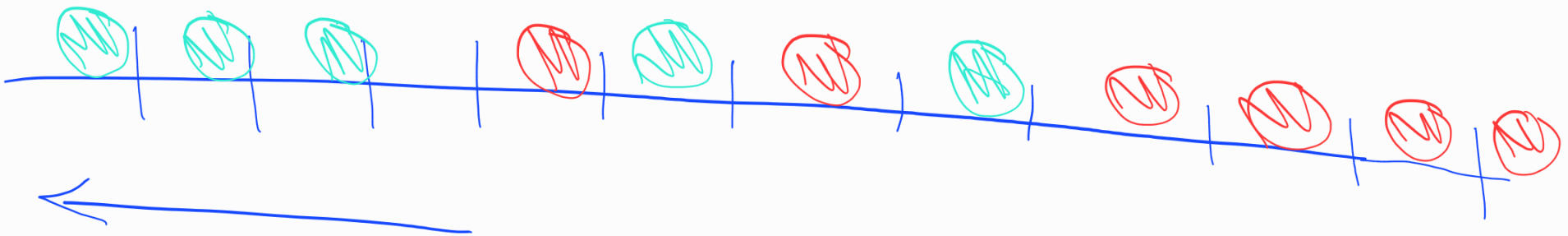
The Problem

* We've got a cancer drug.
  - It works great for some people.
  - ... but it makes other people feel worse.
* How do we decide to give the drug to?
  - Maybe gene expression can help us decide.

Using one gene to decide...

Transcription for gene X



Fewer Transcripts

More transcripts

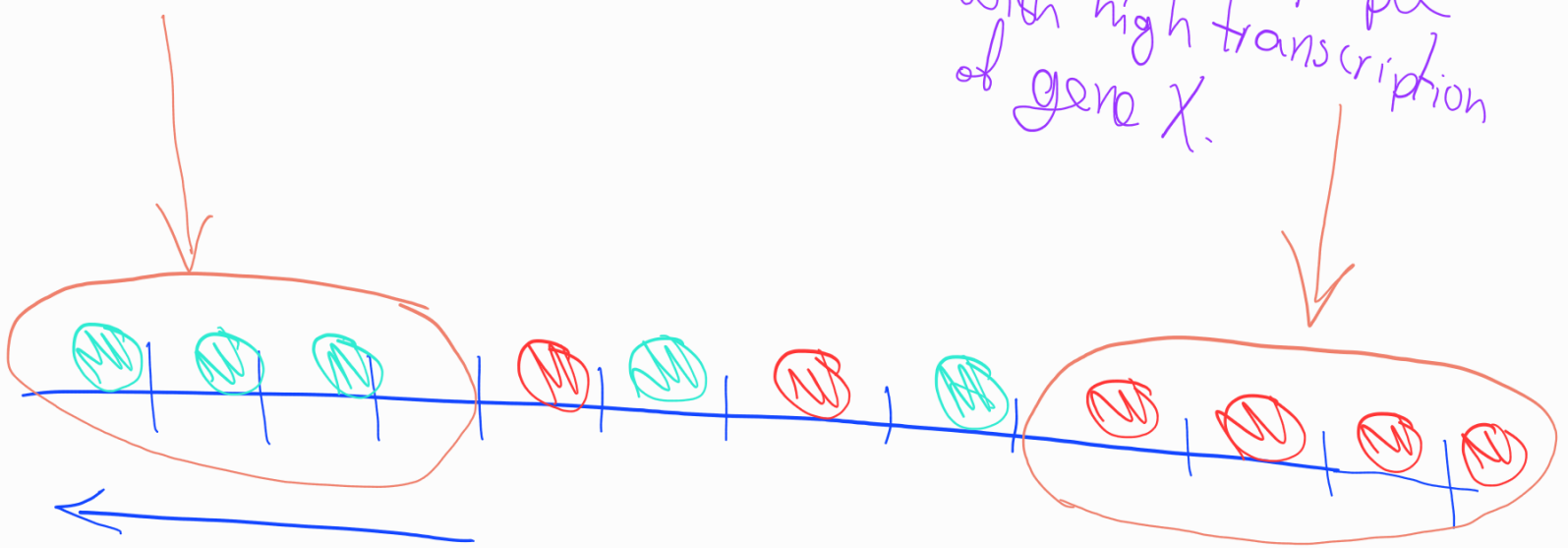
= The drug works!

= The drug does not work :(

Using one gene to decide...

For the most part, the drug in people with low transcription of gene X.

And, for the most part the drug does not work in people with high transcription of gene X.



Fewer Transcripts

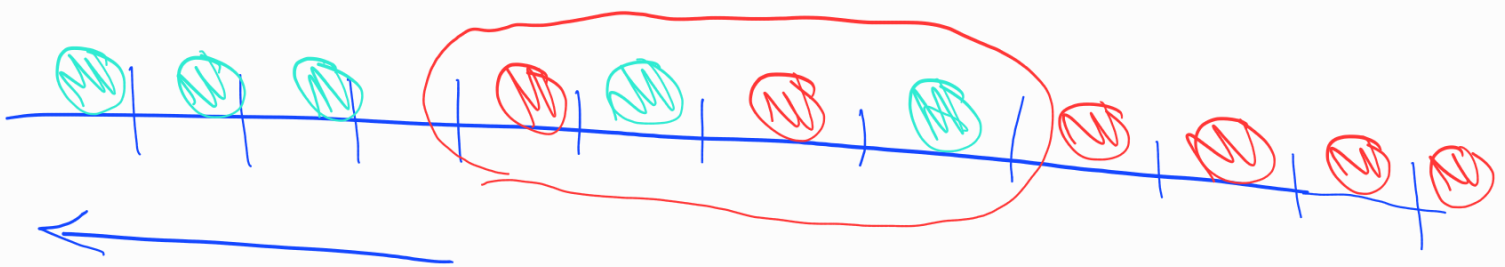
More transcripts

= The drug works!

= The drug does not work :(

Using one gene to decide...

However, there is overlap and no obvious "cutoff" for who to give the drug to



Fewer Transcripts

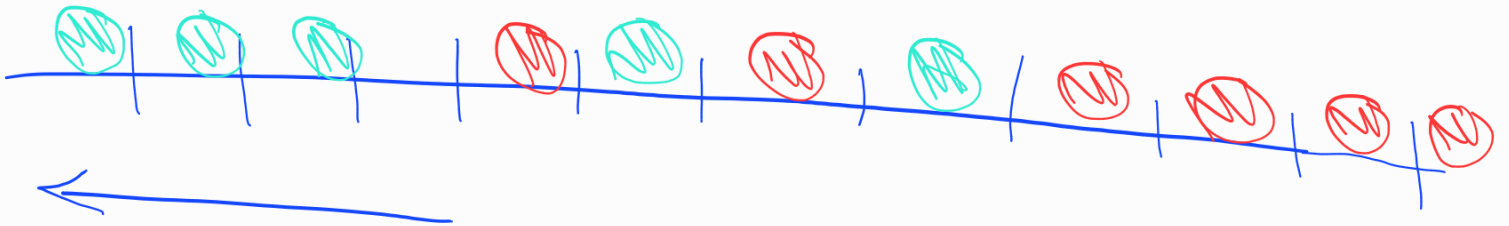
More transcripts

= The drug works!

= The drug does not work :(

Using one gene to decide...

In summary, Gene X does an ok job at telling us who should take the drug (and who shouldn't) Can we do better? What if we used more than one gene?



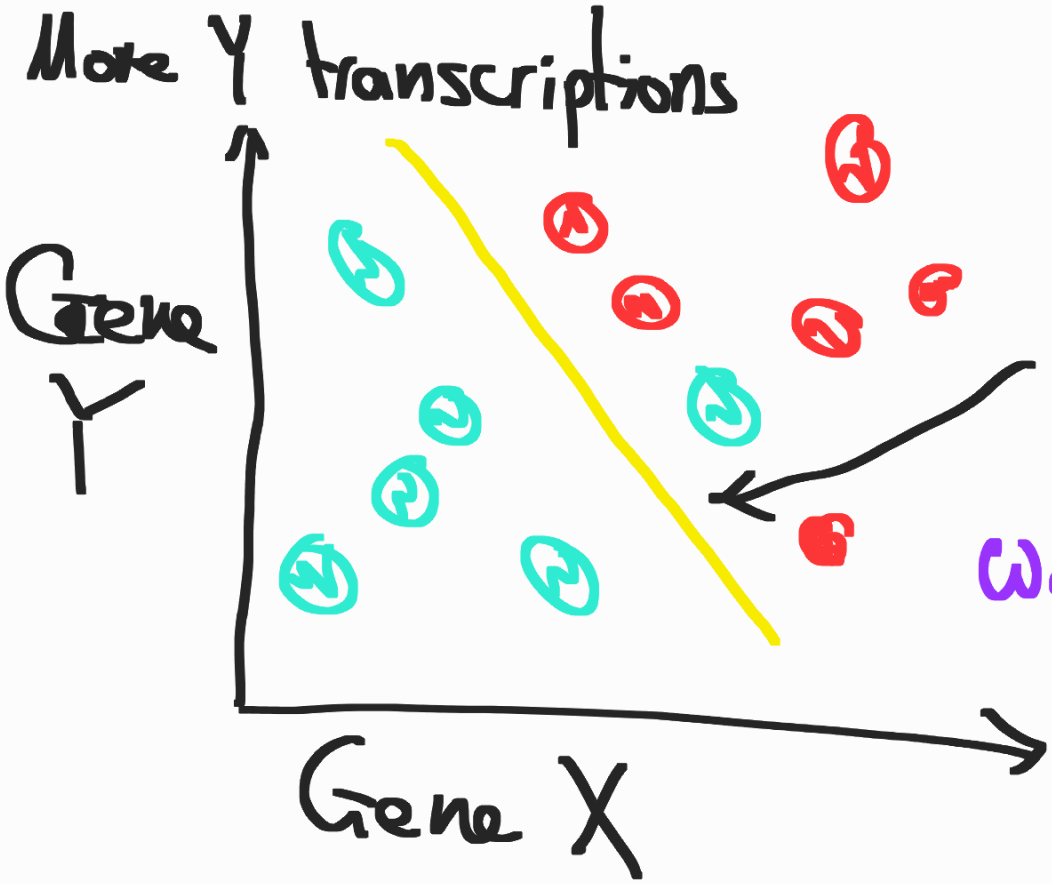
Fewer Transcripts

More transcripts

= The drug works!

= The drug does not work :(

Using two genes to decide...



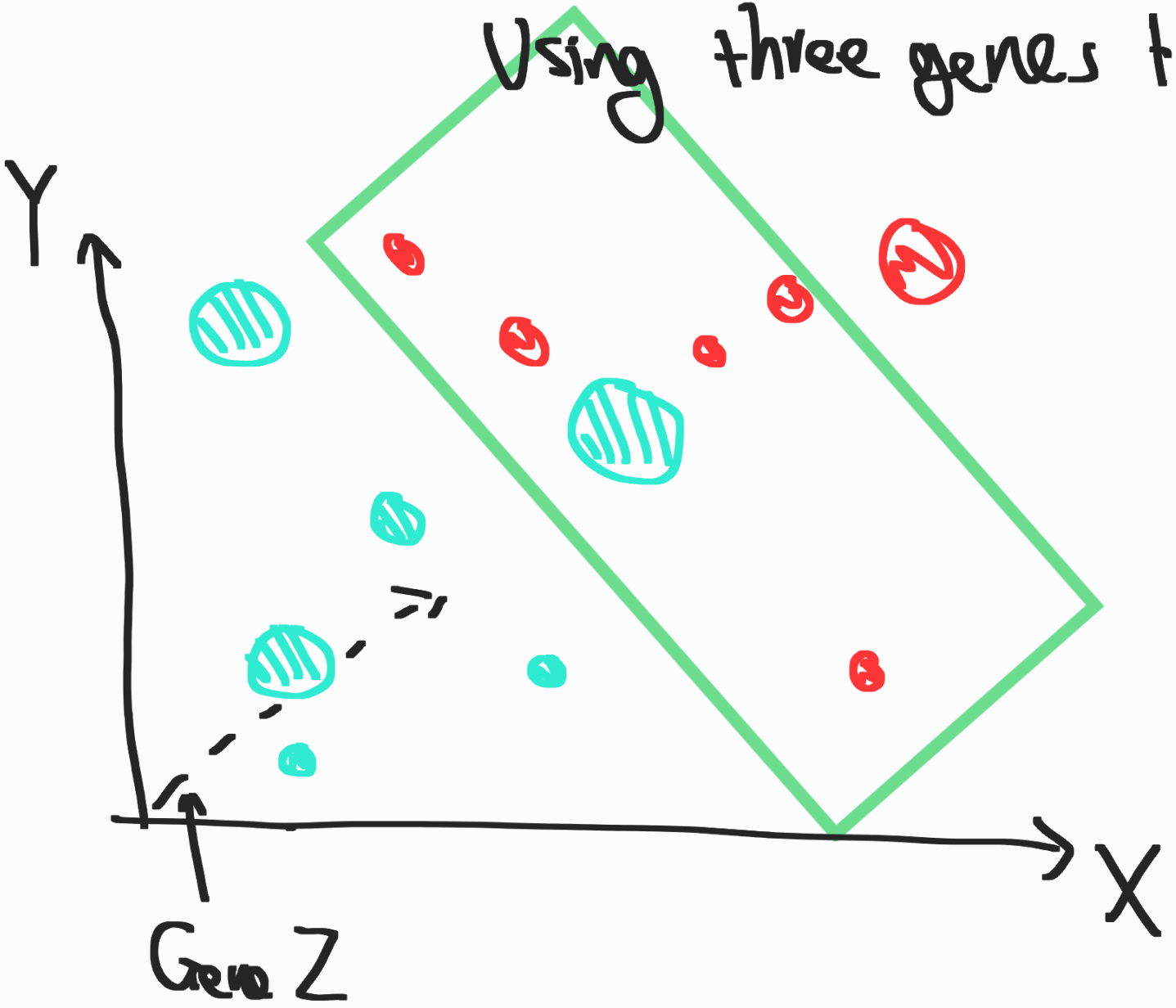
Two genes do a better job separating the two categories.

Would 3 genes be even better?

= The drug works!

= The drug does not work. :(

Using three genes to decide.



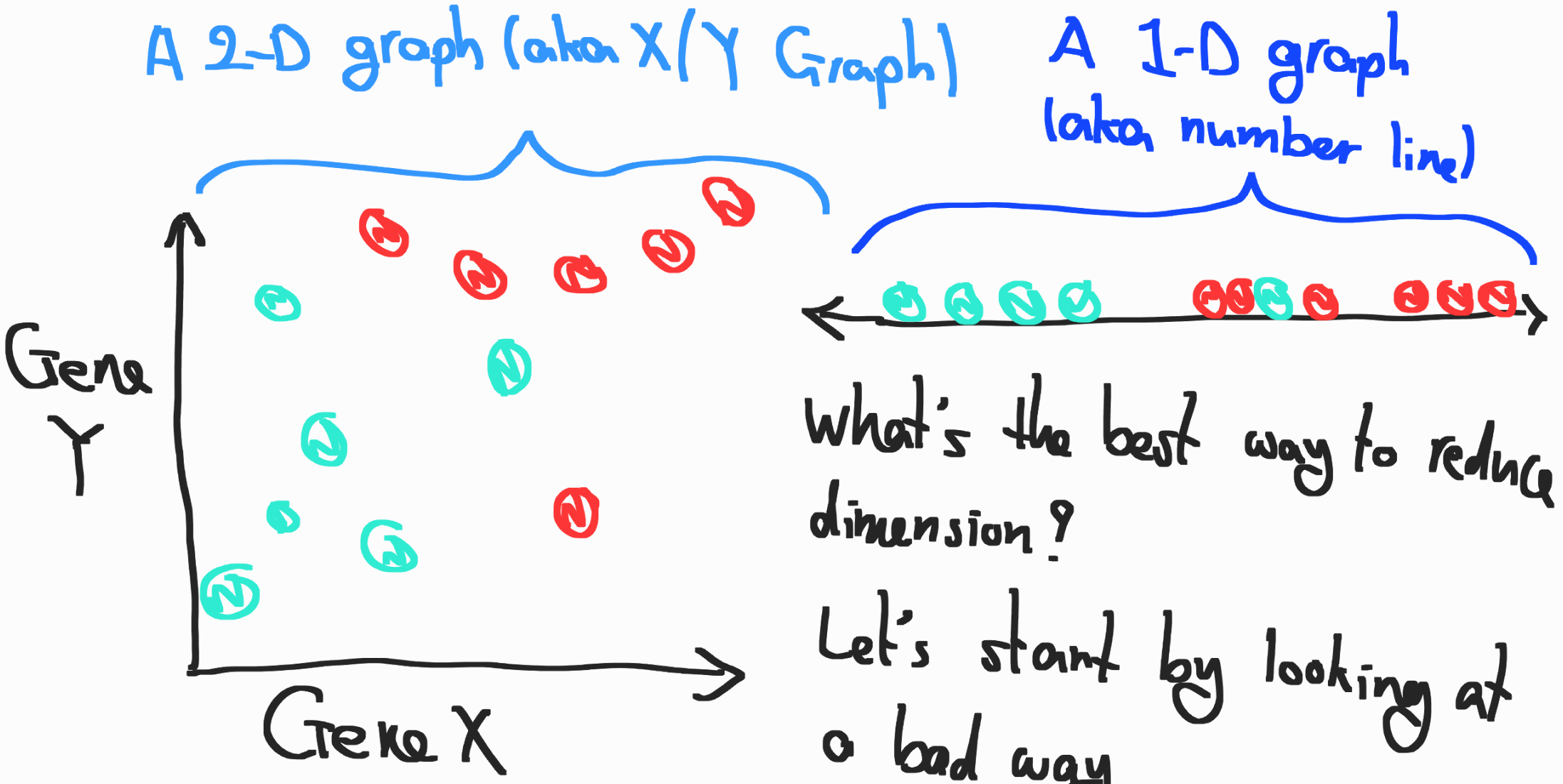
What if we need four (or more) genes to separate the two categories?

Four or more genes...

- We can't draw a 4-D graph... :(
- We ran into this same problem we talked about PCA.
- PCA reduces dimensions by focusing on the genes with the most variation.
  - This is useful for plotting data with a lot of dimensions (or a lot of genes) onto a simple X/Y plot.
  - However, it this case we're not interested in the genes with the most variation.
  - Instead, we're interested maximizing the separability between the two groups so we can make the best decisions.

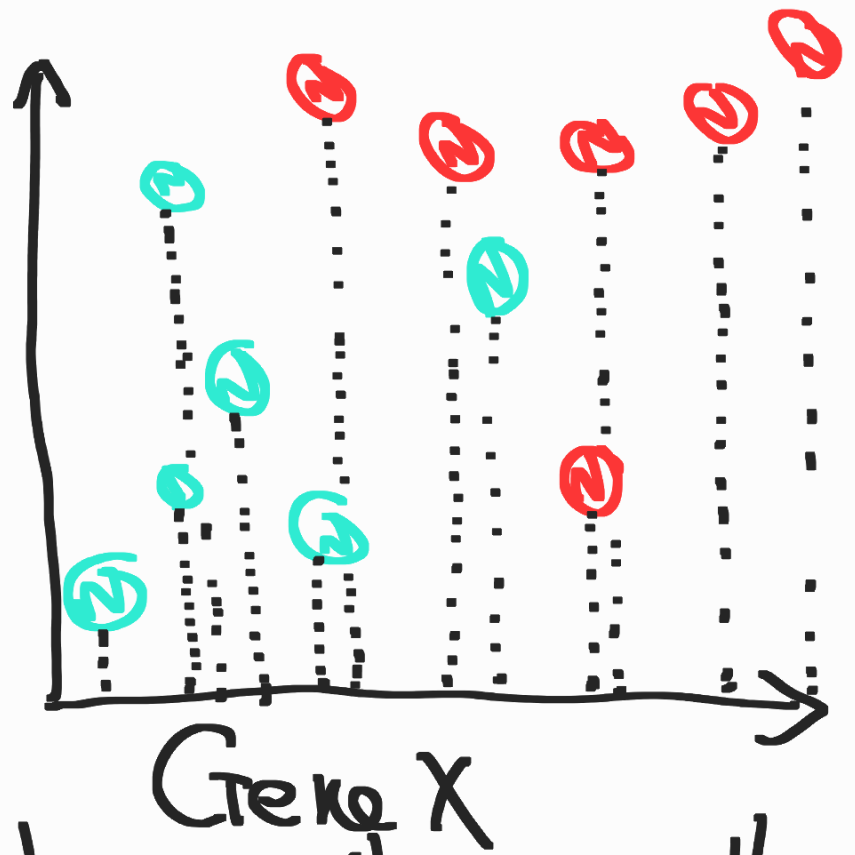
-Linear Discriminant Analysis (LDA) is like PCA, but it focuses on maximizing the seperablity among known categories.

A super simple example



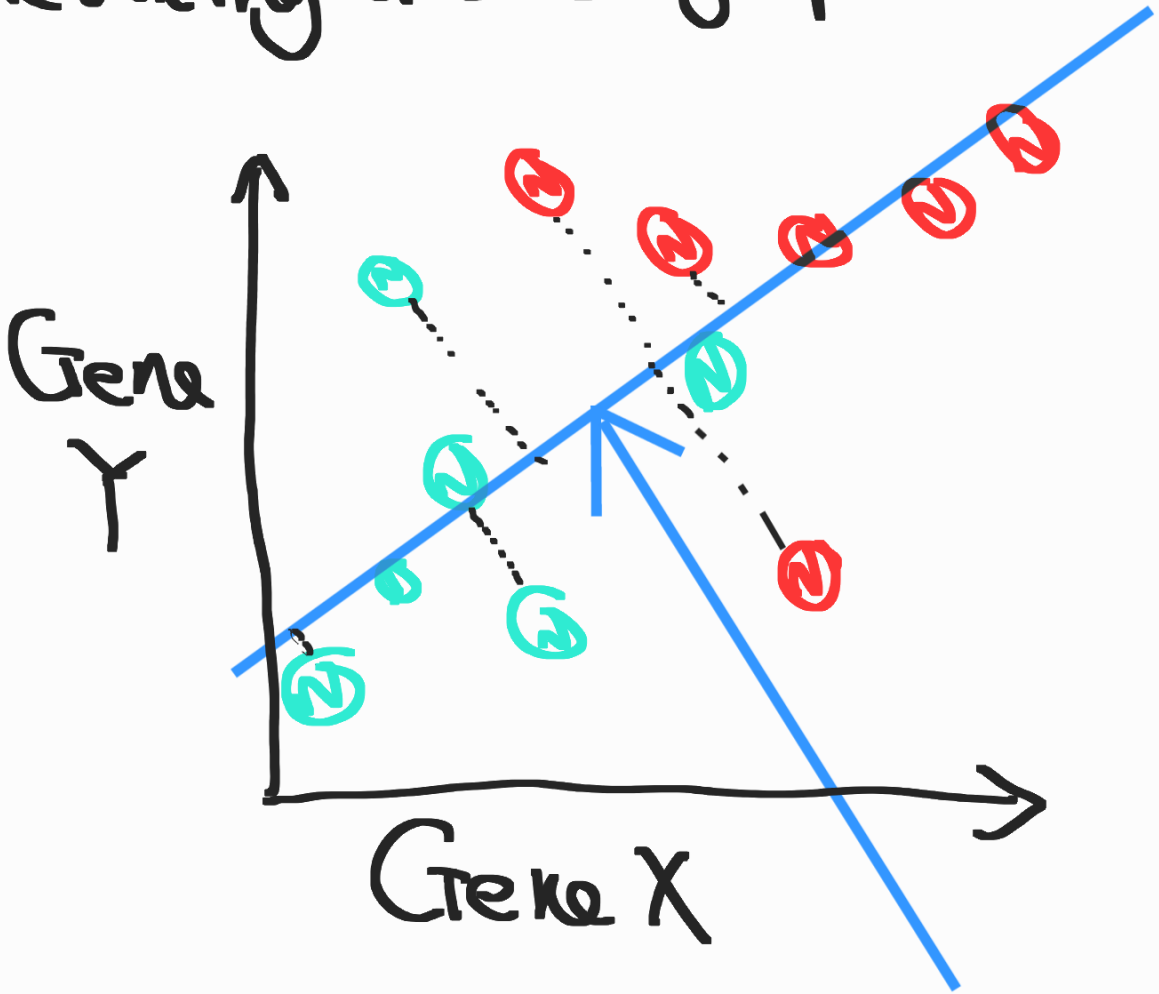
Reducing a 2-D graph to a 1-D graph

one bad option would be to ignore Gene Y



This way is bad because it ignores the useful information that Gene Y provides.

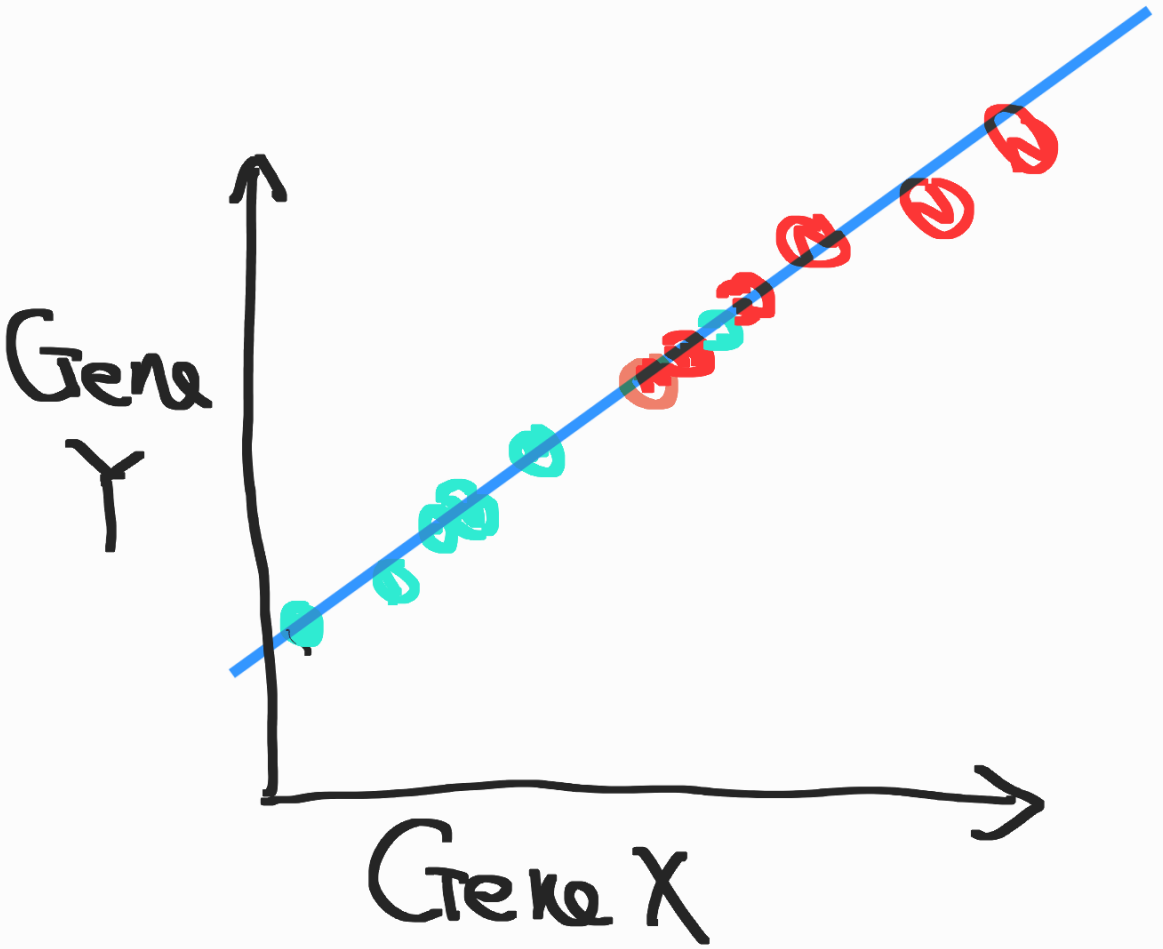
Reducing a 2-D graph to 1-D graph with LDA



LDA uses both genes to create new axis ...

... and projects the data onto this new axis in a way to maximize the separation of the two categories.

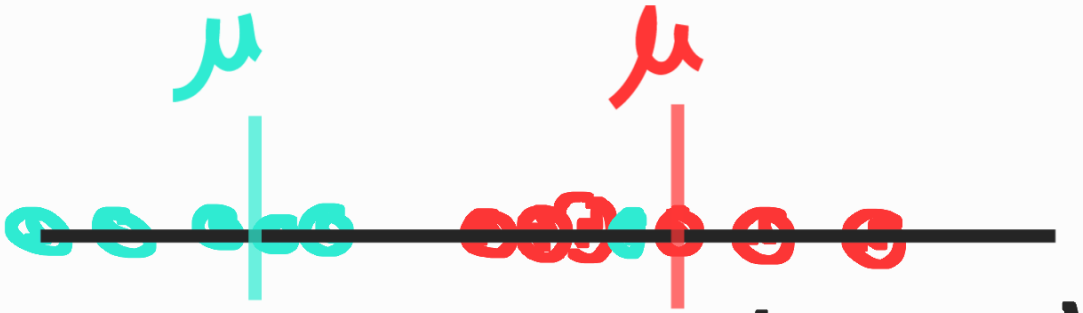
How does it do that?



How LDA creates a new axis...

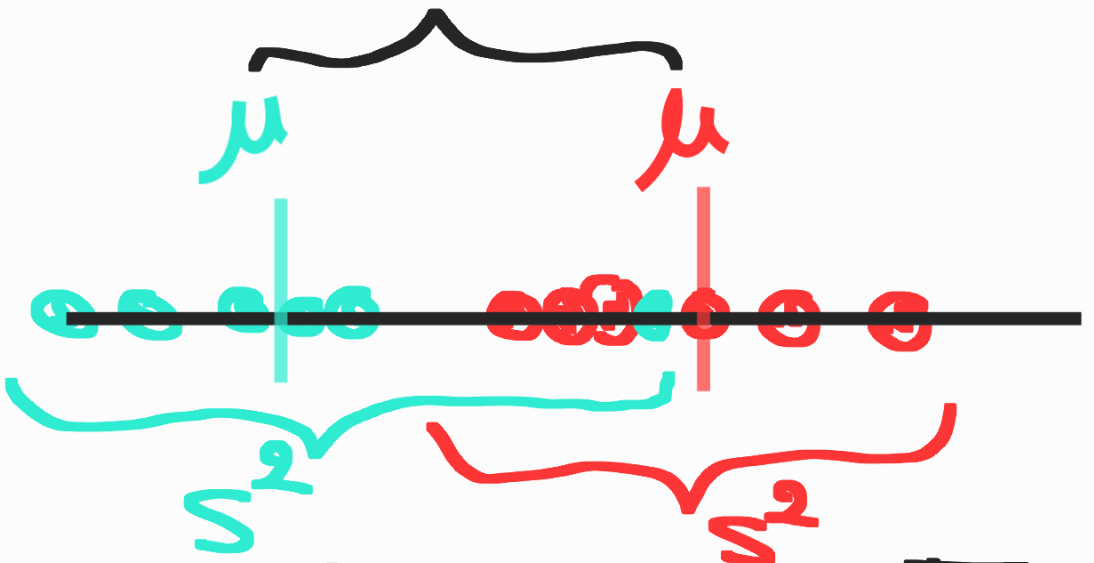
The new axis is created according to two criteria (considered simultaneously):

1) Maximize the distance between means:



2) Minimize the variation (which LDA calls "scatter" and is represented by s^2) within each category.

1) Maximize the distance between means



$$\frac{\overbrace{(\mu - \mu)}^{d}{}^2}{s^2 + s^2} \rightarrow \frac{\text{ideally large}}{\text{ideally small}}$$

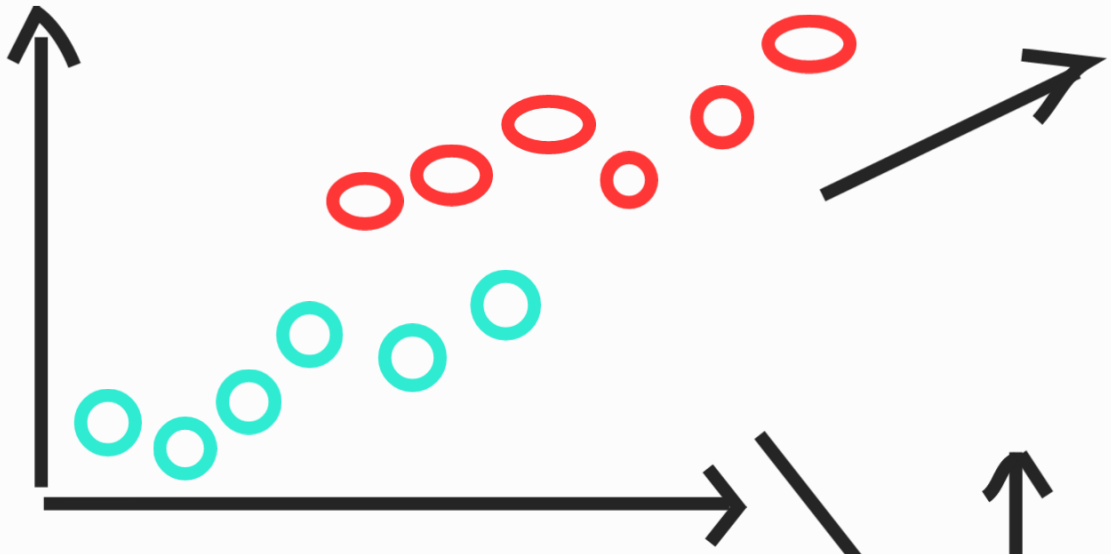
This is the scatter around green dots.

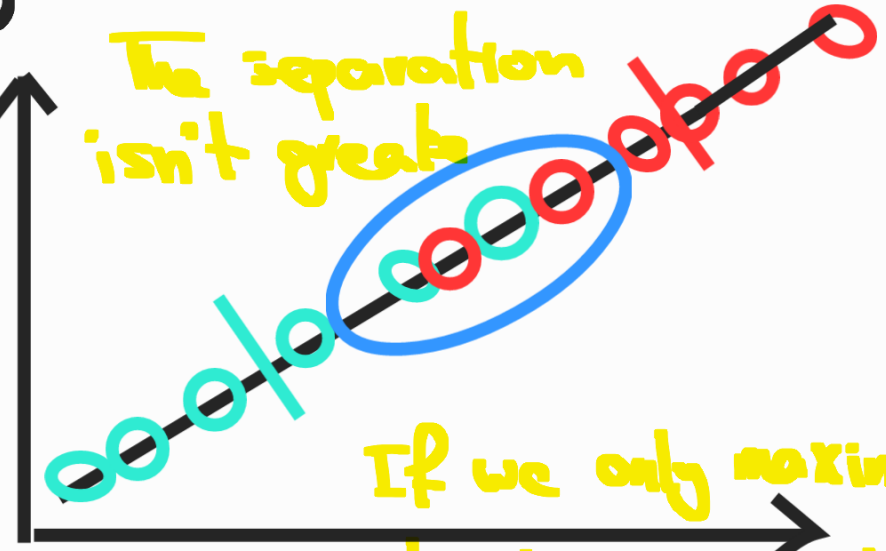
This is the scatter around red dots.

2) Minimize the variation within each category.

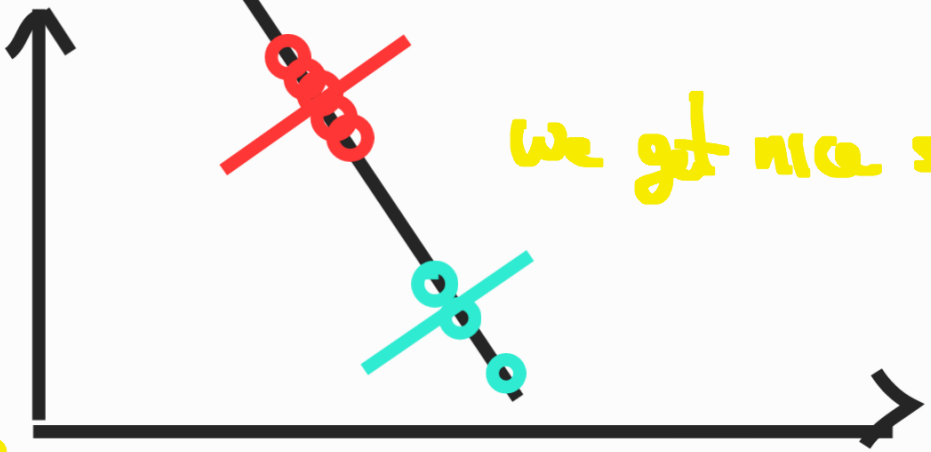
$$\frac{d^2}{s^2 + s^2}$$

An example showing why both distance and scatter are important.





If we only maximize the distance between means.



We get nice separation

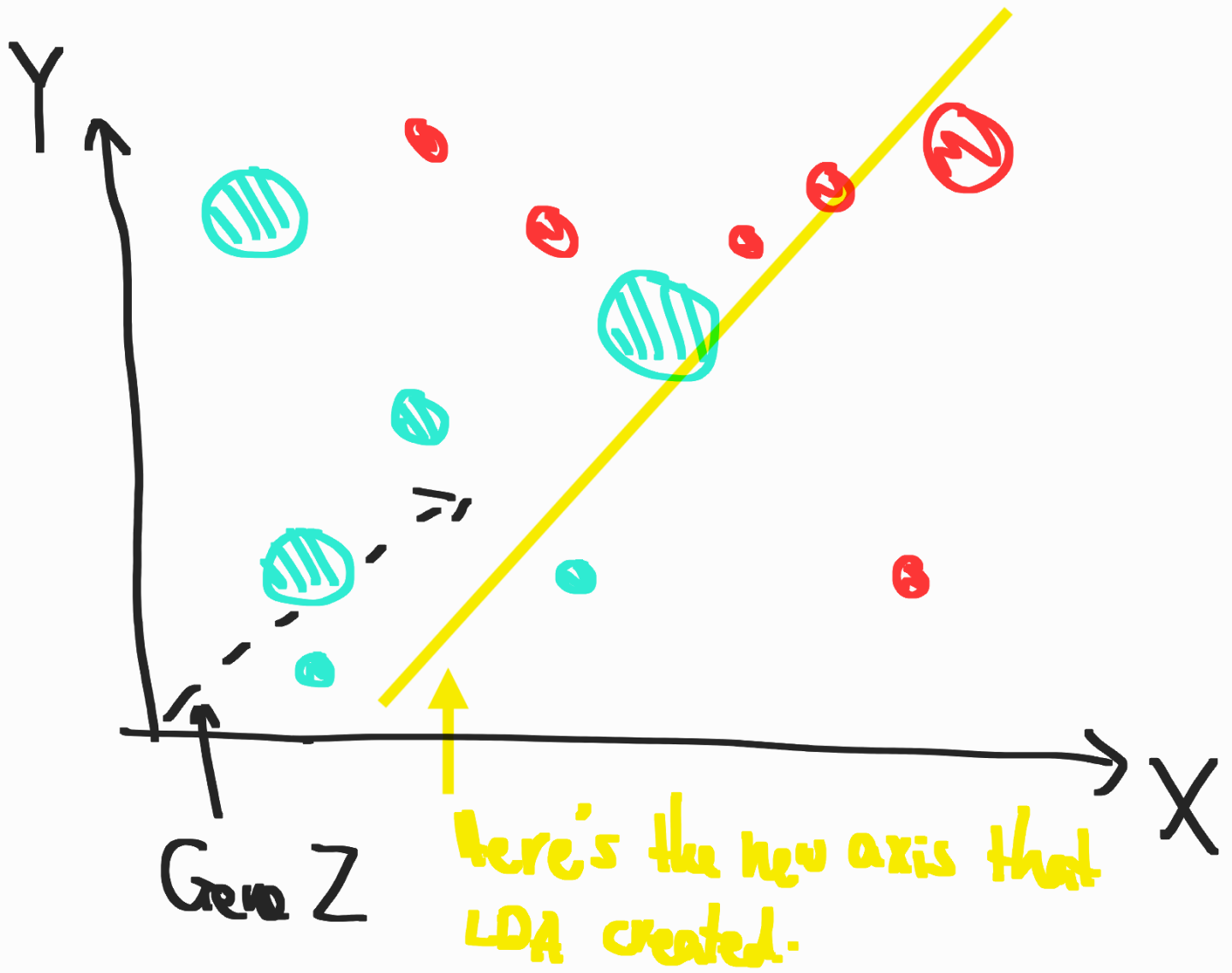
However, if we optimize the distance between means and scatter ...

What if we have more than 2 genes

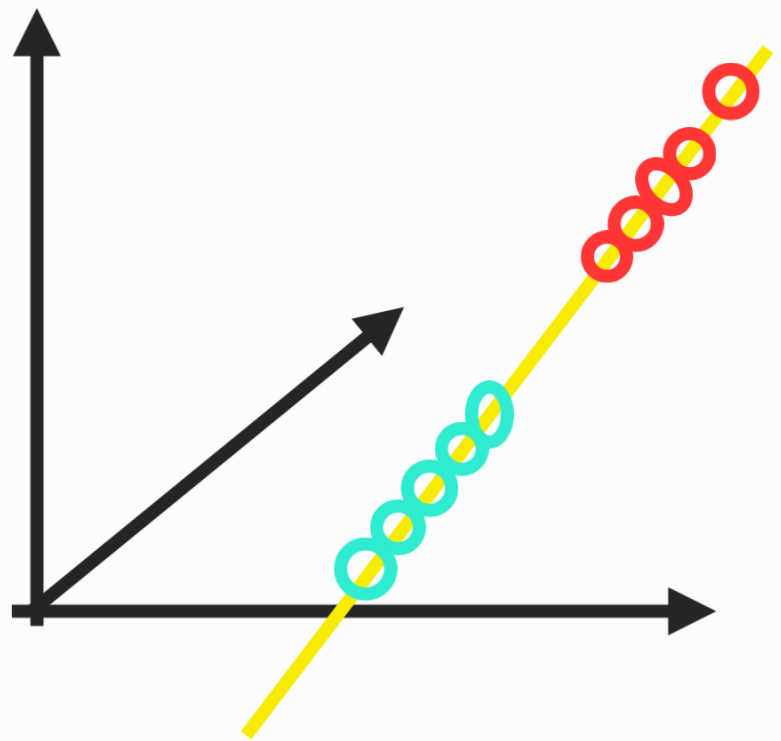
(more than 2 dimensions)?

- The process is the same:
  - Create an axis that maximizes the distance between the means for the two categories while minimizing scatter.

LDA with 3 genes.



The data are projected onto the new axis.



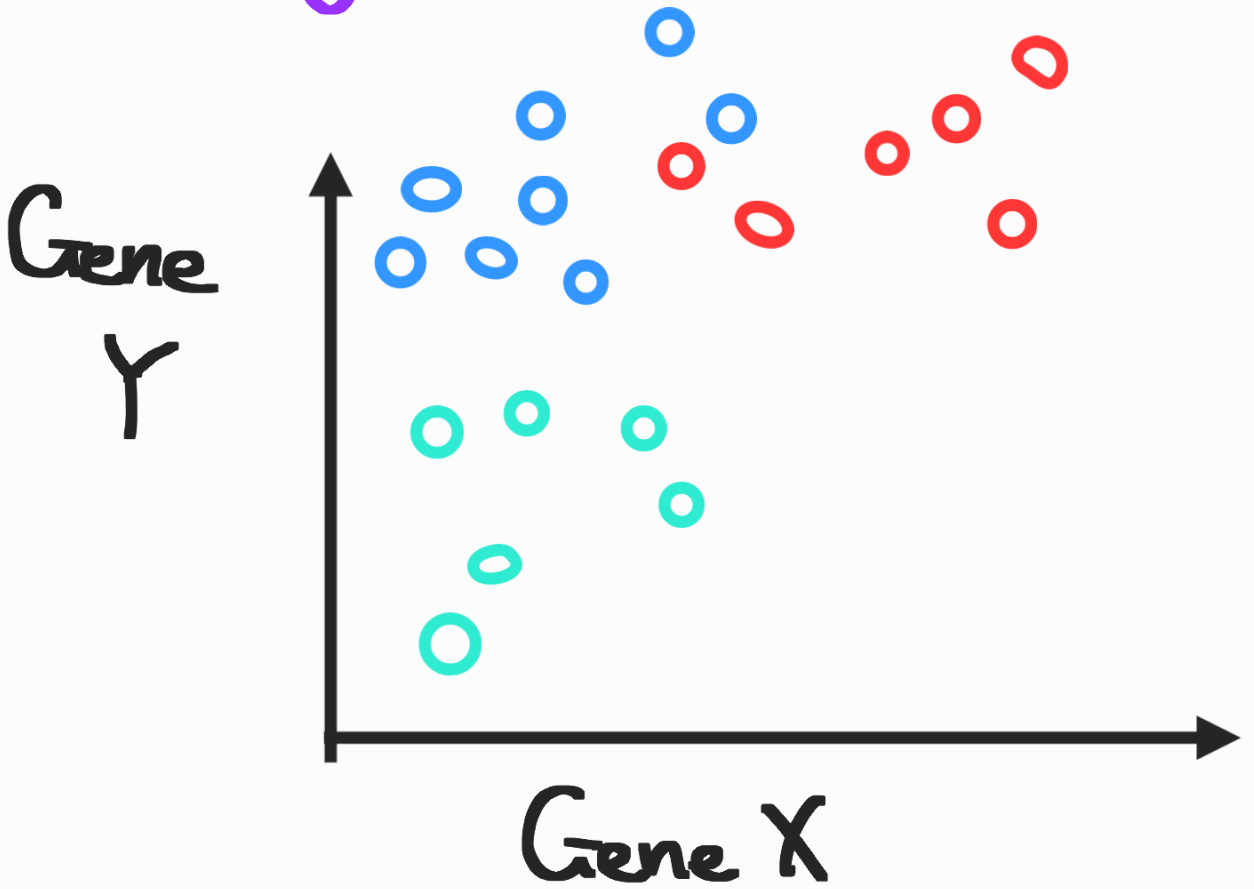
The axis was chosen to maximize the distance between two means (between the two categories) while minimizing the "scatter".

what if we have 3 categories?

- Two thing change, but barely ...

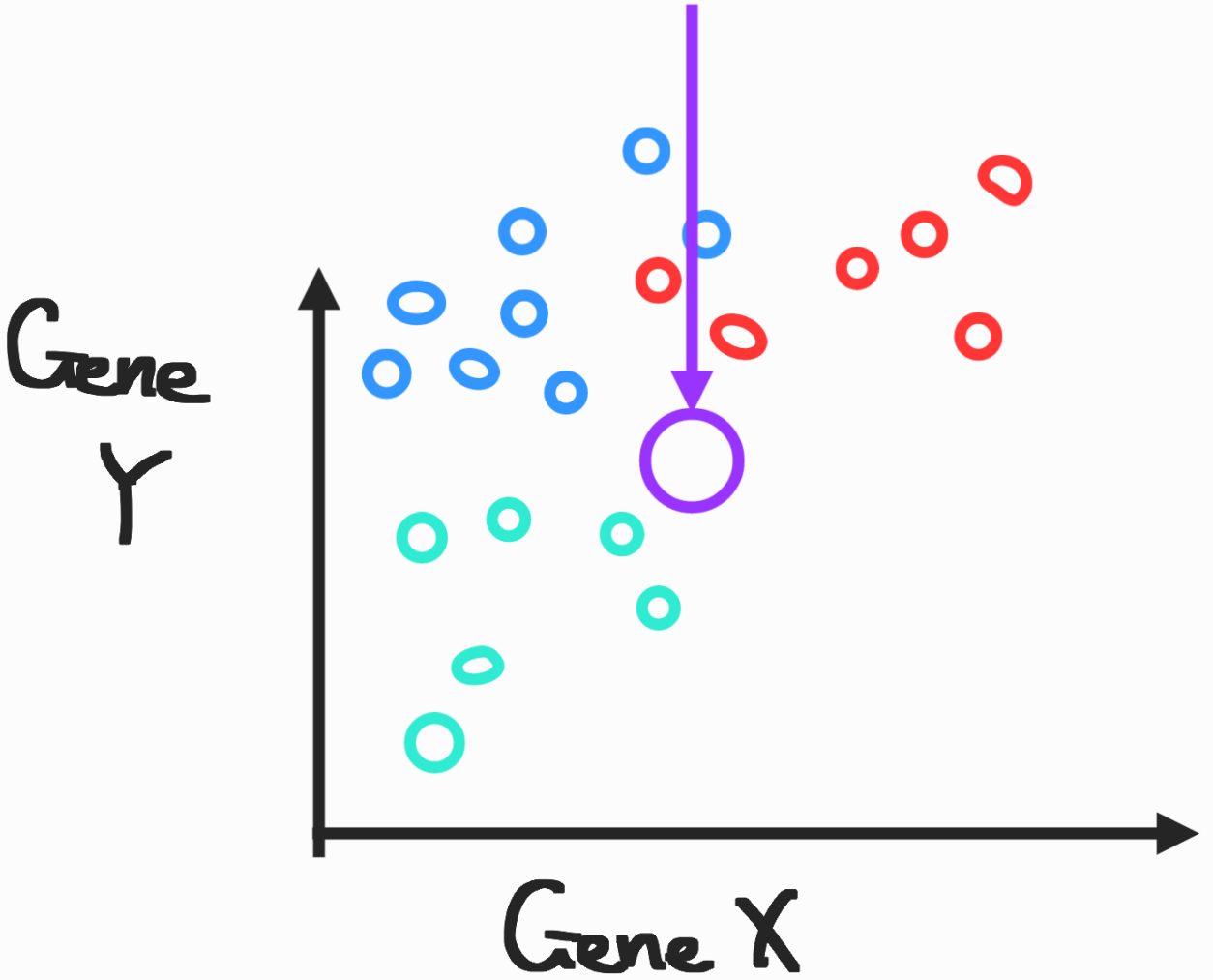
LDA for 3 categories

The first difference is how you measure the distances among the means.



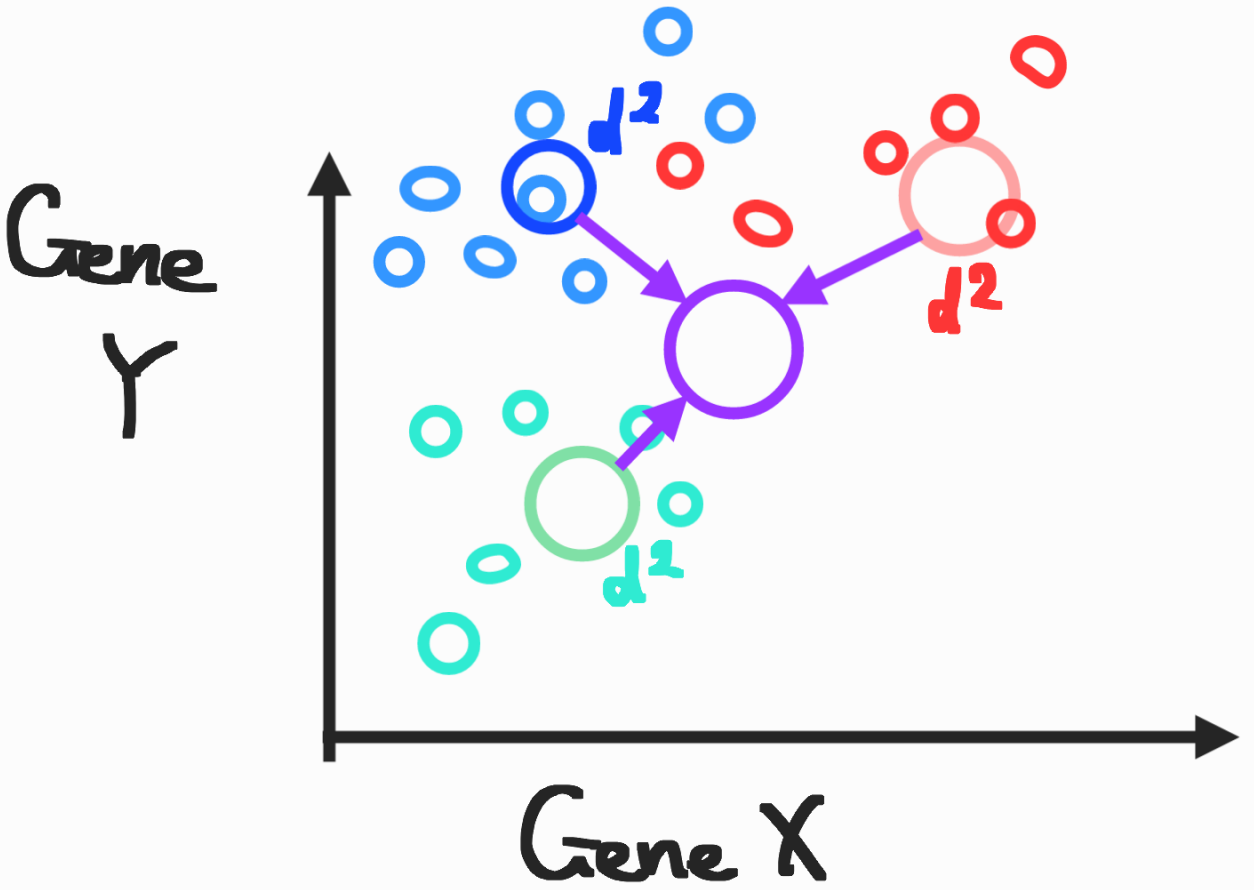
LDA for 3 categories

Find the point that is central to all of data.



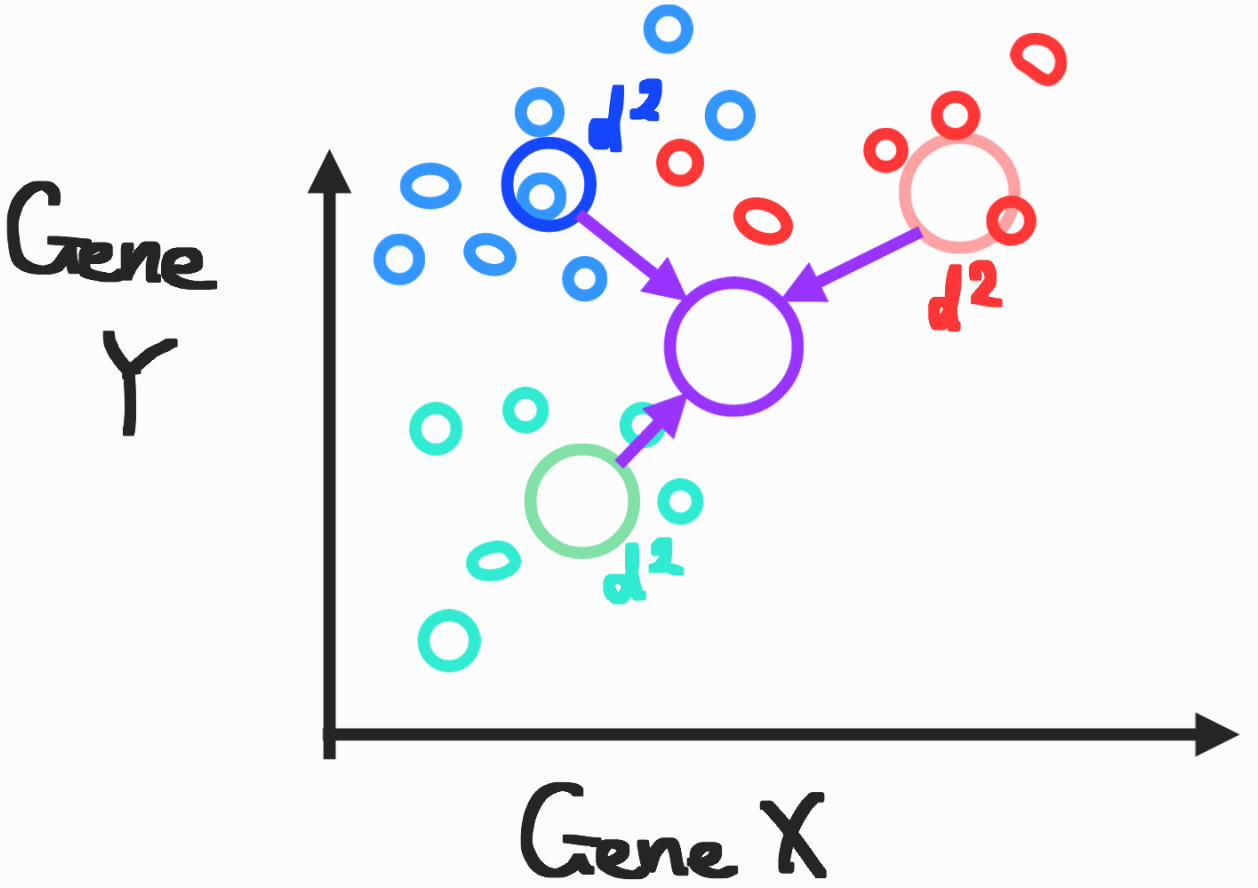
LDA for 3 categories

Then measure the distances between a point that is central in each category and the main central point.



LDA for 3 categories

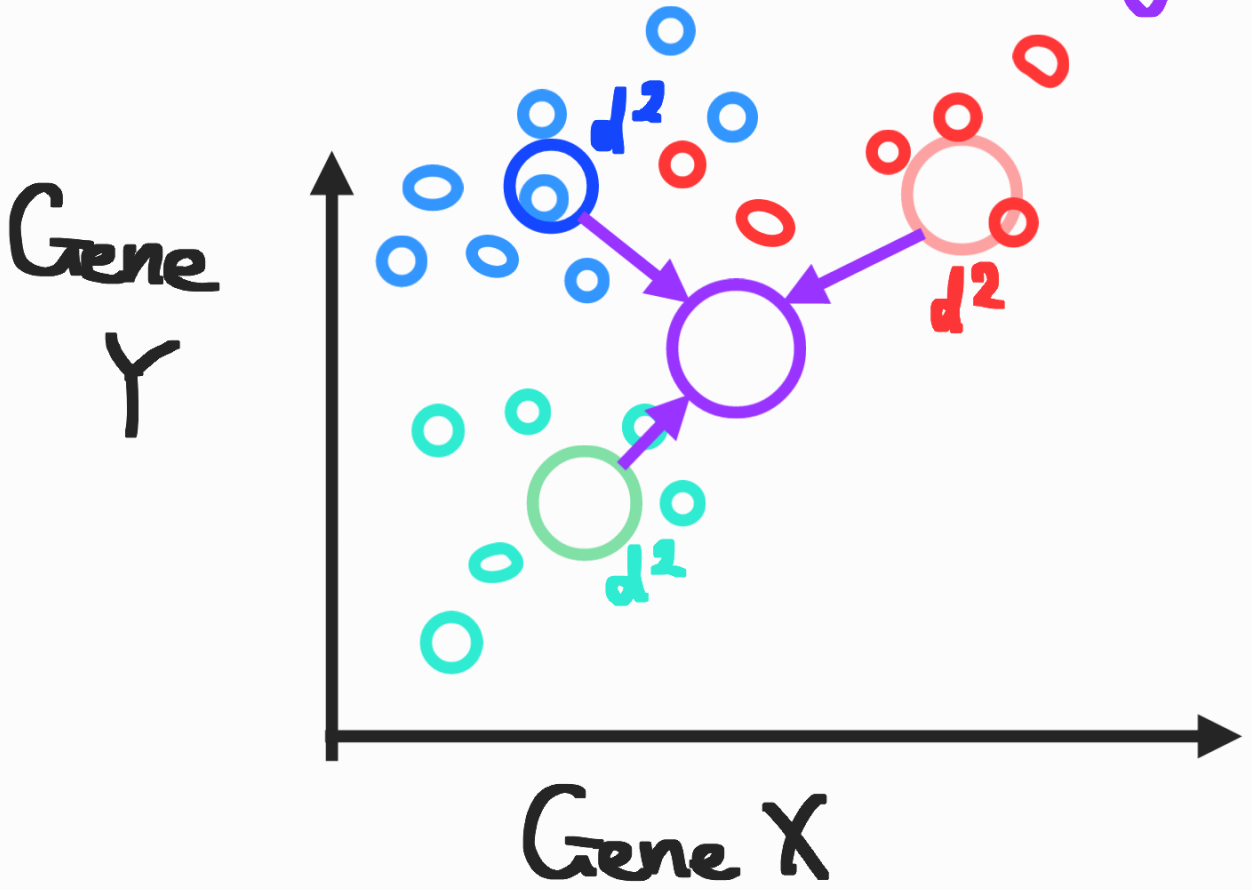
Now maximize the distance between each category and the central point while minimizing the scatter for each category.



LDA for 3 categories

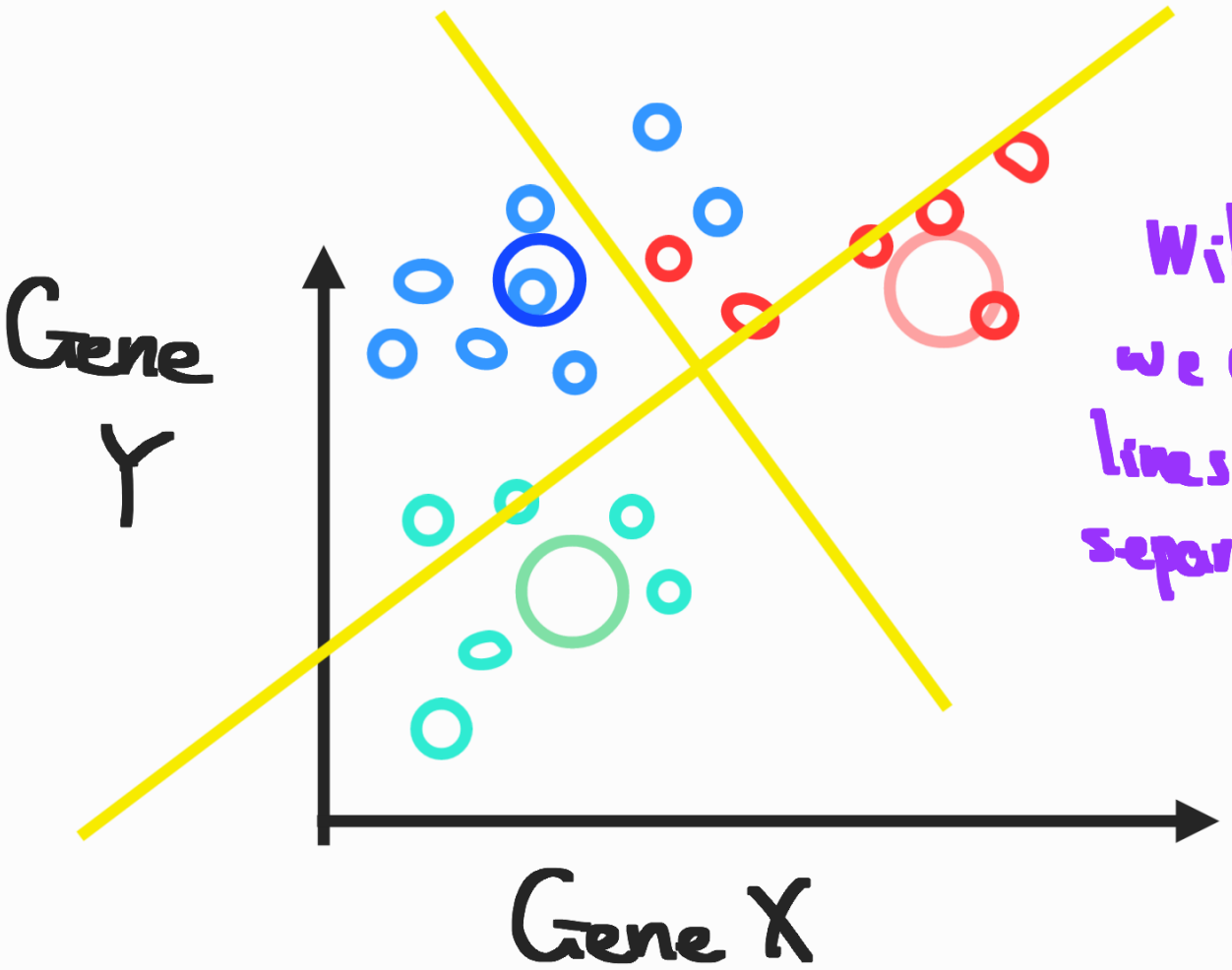
$$\frac{d^2 + d^2 + d^2}{s^2 + s^2 + s^2}$$

This is the same equation as before, but now there are terms for the blue category.



LDA for 3 categories

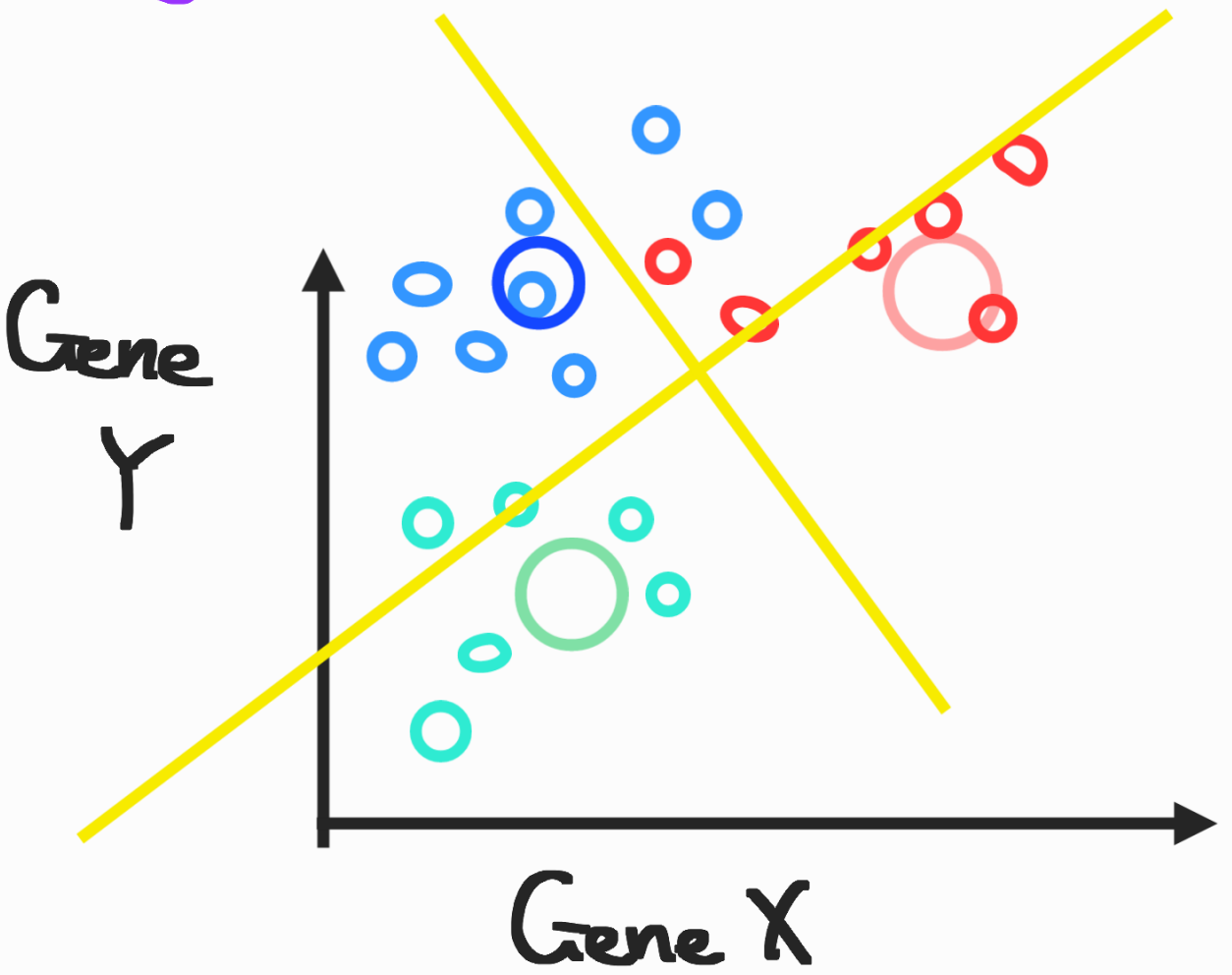
The second difference is LDA creates 2 axes to separate the data. This is because the 3 central points for each category define a plane. (2 points define a line, 3 points define a plane--)



With three points we can draw two lines to optimize separation.

LDA for 3 categories

When we only use 2 genes, this is no big deal. The data started out on a X/Y plot and plotting them on a new X/Y plot doesn't change much



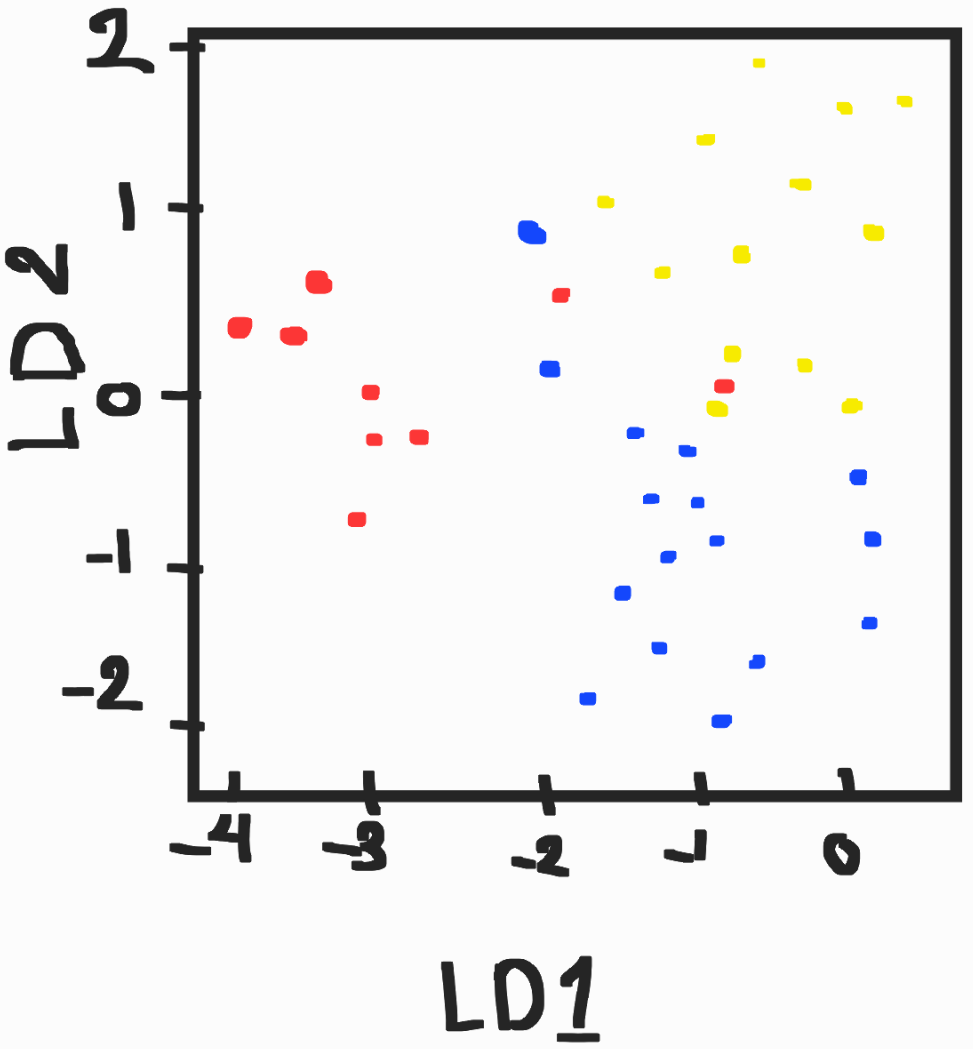
LDA for 3 categories

When we only use 2 genes, this is no big deal. The data started out on a X/Y plot and plotting them on a new X/Y plot doesn't change much

But what if we used data from 10,000 genes?
That would mean we'd need 10,000 dimensions to draw the data.

Suddenly, being able to create 2 axes that maximize the separation of three categories is super cool!!!

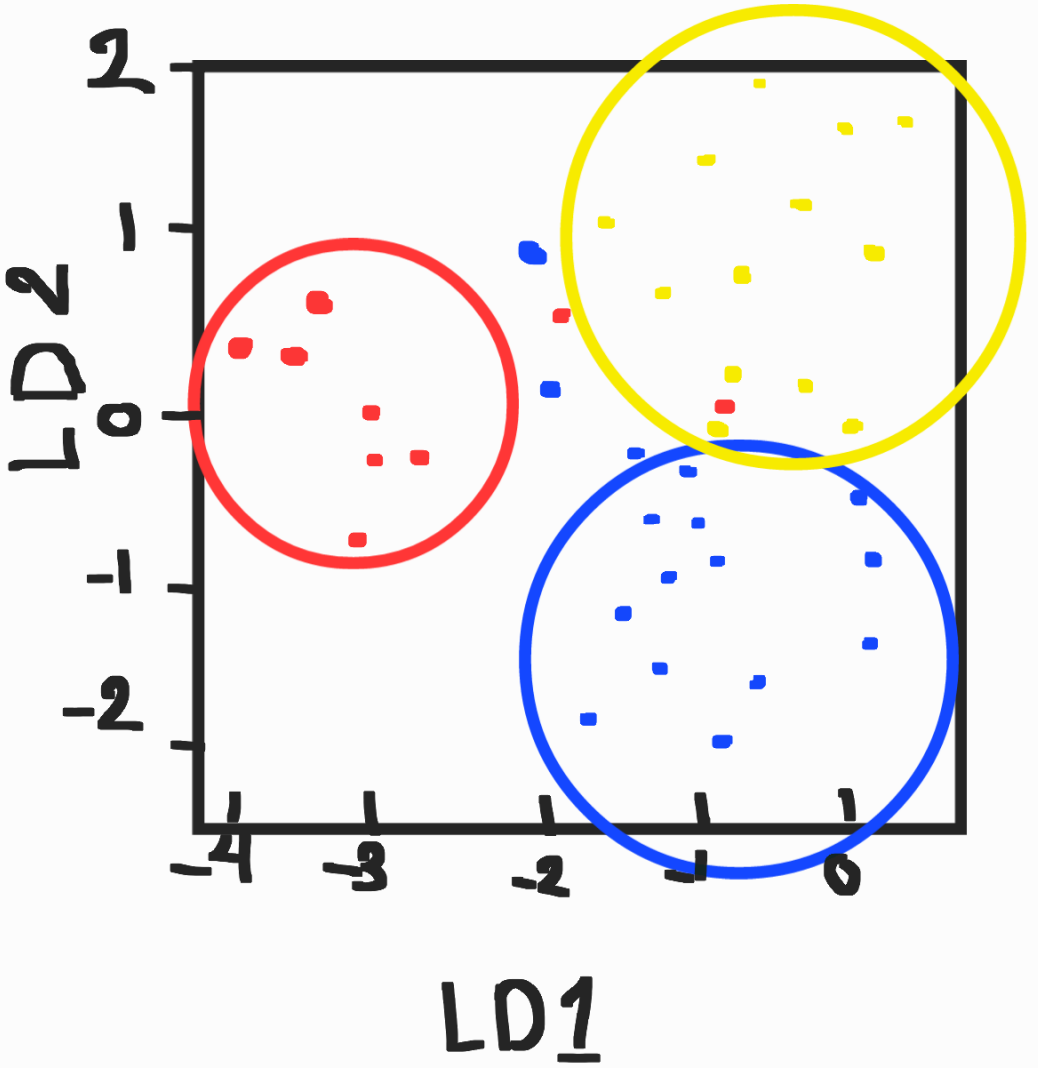
LDA with 3 categories and 10,000 genes



Plotting the raw data would require 10,000 axes.

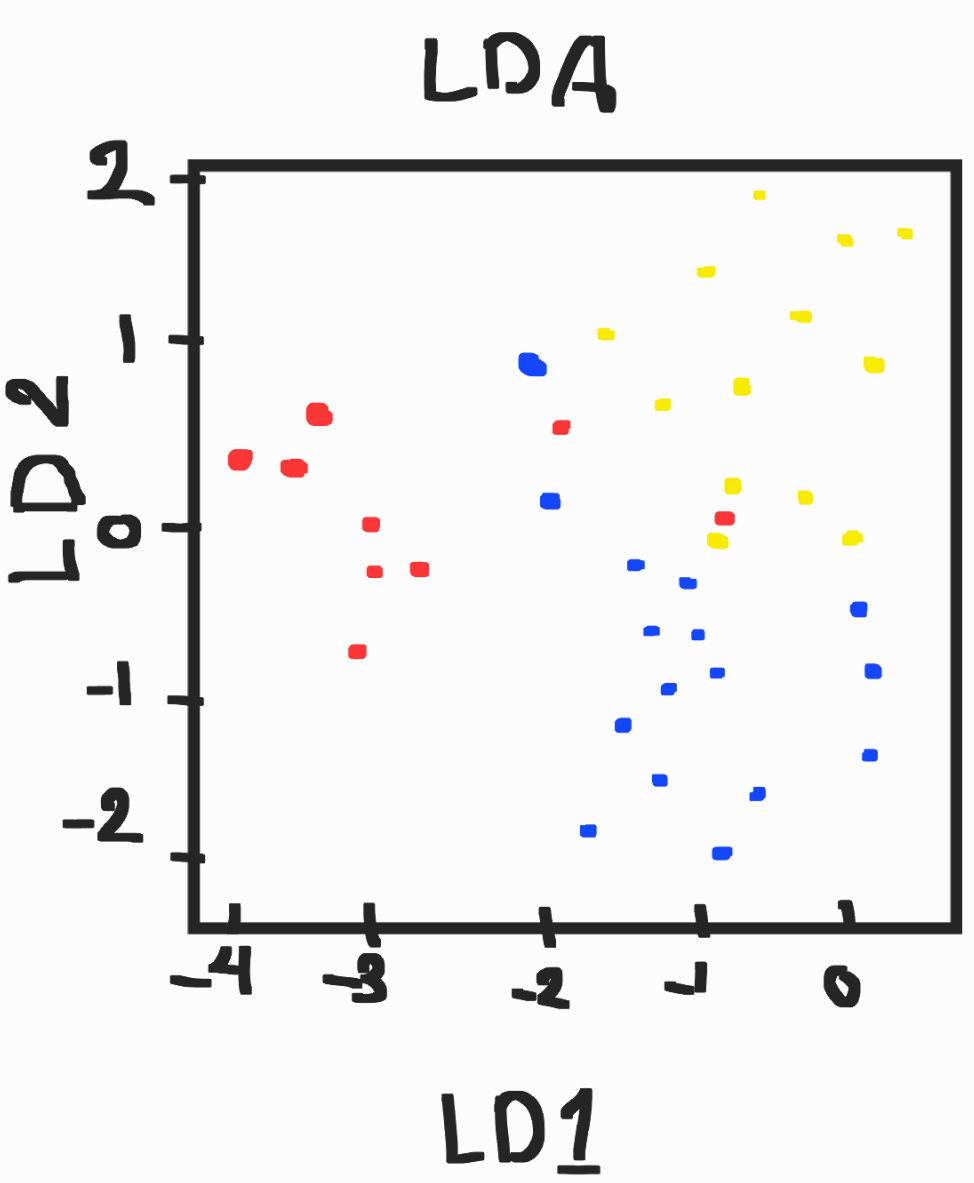
We used LDA to reduce that number to 2.

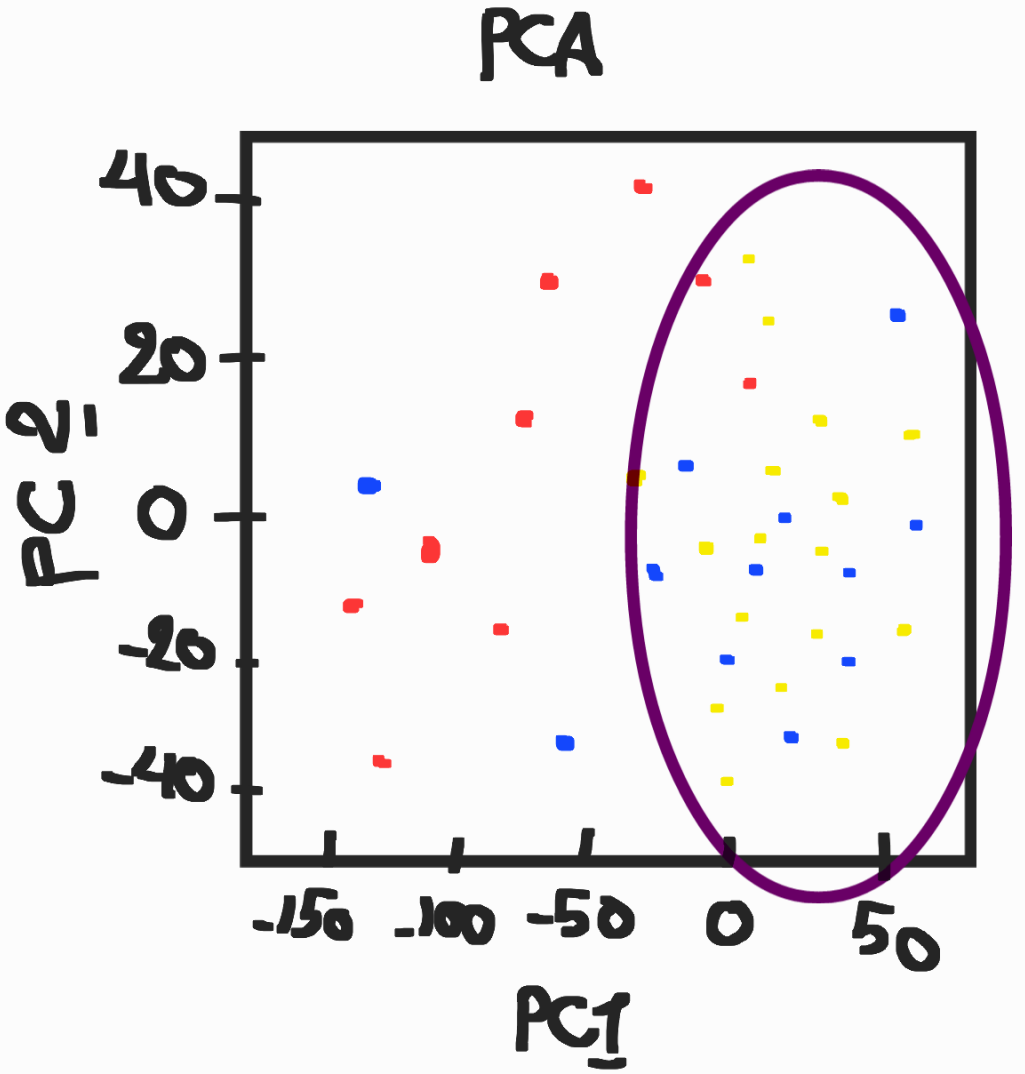
LDA with 3 categories and 10,000 genes



Although the separation isn't perfect, it is still easy to see three separate categories.

Comparing LDA to PCA with 10,000 genes.





Separation isn't nearly as good.

Similarities between PCA and LDA

- Both ranks the new axes in order of importance.
  - PC1 (the first new axis that PCA creates) accounts for the most variation in the data.
    - PC2 (the second new axis) does the second best job.

- LD1 (the first new axis that LDA creates) accounts for the most variation between the categories.
  - LD2 (the second new axis) does the second best job.

In summary

- LDA is like PCA - both try to reduce dimensions.
  - PCA looks at the genes with the most variation.
  - LDA tries to maximize the separation of known categories.