Section 04: Intro to Probability

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The amazing gynandromorph

Here's one very special bird that was spotted in Pennsylvania in early 2019:

Image by Shirley Caldwell, https://www.nytimes.com/2019/02/09/science/cardinal-sex-gender.html

It's a gynandromorphic cardinal, an individual with both female and male characteristics. Gynandromorphism has been observed in vertebrates and invertebrates alike, but the case of the gynandromorphic cardinal is especially interesting (and visually stunning). Male cardinals are typically red, and female cardinals are typically gold, but there can exist considerable variability in plumage. This striking bilateral segmentation could not be due to gynandromorphism at all; it

could also be the consequence of a somatic loss-of-function mutation that occurred very early in this bird's development.

Gynandromorphic cardinals are rare, but very often have this remarkable plumage. Single-sex cardinals are very common, but can occasionally wear a coat of feathers that makes them look like a gynandromorph. So this raises a vexing statistical question: If you see one of these bicolor birds in the wild, what is the probability that it's a gynandromorph?

If we get Bayesian about it, we can figure this out. We'll cover this calculation in.

Markov models

(Another excuse to talk about birds)

In lecture Sean introduced Markov models, which are very relevant for this week's pset. As discussed in class, Markov models are a way to calculate the probability of a sequence of events for which each event's probability depends on what event(s) came before it -- if you have a first order Markov model, the probability of an event depends only on the event that happened directly before, while if you have a second order Markov model, the probability of an event depends on the previous two events. The purpose of this section is to walk you through how you could implement your own Markov model (*cough cough* pset 04), explaining relevant terminology from lecture and the pset along the way.

Let's make a toy Markov model to predict which species of bird is nearby based on the birdsongs we hear in the forest. We're in a forest that has two species of bird, *sleek* and *fluffy*, that each make songs composed of a mix of 'ree ree' calls and hiss-like 'ess ess' songs. If you're wondering how birds can make such a wide range of vocalizations like 'ess' and 'ree' and 'Hello!!!' , you

can wonder at the formidable anatomic structure that is the syrinx.

You record the songs you hear in the forest, and encode the songs as a sequence of n 'ree' and 'ess' calls: 'rrssrssssr' or 'srsssrsr' for example. You want to know whether a bird is *sleek* or *fluffy* based on this pattern. You know that, over the course of a song, the next note that a bird will sing depends in part on the last few notes. So to account for this we will try modeling bird song using a third order **Markov model**, where the next note depends on the previous three notes.

Now let's set up our model!

Random variable

A **random variable** is a variable that takes on one of a defined set of values with some probability. Random variables are usually written as uppercase letters, and the values they assume are written lowercase. The set of values that a random variable can assume is called the sample space.

For our model, let X_i be the random variable of note i. The note can be either 'ree' (r) or 'ess' (s), so the sample space for X_i is $X_i \in r, s$. X_i will take on the value r if the note is 'ree' and s if the note is 'ess'. For example, if the first note in our song was 'ess', then we could denote event $X_1 = s$ as x_1.

Joint probability

To calculate the probability of a given sequence of notes, we need to find the **joint probability**. For example, the probability of the sequence 'srs' is the probability that the first note in our sequence is 'ess' *and* the second note is 'ree' *and* the third note is 'ess'. Using our random variable notation from above, that is $X_1 = s$ and $X_2 = r$ and $X_3 = s$. This gives us the probability:

$$P(srs)$$

Or more generally:

$$P(x_1, x_2, x_3)$$

Conditional probability

Say we want to find the **conditional probability** that the next note in our song is 'ess' *given* that the last three notes followed the sequence 'srs', which we represent as $P(s|srs)$. It might feel more natural to think of the probability of the sequence 'srss', or $P(srss)$. We can relate these two probabilities using the equation for conditional probability:

$$P(srss) = P(s|srs)P(srs)$$

In other words, the probability of getting the sequence 'srss' can be written as the probability of getting 's' once you already have 'srs' multiplied by the probability of having 'srs' in the first place. We can rearrange this to solve for the conditional probability that we are interested in:

$$P(s|srs) = \frac{P(srss)}{P(srs)}$$

Or more generally:

$$P(x_i|x_{i-3}, x_{i-2}, x_{i-1}) = \frac{P(x_{i-3}, x_{i-2}, x_{i-1}, x_i)}{P(x_{i-3}, x_{i-2}, x_{i-1})}$$

Markov model

Now we're ready to define a third order **Markov model** where the next note of a song depends on the previous three notes. To calculate the total probability of a song from this model, we need the two types of parameters we defined above:

- The **initial probability** $P(x_1, x_2, x_3)$ is the joint probability of a particular sequence of three notes occurring. For example, the

initial probability of a sequence starting with 'srs' is the probability of hearing 'ess', then 'ree', then 'ess'.

- The **conditional probability** $P(x_i|x_{i-3}, x_{i-2}, x_{i-1})$ is the probability of observing the note x_i given the notes of the previous three notes. For example, the probability of 's' occurring after the sequence 'srs' is the probability of hearing 's' given that the previous three notes were 'srs'.

To find the total probability of a sequence using this model, we start by calculating the initial probability of the first three notes. For the sequence 'srsssrsr', this is $P(srs)$. Next, for $i = 4$ we we want to know the probability of 's' after the sequence 'srs', which we write as $P(s|srs)$. For $i = 5$, we want to know the probability of 's' after the sequence 'rss', or $P(s|rss)$. And so on.

The total probability of a sequence from a 3rd order Markov model is then:

$$P(x_1, x_2, \ldots x_n) = P(x_1, x_2, x_3) \prod_{i=4}^{n} P(x_i|x_{i-3}, x_{i-2}, x_{i-1})$$

Training datasets

We have an equation for calculating the probability of a sequence from a third order Markov model... but how do we actually set the initial probability and conditional probability parameters? This is where a **training dataset** comes in. We have to train on a dataset of known songs for the *sleek* birds in order to calculate the probability that the new song we hear is from *sleek*.

To calculate the **initial probability** $P(srs)$ for example, we can count how many times we see the sequence 'srs' in the training dataset and divide by the total number of 3-note sequences in the dataset. We can repeat this process for every

possible 3-note sequence (3-mer, if you will) to find all initial probabilities.

Then to calculate the **conditional probability** $P(s|srs)$ for example, we can look back to the formula for conditional probability from above: $P(s|srs) = \frac{P(srss)}{P(srs)}$ This shows us we need both $P(srs)$ and $P(srss)$. We now know how to find $P(srs)$ form the initial probabilities. Similarly, to find $P(srss)$, we can count how many times we see the sequence 'srss' in the training dataset and divide by the total number of 4-note sequences in the dataset. We can again repeat this process for every possible 3-mer and 4-mer to find all conditional probabilities.

We can follow this process once to calculate our parameters for the *sleek* training dataset. Then we can repeat the process to calculate our parameters for the *fluffy* training dataset separately. Great – now our parameters are set!

Testing datasets

In the problem set, we are told to use half of the sequences as the training set, and half as the test set. The reason for this is we want to use data from known origins to train our model (get the probability parameters discussed above), and we also want to use data from known origins to test our model (see if we can figure out the bird species for a new song using our Markov model). But we DON'T want to use the same pieces of data to train and test the model! Depending on your data and model, you may use a larger or smaller fraction of the total dataset to train the model.

So how do we test the model? We want to see how well our model identifies the singer of our remaining recorded birdsongs. For each sequence in the **test dataset**, we should calculate the probability that the sequence came from *sleek* or *fluffy*. We do this by calculating the total probability of a sequence $x = x_1, x_2, \ldots, x_n$

using either the *sleek* parameters we trained or the *fluffy* parameters we trained:

- The probability of each test sequence x given the Markov model with *sleek* parameters (H_0) is $P(x|H_0)$.
- The probability of each test sequence x given the Markov model with *fluffy* parameters (H_1) is $P(x|H_1)$.

Log-odds score

We now know the probability that a specific sequence came from *sleek* or from *fluffy*. But what we really want to know is how likely it is that the song came from *sleek* VERSUS *fluffy* (or the other way around, depending on what you consider a 'positive' – for this exercise we will consider *sleek* to be a positive result).

This is given by the **log-odds score**, which is the logarithm of the ratio of the probability of that sequence x occurring under the third order Markov model with *sleek* vs. *fluffy* parameters:

$$\text{log-odds score} = \log \frac{P(x|H_0)}{P(x|H_1)}$$

Note that since this is a logarithm of a ratio, we can write it as the difference of two logs:

$$\text{log-odds score} = \log P(x|H_0) - \log P(x|H_1)$$

A note about log probabilities

If you remember from above, the probability $P(x_1, x_2, \ldots, x_n)$ is the product of numerous probabilities, so this can also be written as a sum of logarithms of probabilities. Why is this nice? Sometimes our probabilities are very small, and multiplying many small numbers together can give you underflow errors in Python (where the value gets rounded to zero because it's very very small). In future weeks, this will become super important!

Here, we are able to take the log because the probabilities we're dealing with are all positive – sometimes you have trouble when probabilities are 0, so you add a small pseudocount.

Model performance

Now that we have an idea of how to construct a Markov model, how do we actually assess its performance? How do we know if our third order Markov model is actually any good at discriminating birdsongs from *sleek* and *fluffy* that we hear in the forest?

Score threshold

First off, we have a log-odds score for every sequence in our test dataset. How do we determine which songs are actually from *sleek* and which ones are from *fluffy*? We need to define a **score threshold** or cutoff – any sequence with a log-odds score above the threshold is from *sleek* and anything below it is from *fluffy*. Luckily we know the true species assignment of every song in our test dataset.

For any threshold that we set, there will be a corresponding number of:

- **true positives (TP)**: *sleek* songs that are identified as *sleek*
- **true negatives (TN)**: *fluffy* songs that are identified as *fluffy*
- **false positives (FP)**: * fluffy *songs that are identified as * sleek*
- **false negatives (FN)**: * sleek *songs that are identified as * fluffy*

We can calculate these values for a range of thresholds (say, the range of log-odds scores we get across the test dataset), and see how well we do at distinguishing the species. There are many metrics that combine TP, TN, FP, FN that you can consider when setting a threshold, and the pset

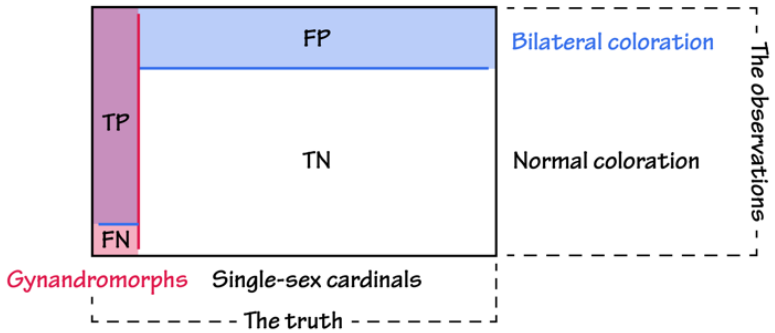
mentions a few.

Confusion matrix

A common way to represent the TP, TN, FP, FN values for a given model is a **confusion matrix**. This is an awful name for a table containing these values. For example:

		Actual	**Actual**
		sleek	fluffy
Predicted	sleek	TP	FP
Predicted	fluffy	FN	TN

Graphically, the confusion matrix for the gynandromorph problem might look something like this:



There are many other metrics we can calculate on these counts. Here are a few that will come in handy:

- **true positive rate (TPR)** = $\frac{TP}{TP+FN}$
- **true negative rate (TNR)** = $\frac{TN}{TN+FP}$
- **false positive rate (FPR)** = $\frac{FP}{TN+FP}$
- **false negative rate (FNR)** = $\frac{FN}{TP+FN}$

You will also often hear the terms **sensitivity** and **specificity**. Sensitivity is the fraction of positive sequences that were correctly identified as positive. Specificity is the fraction of negative sequences that were correctly identified as

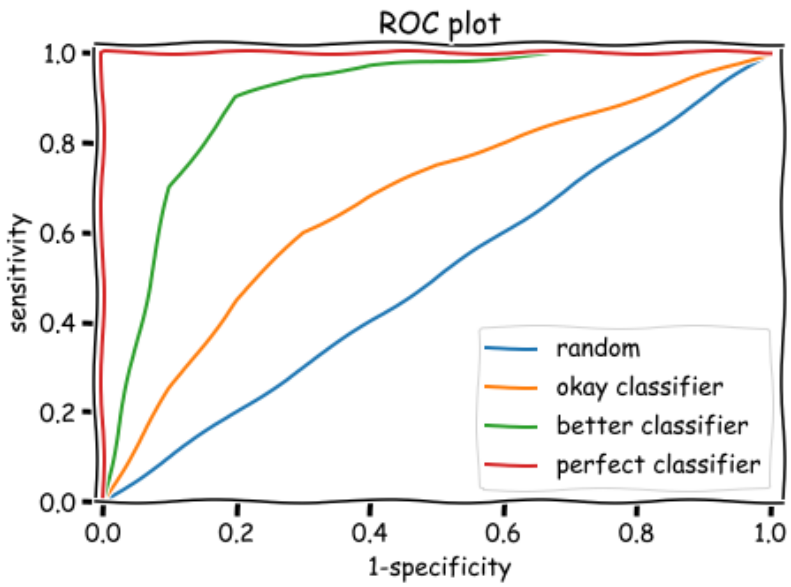
negative. In other words:

- **sensitivity** = TPR
- **specificity** = TNR
- **1 - specificity** = FPR

In general, we want to choose a threshold that yields good sensitivity and specificity.

ROC plot

A nice way to visualize the tradeoff between sensitivity and specificity for different thresholds is a **ROC plot** (often pronounced 'rock plot'). ROC plots compare the performance of binary classifiers (i.e. a model that sorts inputs into positives and negatives). To generate a ROC curve, we plot **FPR vs. TPR**, or **1-specificity vs. sensitivity** at each threshold.



By looking at this plot, you can see how true positives and false positives vary as you change the threshold. If you make the threshold very high, you need a very high log-odds score to be classified as positive (*sleek*) – you will probably have a very low false positive rate, but you will probably also have a very low true positive rate, losing a lot of the actual *sleek* songs. Alternatively, if you make the threshold very low, you will probably classify all of your positive (*sleek*)

sequences as *sleek*, but you will also misclassify a lot of negative (*fluffy*) sequences as *sleek*.

You can use a ROC plot to determine what your threshold will be – for example, you may want a low false positive rate of 5% or less, and a ROC plot will help you find the corresponding score threshold to achieve this.

False discovery rate (FDR)

As mentioned in class, ROC plots can be deceiving when you have very high background – very few *sleek* sequences and very many *fluffy* sequences. At this point, even if you have high sensitivity, and identify a large fraction of the *sleek* sequences, you will also identify many *fluffy* sequences as belonging to *sleek*. In this case, a useful metric is the **false discovery rate**:

- **false discovery rate (FDR)** = $\frac{\text{FP}}{\text{FP+TP}}$

The FDR tells you how much the noise is drowning out the signal. We'll also come back to this idea of FDR in future weeks and explore it further.

Practice problems

To try implementing your own Markov model for this example, download and complete these practice problems: w04-section-problems.ipynb. You will need the supplementary files: sleek_data.txt and fluffy_data.txt.

Probabilities

At the end of Sean's lecture notes, there is a nice example of how to manipulate joint probability tables. We're going to look at how we could compute some useful probabilities from these data. Open a jupyter notebook and try the following exercises to get the hang of how you might convert some of the equations mentioned

in class into Python code! The example is the following:

> Suppose we've done a single cell RNA-seq experiment, where we've treated cells with a drug (or left them untreated), and we've measured how often (in how many single cells) genes A and B are on or off. Our data consist of counts of 2000 individual cells:

```
# Counts:
            T=no              T=yes
         B=ON   B=off      B=ON  B=off
A=ON     180    80         10    360
A=off    720    20         90    540
```

In code:

```
# Represent these counts as 2D-numpy arrays
treat_no_counts = np.array([[180, 80],[720, 20]])
treat_yes_counts = np.array([[10, 360],[90, 540]])
counts = np.array([treat_no_counts, treat_yes_counts])

print('T=no')
print(counts[0])

print('\nT=yes')
print(counts[1])
```

Joint probability

> The **joint probabilities** $P(A, B, T)$ sums to one over everything. So normalize by dividing everything 2000 (the total # of cells):

```
# P(A,B,T)
            T=no              T=yes
         B=ON   B=off      B=ON   B=off
A=ON     0.09   0.04       0.005  0.18
A=off    0.36   0.01       0.045  0.27
```

In code:

```
# Double check the total number of cells in 2000
```

```
n_cells = np.sum(counts)
print('Total number of cells in %i' % n_cells)

# Normalize probabilities by dividing by 2000
joint = counts / n_cells

print('T=no')
print(joint[0])

print('\nT=yes')
print(joint[1])

np.sum(joint)
```

Marginalization

> Any **marginal distribution** is a sum of the joint probabilities over all the variables you don't care about, leaving the ones you do. For example, to get $P(T)$, we sum over A,B: $P(T) = \sum_{A,B} P(A, B, T)$, which leaves:

```
# P(T)
           T=no              T=yes
           0.5               0.5
```

In code:

```
# Get P(T) by marginalizing (summing) over A and B
print('P(T=no) = %.1f' % np.sum(joint[0]))
print('P(T=yes) = %.1f' % np.sum(joint[1]))
```

Conditional distributions

> A **conditional distribution** can be arrived at in a couple of different ways. One is to imagine building a separate joint probability table for each value of the condition. So we could for example focus just on the condition T=no; the subtable with T=no is:

```
# Counts
             T=no
         B=ON    B=off
```

```
A=ON     180    80
A=off    720    20
```

> and if we normalize that we get $P(A, B \mid T = no)$:

```
# P(A,B | T=no)
         B=ON   B=off
A=ON     0.18   0.08
A=off    0.72   0.02
```

In code:

```
# Get P(A,B | T=no) by isolating T=no and renormalizi
joint_treat_no = joint[0]
joint_treat_no = joint_treat_no / np.sum(joint_treat_

print('P(A,B | T=no):')
print(joint_treat_no)

np.sum(joint_treat_no)
```

Marginalizing a conditional

> If we marginalize a conditional distribution, the conditioning stays as it was. For example, $P(B \mid T = \text{no}) = \sum_A P(A, B \mid T = \text{no})$, so:

```
# P(B | T=no):
            T=no
         B=ON  B=off
         0.9   0.1
```

In code:

```
# Get P(B | T=no) by marginalizing (summing) over A
print('P(B | T=no): ')
np.sum(joint_treat_no, axis=0)
```

A note about downloading files

If you have trouble the downloading the files we link, here's an alternate approach using the command line:

For Macs, use `cd` to navigate to the directory where you want to save the notebook, then use `curl` to download the files directly from the website link (I got this link by right clicking on the notebook link above and selecting `copy link address`):

```
cd mcb112

curl http://mcb112.org/w04/w04-section-problems.ipynb
curl http://mcb112.org/w04/sleek_data.txt -o 'sleek_d
curl http://mcb112.org/w04/fluffy_data.txt -o 'fluffy

jupyter notebook
```

The `-o` option lets us specify what name we want the downloaded file to have. Here, we've named the file `w04-section-problems.ipynb`, so we should see that in our files now.

For Windows with the Ubuntu subsystem, use `cd` to navigate to the directory where you want to save the notebook, then use the `wget` command:

```
cd mcb112

wget http://mcb112.org/w04/w04-section-problems.ipynb
wget http://mcb112.org/w04/sleek_data.txt
wget http://mcb112.org/w04/fluffy_data.txt

jupyter notebook
```
