# Deep generative models for biologists

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# Outline

# Discriminative and generative models

Say we have a set of variables $\mathrm{x} = (x_1, x_2, ..., x_n)$ which might have some statistical dependence

The variable x might be an amino acid sequence, DNA sequence, microscopy image, etc.

In supervised discriminative learning, we may use observations of x to try and learn distributions such as $p(x_2|x_1)$ (i.e., inference)

In supervised generative learning, we try to explicity learn the joint distribution $p(\mathrm{x}) = p(x_1|x_2, ..., x_n)p(x_2|x_3, ..., x_n), ..., p(x_n)$, which is generally more difficult.

# The basic sampling problem

Suppose we are given a joint distribution

$$p(\mathrm{x}) = \frac{1}{Z}\tilde{p}(\mathrm{x})$$

where $p(\mathrm{x})$ is easy to compute but $Z$ is (too) hard to compute.

This very important situation arises in several contexts:

1. In Bayesian models where $p(x_1, x_2) := p(x_1|x_2)p(x_2)$ is easy to compute but $Z = \int p(x_1|x_2)p(x_2)dx_2$ can be very difficult or impossible to compute.

2. In models from statistical physics, e.g. the Ising model, we only know $\tilde{p}(\mathrm{x}) = e^{-H(\mathrm{x})}$ where $H(\mathrm{x})$ is the Hamiltonian - the Ising model is an example of a Markov network or an undirected graphical model.

# Approximating the joint distribution

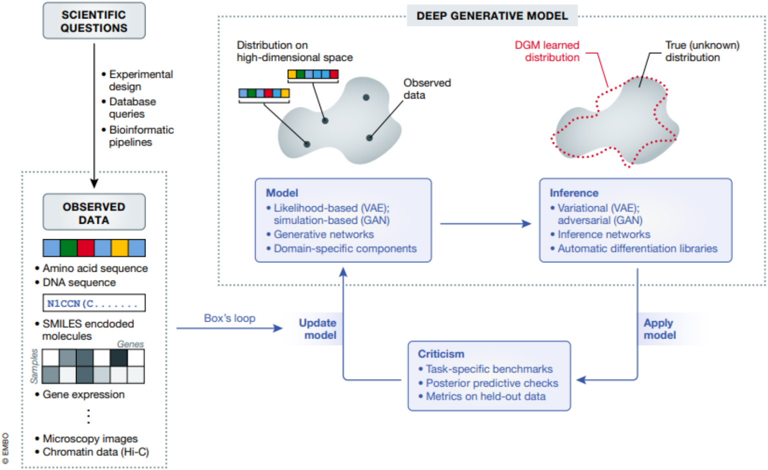
We would like to approximate $p(\mathrm{x})$

Variational methods are generally useful for Bayesian inference like $p(x_1|x_2)$ but can also be used to evaluate $p(\mathrm{x})$ by autoencoding $\mathrm{x}$ (called a variational autoencoder)

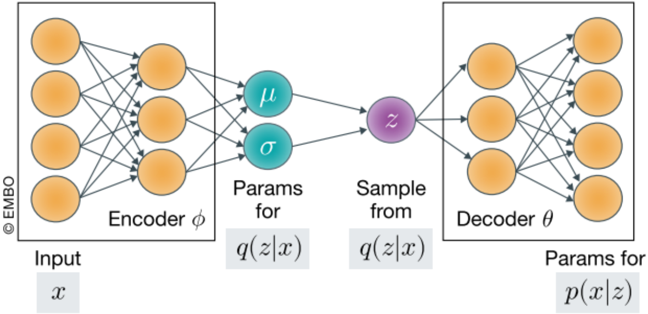
Generative adversarial networks (GANs) model $p(\mathrm{x})$ directly

In special scenarios, we may know $\tilde{p}(\mathrm{x})$ and we can use Monte-Carlo Markov Chain (MCMC) methods

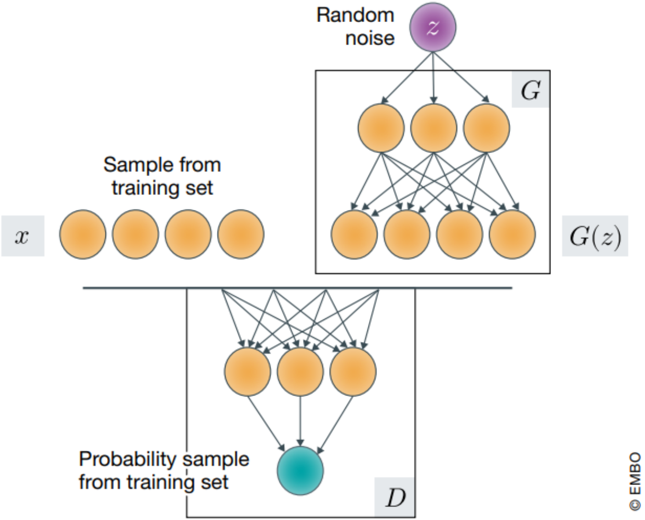
# Applying deep generative models to biological data



# Generative models: variational autoencoder



# Generative models: adversarial networks



# Cool biological applications of VAEs and GANs

Sequencing, Imaging, Other stuff

# Monte-Carlo Markov Chain (MCMC)

- MCMC algorithms were originally developed in the 1940's by physicists at Los Alamos
- They were interested in modeling the probabilistic behavior of collections of atomic particles
- Simulation was difficult – the normalization constant $Z$ was not known
- The term "Monte-Carlo" was coined at Los Alamos.
- Ulam and Metropolis overcame this problem by constructing a Markov chain for which the desired distribution was the stationary distribution
- Introduced to statistics and generalized with the Metropolis-Hastings algorithm (1970) and the Gibbs sampler of Geman and Geman (1984).

# Monte-Carlo Markov Chain (MCMC)

MCMC is used when we know the functional form of $p(\mathrm{x})$ up to the normalization constant e.g., Ising model

MCMC methods do not model $p(\mathrm{x})$ directly but allow us to draw samples $\mathrm{x} \sim p(\mathrm{x})$

# Gibbs sampling

- Suppose $p(\mathrm{x})$ is a p.d.f. or p.m.f. that is difficult to sample from directly.
- Suppose, though, that we *can* easily sample from the conditional distributions e.g., $p(x_1|x_2, ..., x_n)$.
- The Gibbs sampler proceeds as follows:
  1. set x to some initial starting values
  2. then sample $x_1|x_2, ..., x_n$, then sample $x_2|x_1, ..., x_n$, and so on.

# Gibbs sampling

0. Set $(x_0, y_0)$ to some starting value.
1. Sample $x_1 \sim p(x|y_0)$, that is, from the conditional distribution $X \mid Y = y_0$.
   Current state: $(x_1, y_0)$
   Sample $y_1 \sim p(y|x_1)$, that is, from the conditional distribution $Y \mid X = x_1$.
   Current state: $(x_1, y_1)$
2. Sample $x_2 \sim p(x|y_1)$, that is, from the conditional distribution $X \mid Y = y_1$.
   Current state: $(x_2, y_1)$
   Sample $y_2 \sim p(y|x_2)$, that is, from the conditional distribution $Y \mid X = x_2$.
   Current state: $(x_2, y_2)$

   $\vdots$

Repeat iterations 1 and 2, M times.

# Markov blankets

When one wants to infer a random variable with a set of variables, usually a subset is enough.

The useful information is called a Markov blanket

# Probabilistic graphical models

# Using Gibbs sampling with graphical models

# References I