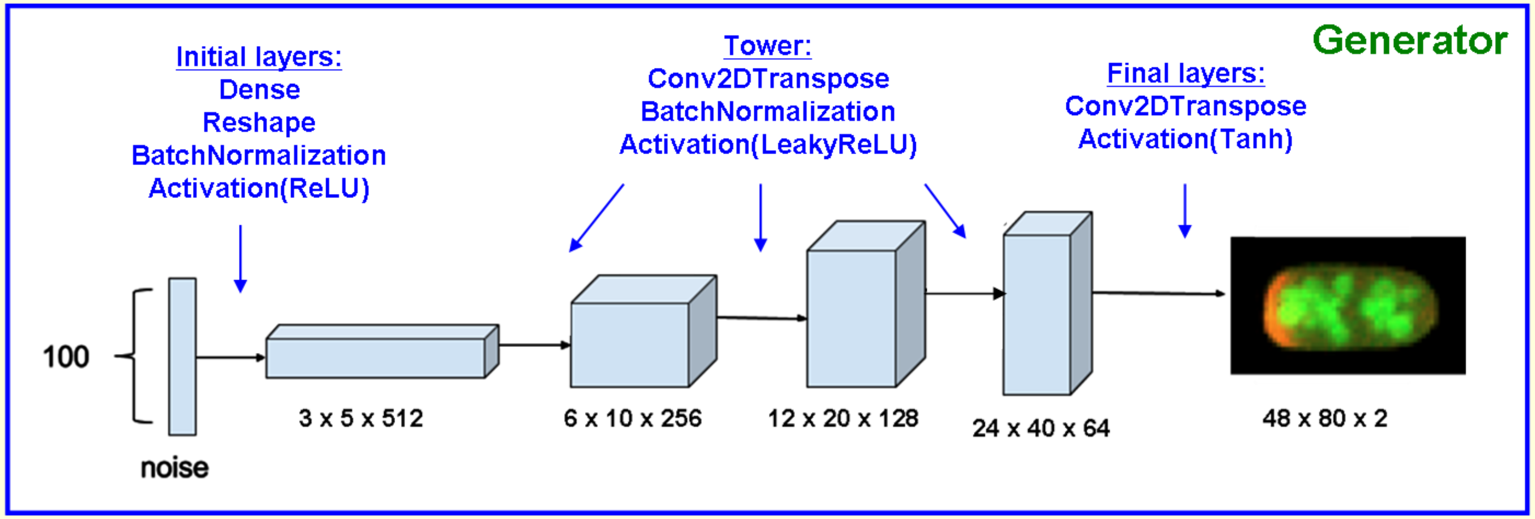
J.Dodgson et al, https://www.biorxiv.org/content/10.1101/116749v1.full

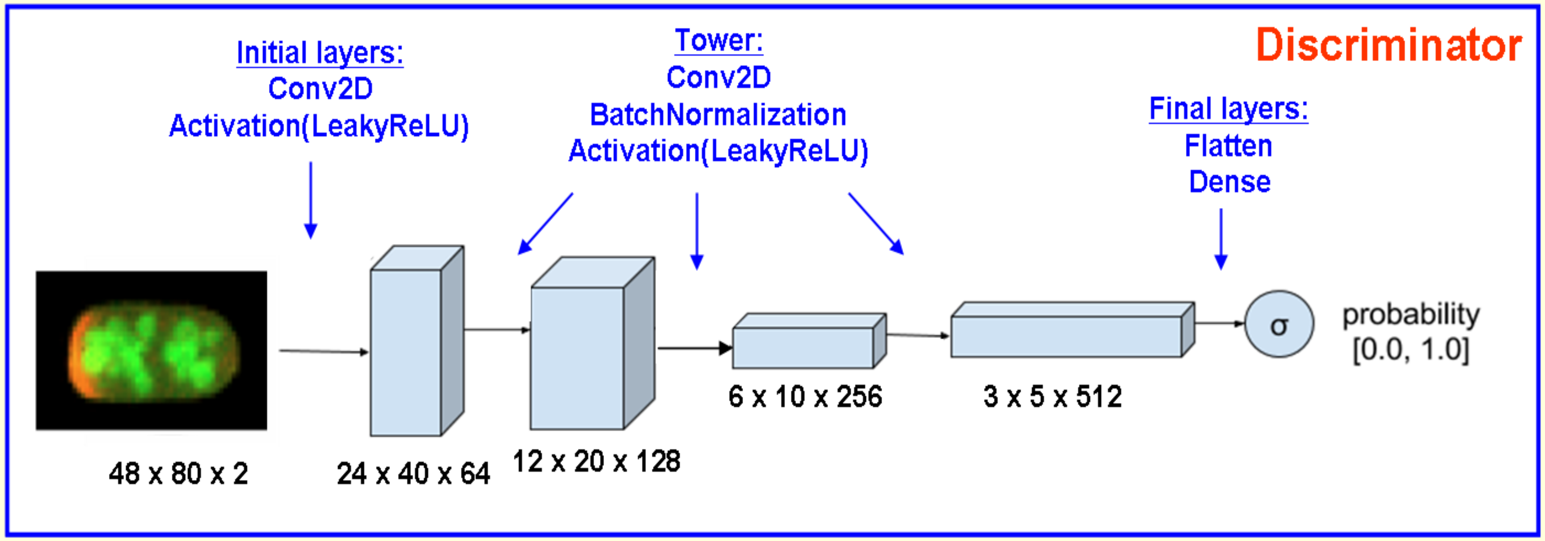


Features:

- **2D fluorescence microscopy images** of Fission yeast cells, each (7 ÷14) x 4 μm
- 2-channel images of size **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:

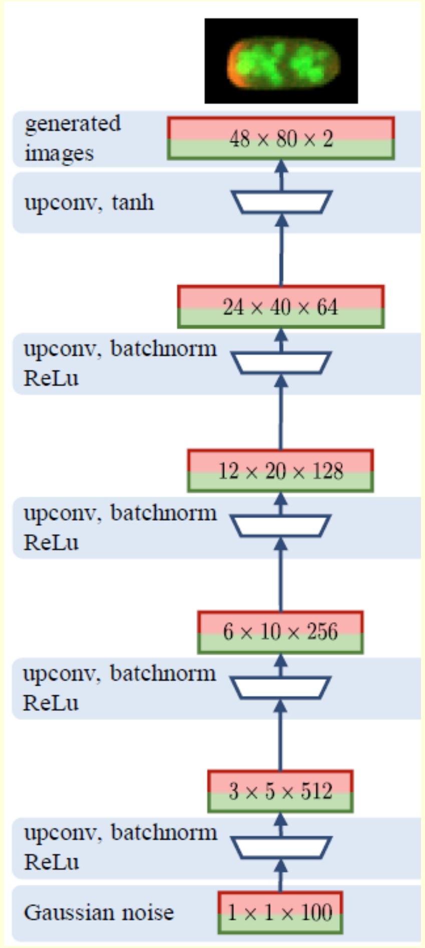
- the most basic model implemented as a part of the BioGANs application

- due to the mode collapse, can only generate green channels for a subset of polarity factors

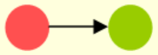
BioGANs generator architrectures: DCGAN, DCGAN-separable and DCGAN-starshaped

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

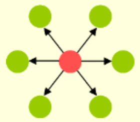
DCGAN

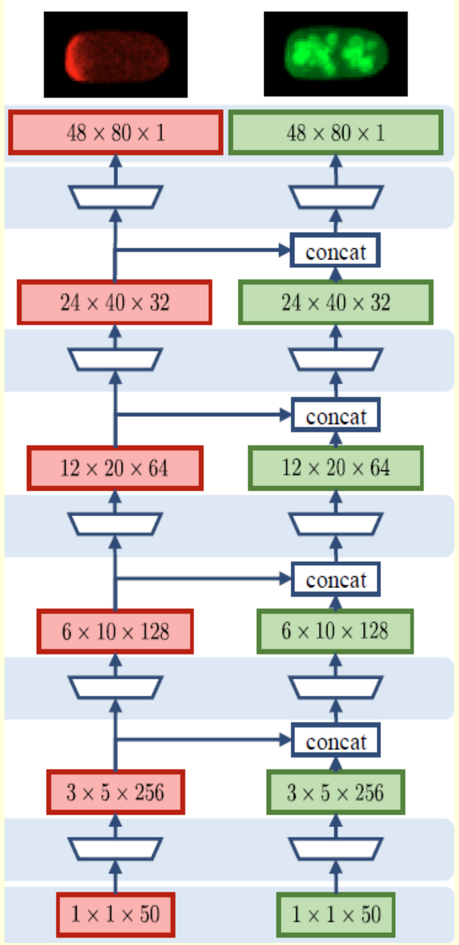


DCGAN-separable



DCGAN-starshaped

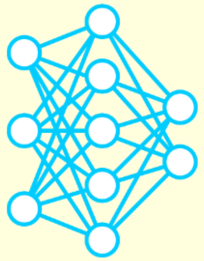




Two shortcomings of the DCGAN Generator:

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

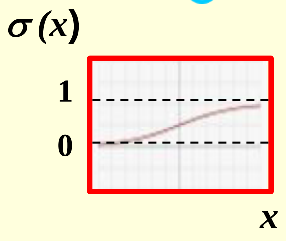
The Wasserstein GAN (WGAN)



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:

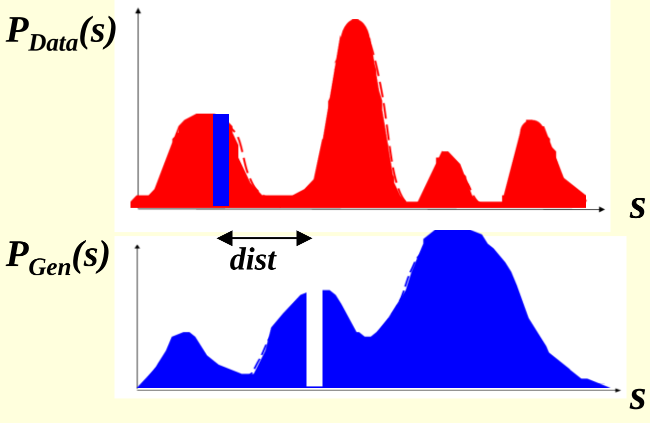
$D(I, w) = \sigma(F(I, w)) \Rightarrow \nabla_w D = \sigma' \cdot \nabla_w F \rightarrow 0$ at saturation



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:

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

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

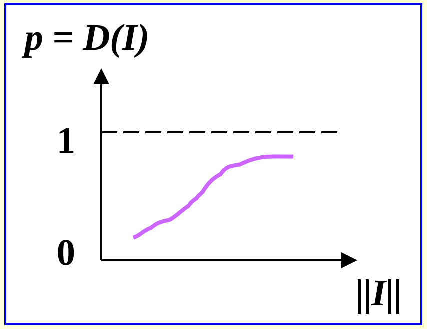
$$\boxed{EMD \approx -E\,[s^{Data} \cdot s^{Gen}]}$$

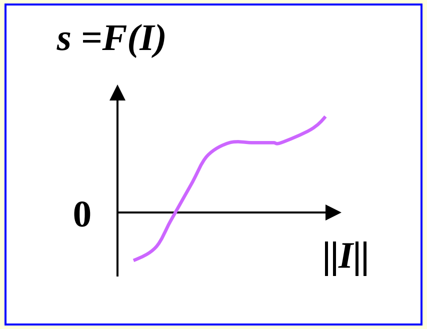
$EMD \rightarrow$ min
forces the two distributions
to have maxima
at the same locations

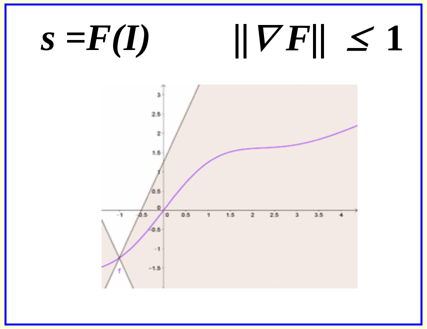
WGAN with gradient penalty (WGAN-GP)

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: $\mathbf{Z = A(\sum w_i \cdot X_i + b)}$

WGAN-GP:
penalize the loss to force $\|\nabla F\|$ *be close to* 1

$$\boxed{\textit{WGAN-GP loss} = EMD + \lambda \cdot E[(\|\nabla F\| - 1)^2]}$$

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 lr = 0.00005

WGAN-GP features:
(1) }
(2) } 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 $\|I\| \approx 1$**:**

```
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)
```

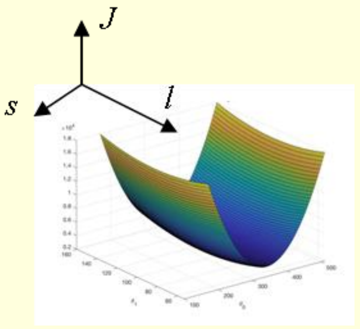
The Root Mean Squared Propagation (RMSProp) optimizer

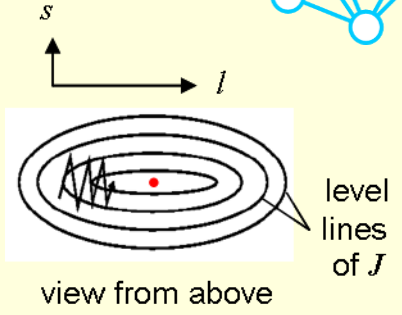
Slides: http://www.cs.toronto.edu/~tijmen/csc321/slides/lecture_slides_lec6.pdf
Video: https://goo.gl/XUblyJ

Basic gradient descent formula for updating weights:

$$\boxed{w_{t+1} - w_t = -\gamma \cdot \nabla_w J(w_t)}$$

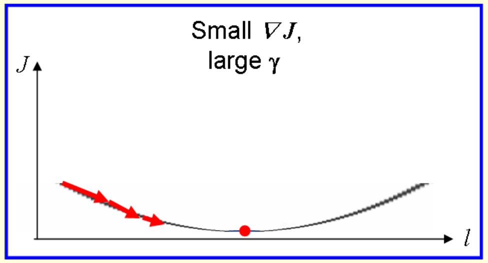
w = vector of weights
t = update #
γ = learning rate
$\nabla_w J$ = gradient of the loss

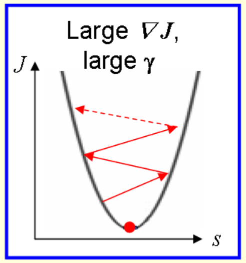


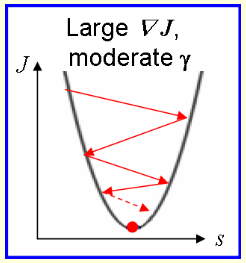


The RMSprop gradient descent formula:

$$w_{t+1} = w_t - \underbrace{\frac{\gamma}{\sqrt{E[\nabla_w J(w_t)^2] + \varepsilon}}}_{\text{effective } \gamma} \cdot \nabla_w J(w_t)$$







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 ∇J)

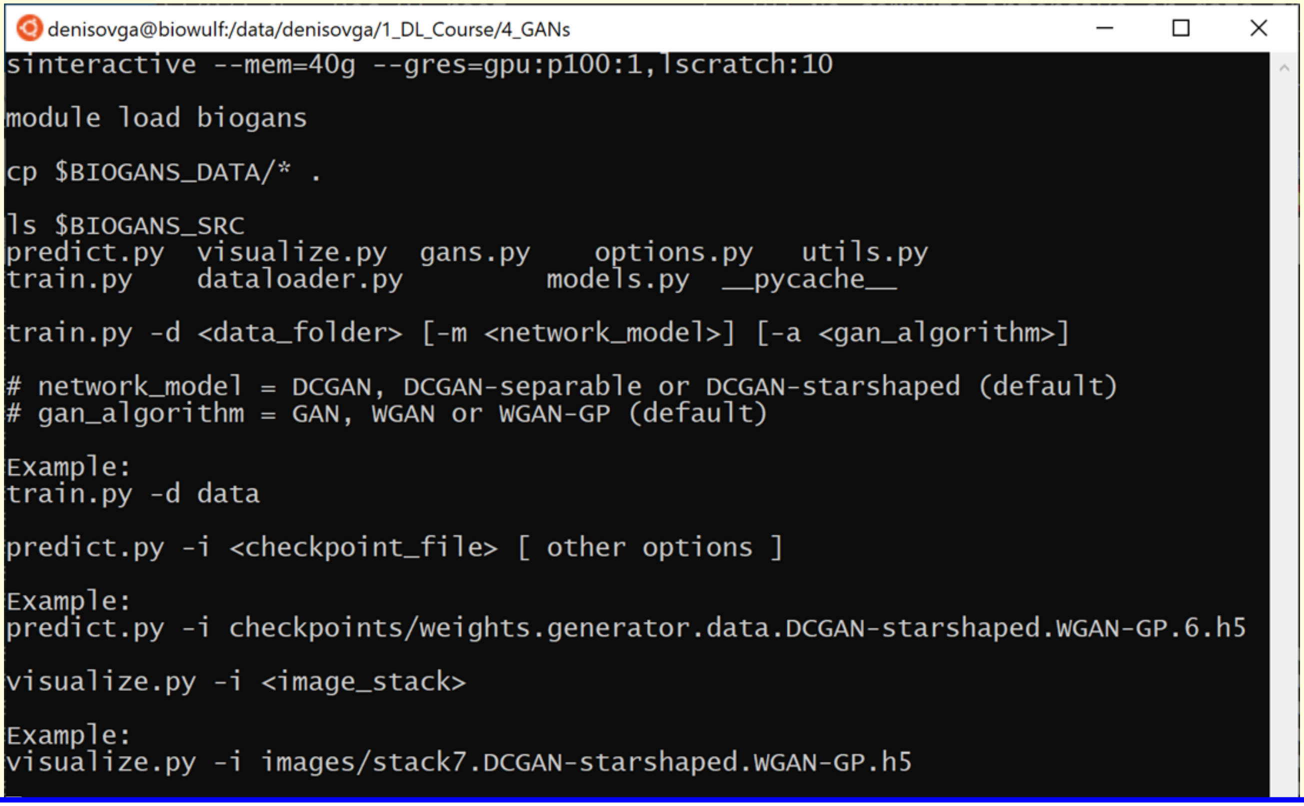
$$\boxed{E[\nabla_w J(w)^2]_t = \rho \cdot E[\nabla_w J(w)^2]_{t-1} + (1-\rho) \cdot \nabla_w J(w_t)^2}$$

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, …)
```

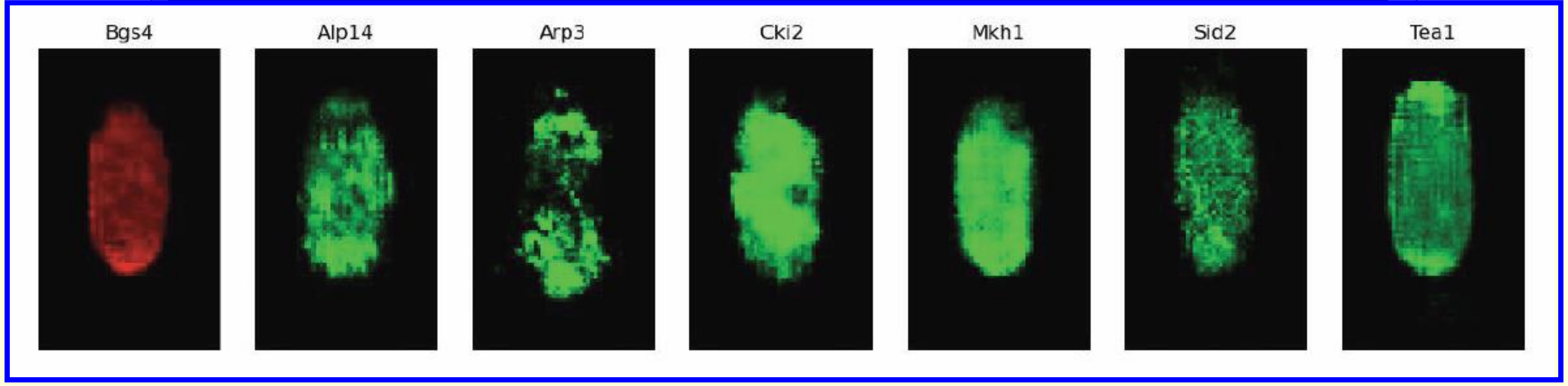
How to run the BioGANs application on Biowulf?

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



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

```
sinteractive --mem=40g --gres=gpu:p100:1,lscratch:10

module load biogans

cp $BIOGANS_DATA/* .

ls $BIOGANS_SRC
predict.py  visualize.py  gans.py    options.py   utils.py
train.py    dataloader.py          models.py   __pycache__

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