The relationships between spinal abnormalities, neuronal plasticity, and chronic low back pain in an animal model

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Outline

- Review of the substantive questions
- Causation and mediation
- Radiating pain
- Axial pain
- Longitudinal behaviour measures

Scientific question

- The original presentation ended with the following question:

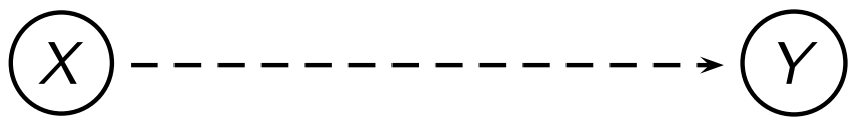
  What is the relationship between disc degeneration, disc innervation, and (radiating and axial) low back pain?
- From a modelling perspective, it is very important to understand the different meanings of the word "relationship."
- In this case, the real problem was one of "causal relationship," rather than simply trying to predict.
- Directed acyclic graphs (DAGs) allow us to interpret statistical models in the language of causation.

Graphs and causation

- We will interpret an arrow between two variables in a graph as implying that one variable *causes* another variable (a much stronger designation than just *association*).
- As an example, in the graph below, we would say that L causes A and A causes D.

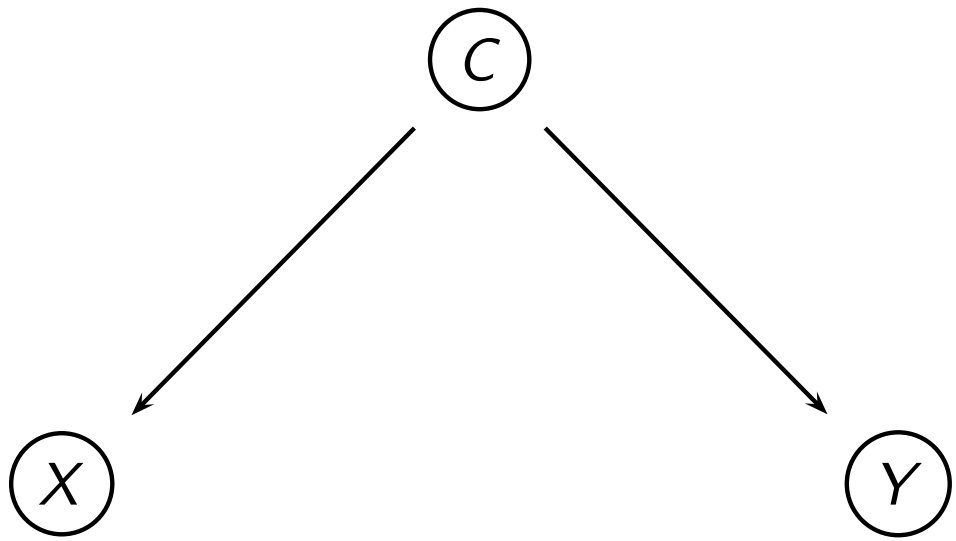
Toy example

- Imagine that we collect data on umbrella usage (X) and we want to determine whether it causes rainfall (Y).
- We will observe that X and Y are likely to be *associated* in our data.
- If it is not raining at the beginning of the day, our umbrella usage (X) will precede the rainfall.
- We can ask whether the dashed arrow represents the true causal model.



Toy example: Confounding

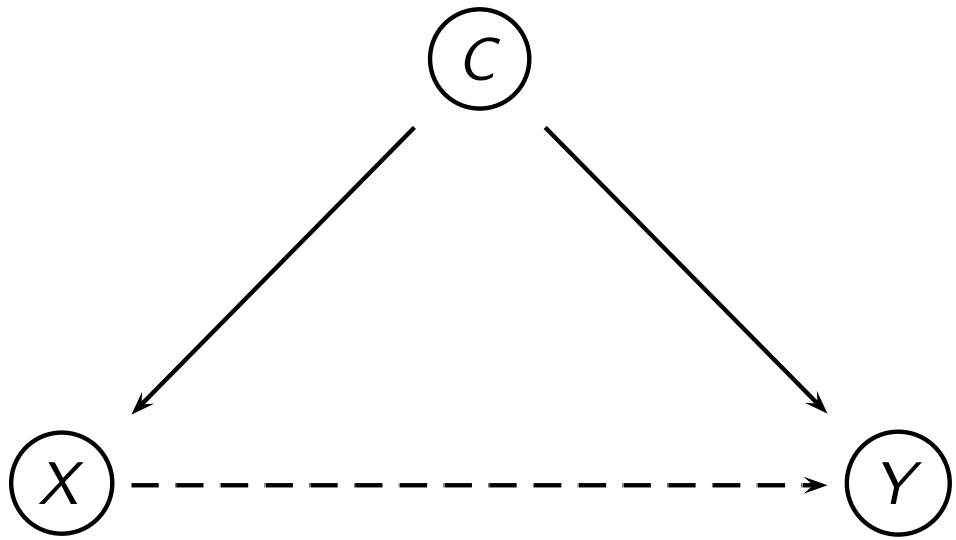
- One way that we could observe an association between X and Y although the postulated causal relationship does not hold would be if there were a *confounding variable* C causing X and Y that we did not take into account.



- In this case, the marginal association of X and Y would be non-zero, but the *conditional* association of X and Y would be zero.

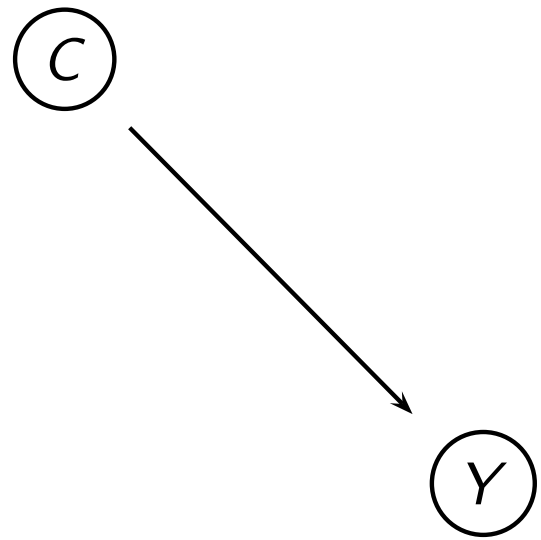
Toy example: Confounding

- If there is an association between X and Y, we still need to condition on C to recover the correct *causal* association that is not due to C.



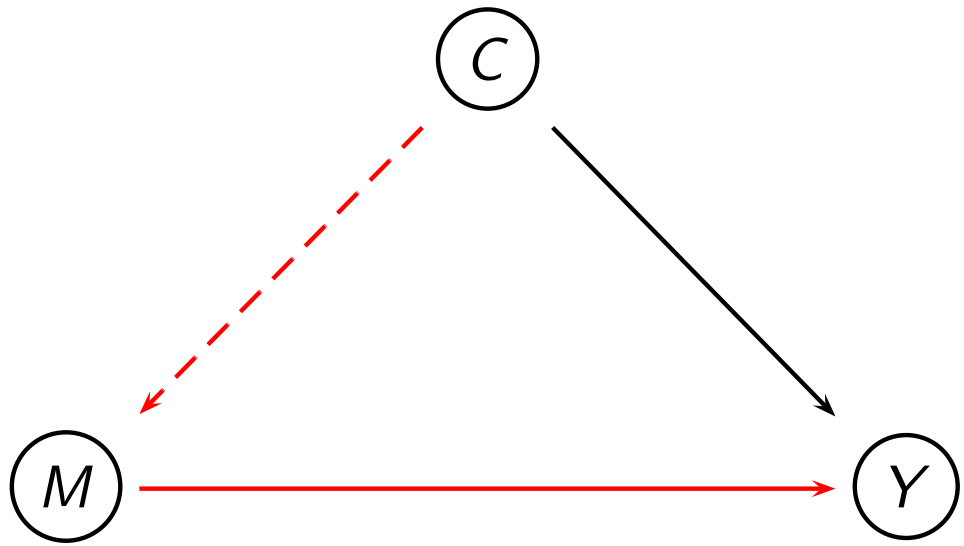
Toy example: Mediation

- Another way to view the example causal graph is to consider the total effect of C on Y (for example, let C be a drug treatment meant to reduce the risk of heart attack).



Toy example: Mediation

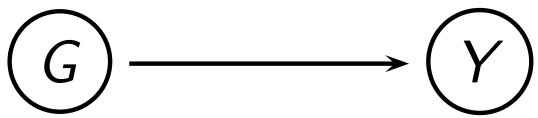
- We can consider decomposing the total effect of C on Y into a *direct effect* and an *indirect* effect of C on Y through a *mediator* M.



- For example, if C is a blood pressure medication, we may have that all (or most) of the total effect of C on Y is through the blood pressure itself (M).

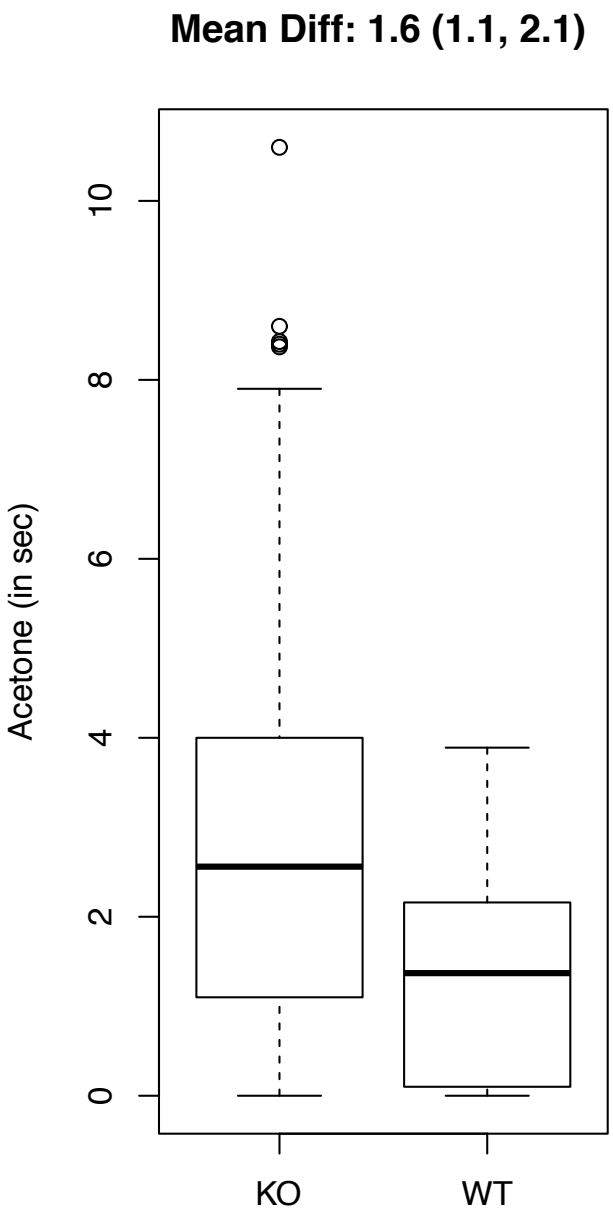
Application to our research questions

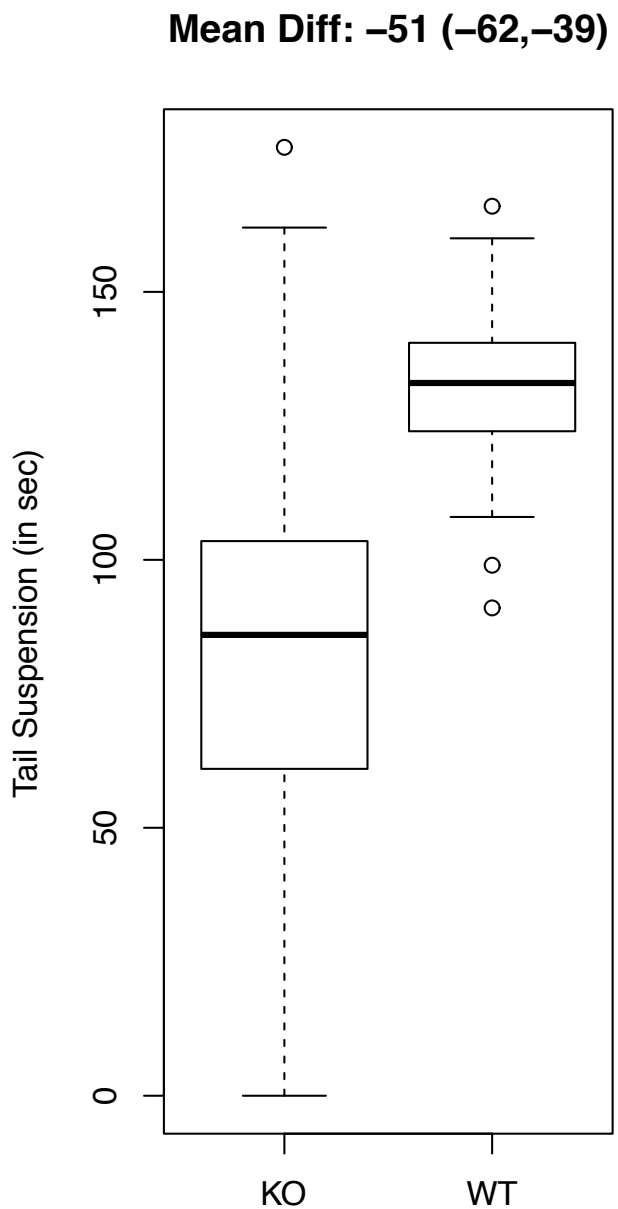
- The biological experimental design can yield *causal* interpretations of the association between genotype (SPARC-null vs. wild type mice) and outcome.
- The experimenters control the genotype of the mice, which means that we can clearly write



and most importantly, there does not exist any other node U having arrows directed into G (as this is controlled by the experimenters), which means that there are no arrows into G and Y (confounding).

Disc Height

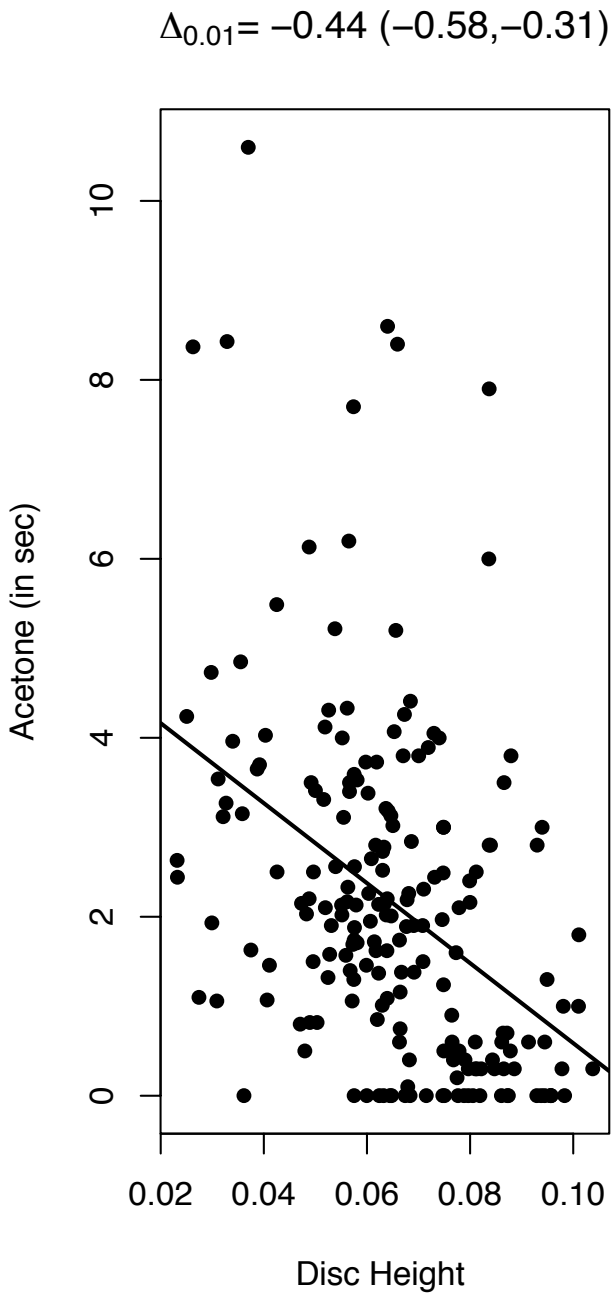

Mean Diff: 1.6 (1.1, 2.1)
Acetone (in sec)
0
2
4
6
8
10
KO
WT

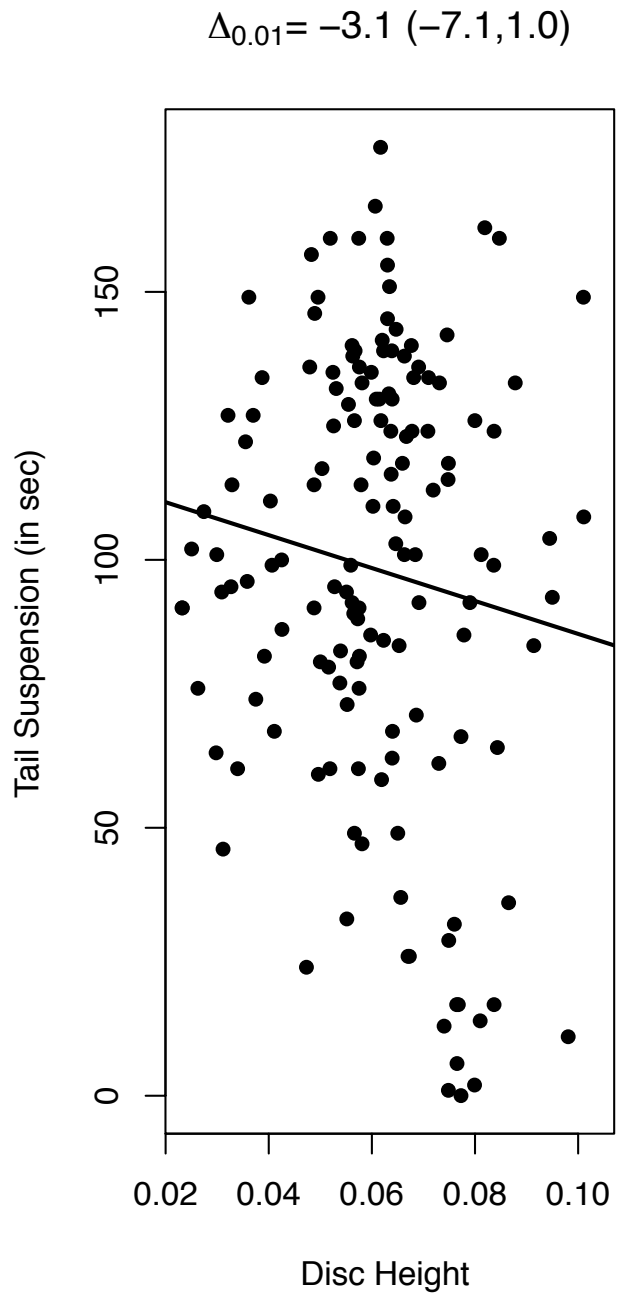

Mean Diff: –51 (–62,–39)
Tail Suspension (in sec)
0
50
100
150
KO
WT

Disc Height

- Of course, now we have only considered the total effect of the genotype.
- The real question of the researchers concerns disc degeneration (as measured by disc height measurements, for example) and disc innervation (as measured by sensory nerve length).

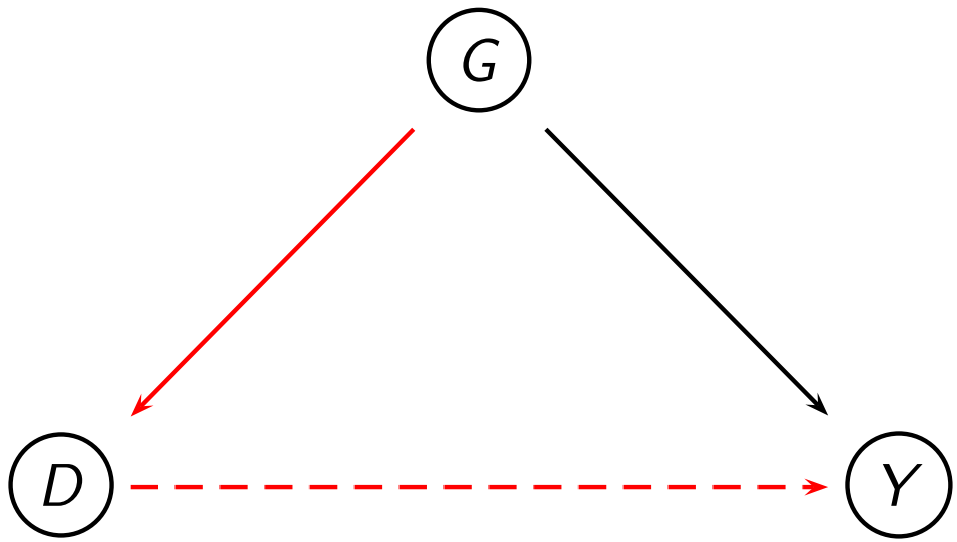
Disc Height


$\Delta_{0.01}$= −0.44 (−0.58,−0.31)
Acetone (in sec)
0
2
4
6
8
10
0.02
0.04
0.06
0.08
0.10
Disc Height


$\Delta_{0.01}$= −3.1 (−7.1,1.0)
Tail Suspension (in sec)
0
50
100
150
0.02
0.04
0.06
0.08
0.10
Disc Height

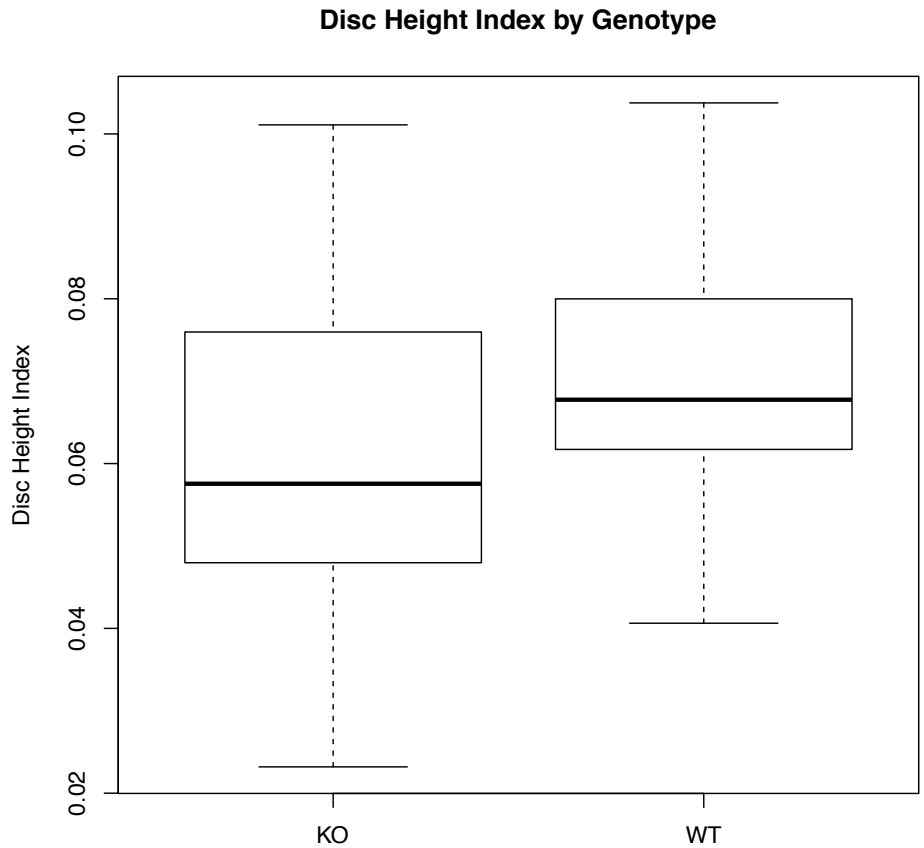
Disc Height

- However, this does NOT represent the direct causal effect of disc height on the outcomes, as we *know* that the genotype is a cause of the disc degeneration.



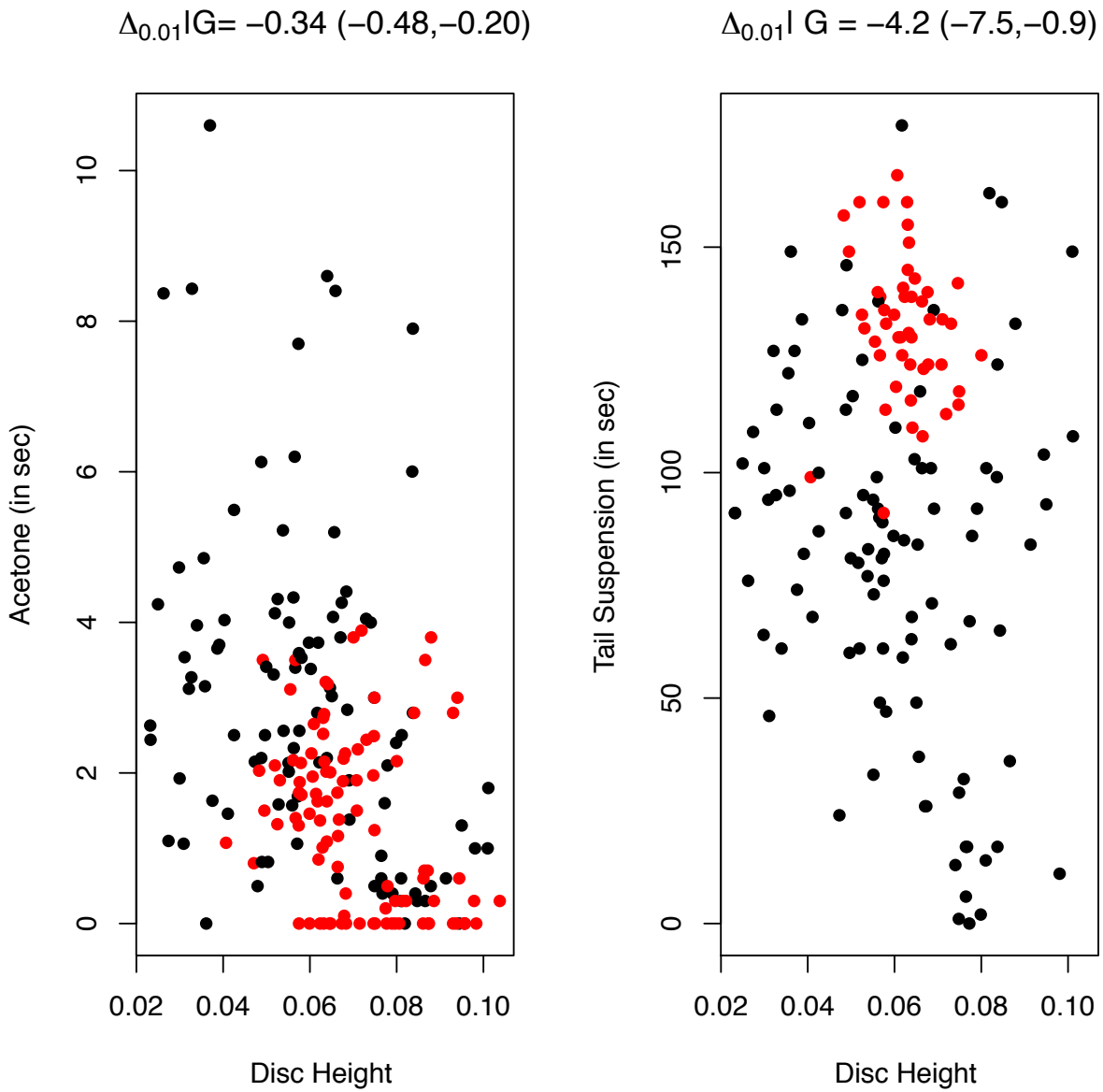
- What we are really interested in is a question of *mediation*, i.e., the effect of genotype on outcome *mediated* by disc height.

Disc Height



- We see a clear, *causal* association between Genotype and disc height, so we must be worried about the potential for confounding.

Disc Height



- Wild Type in Red

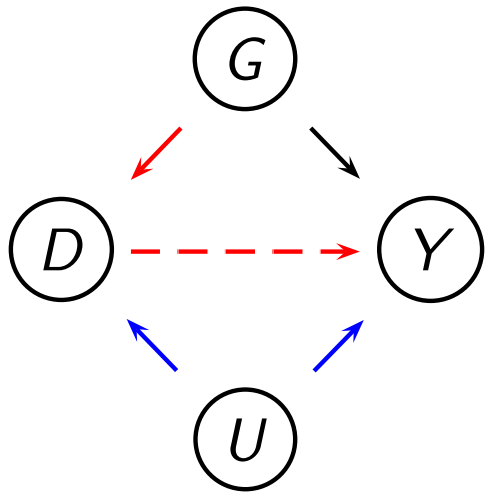
Disc Height

- We see that the association conditional on Genotype is different from the association when Genotype is not controlled for.
- We can test for the existence of the *indirect* effect of Genotype through Disc Height using the *Sobel test* for mediation.
- We find that there is statistically significant evidence of mediation of the effect of Genotype on the Acetone time through Disc Height (-0.4: -0.6,-0.1) but not for the Tail Suspension (-1.2: -3.8, 1.4).

When you assume, you make an...

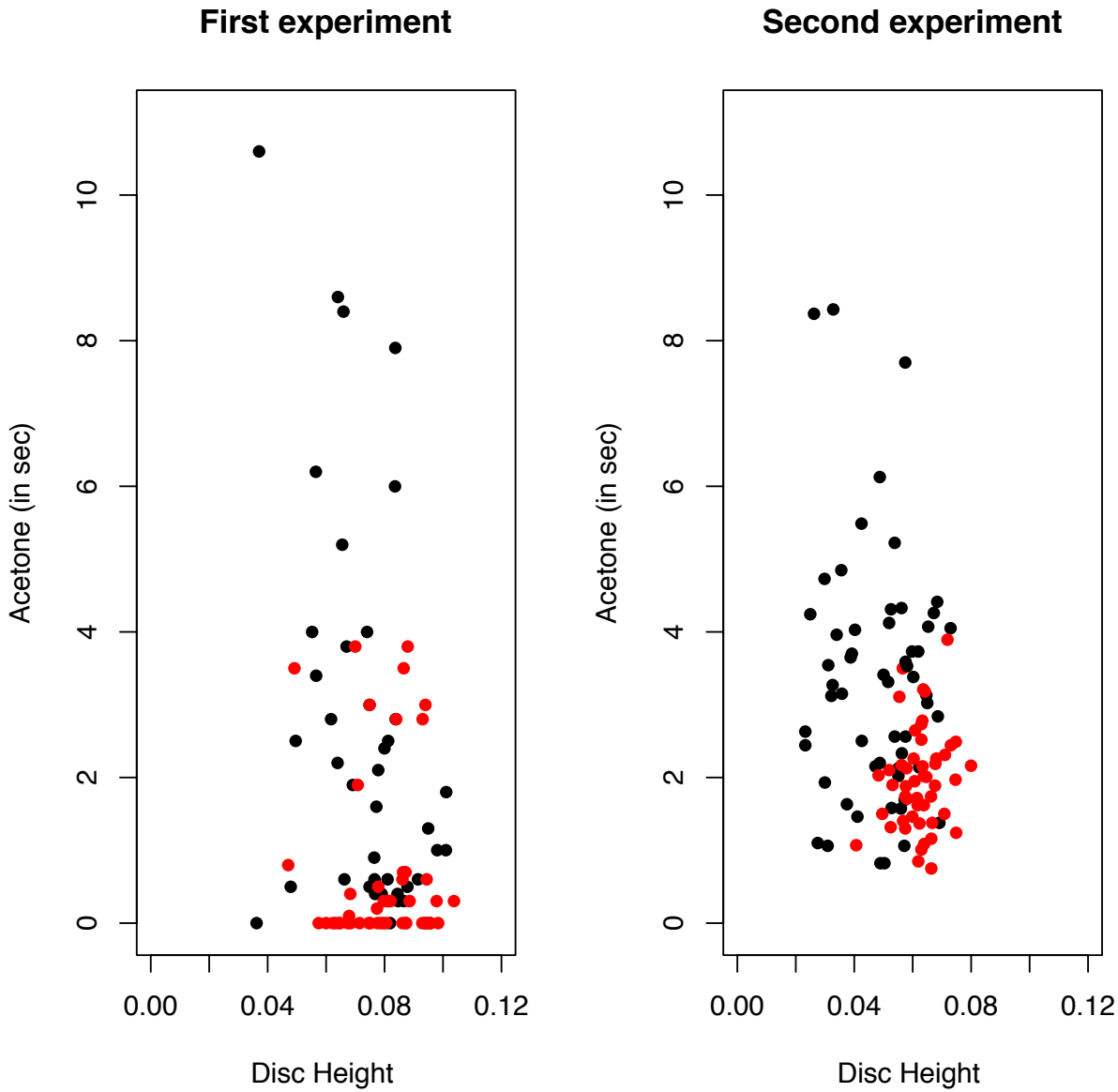
- One of the important assumptions of the Sobel test is that there is no unmeasured confounding of the direct and indirect effects.
- We know that the direct effect of Genotype on the outcomes is not confounded, because the experimenter controlled the Genotype.
- Disc height measurement, however, could be confounded by outside variables.

When you assume, you make an...



- We posited that one possible confounder was the experimenter (i.e., the person who measured the disc height and the person who measured the outcome).
- Here are the Acetone results divided by experimenter:

When you assume, you make an...



When you assume, you make an...

- Adjusting for the causal effect of the experimenter shows that there is no reliably measurable association between disc height and acetone.
- The figures make any sort of model combining the data quite tenuous, as it is difficult to argue that the data are coming from the same data-generating mechanism.
- Even if combining the data sets were plausible, adjusting for *moderated* effects in the presence of mediation (and vice versa) requires statistical techniques that have a higher power and data that are significantly more detailed.

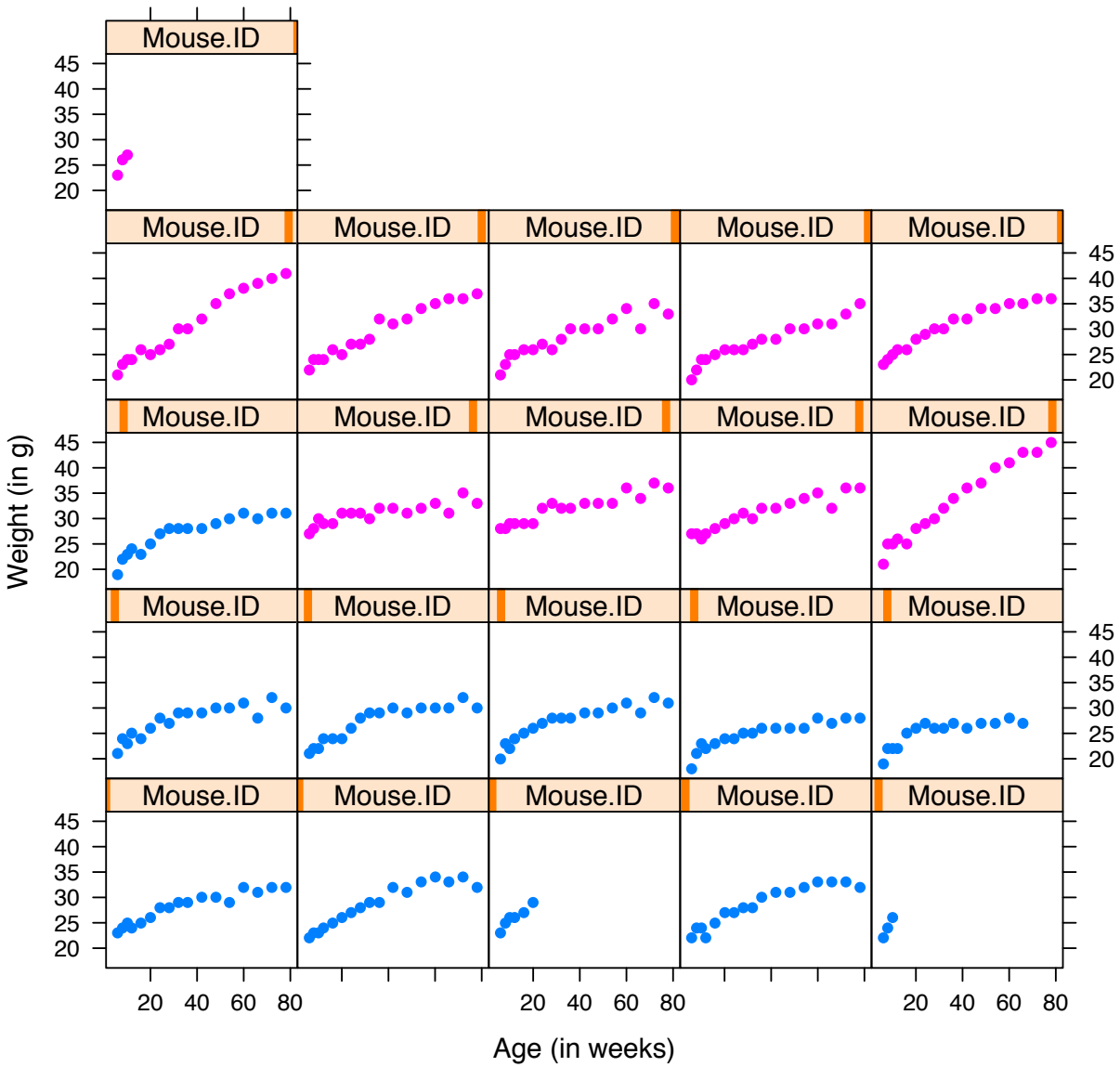
Summary of univariate results

- We found a consistent causal effect of genotype on outcomes, found that differences in experiments made it challenging to estimate the mediation in a reliable fashion for either disc degeneration (as measured by DHI or FAST) or disc innervation (as measured by total sensory nerve length).
- Some data from the experiments can be obtained by having it re-analyzed by a second rater (for example for measures derived from X-ray measurements or biological specimens recorded by photograph).
- Use of DAGs suggests a new way to think about how the intermediate outcomes relate to the genotype and the final outcome.

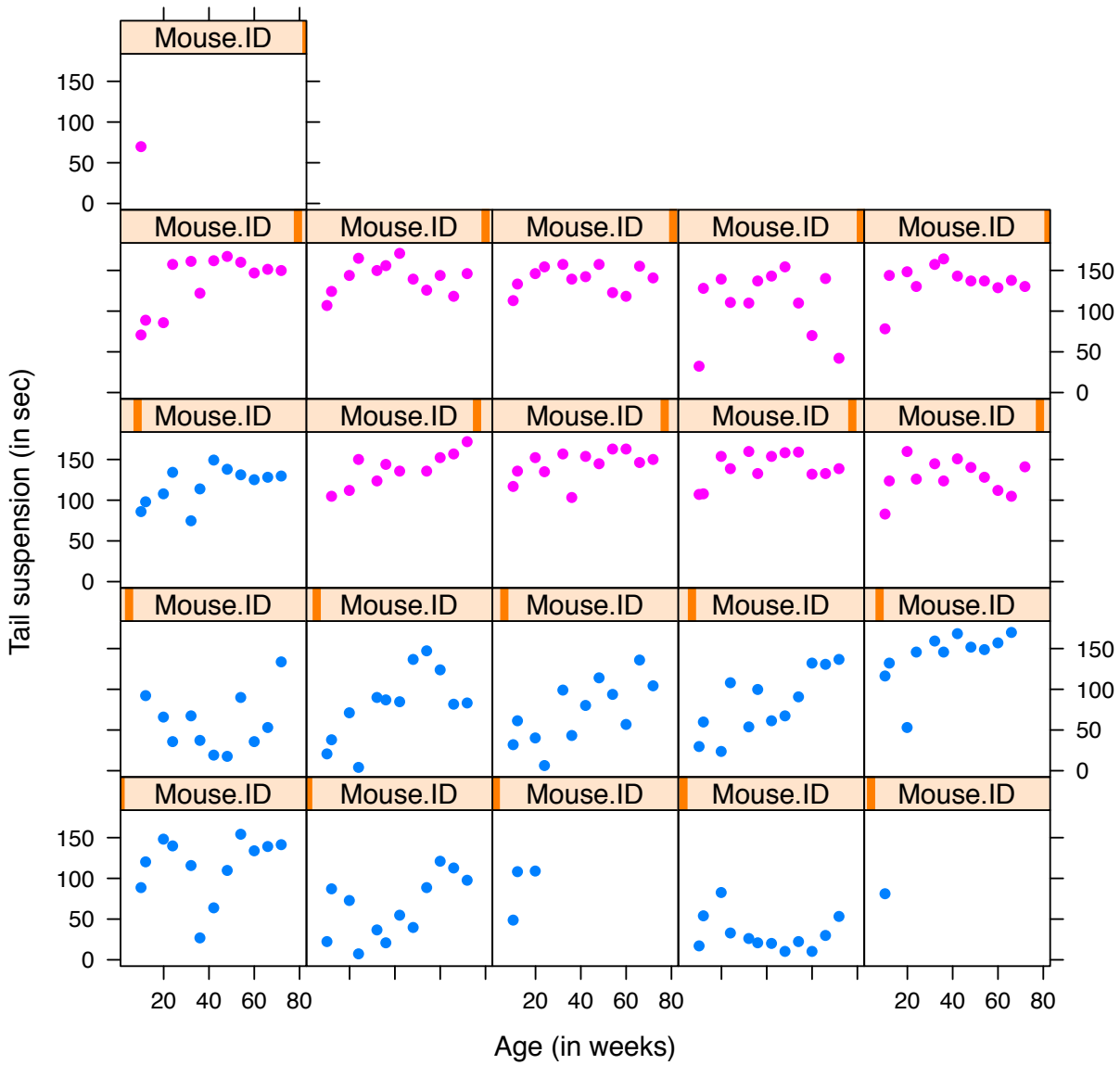
Some longitudinal exploration

- We also explored some longitudinal data using some of the same techniques.
- In some experiments, behavioural data was collected longitudinally and so one can correct better for heterogeneity between the mice.
- For example, some mice may have different weight or behavioural trajectories and this is a potentially removable source of variation in the modelling.
- In this problem, we were primarily interested in evidence of whether the effect of Genotype on outcomes was mediated by Weight.

Some longitudinal exploration



Some longitudinal exploration



Some longitudinal exploration

- In this case, we did find evidence of possible mediation of the effect of genotype on tail suppression through weight.
- The potential for unmeasured confounding, however, makes the longitudinal problem even more difficult to tackle.
- We need more causal methods having a higher power and a more careful modelling of possible confounders for weight.

Conclusion

- The use of directed acyclic graphs (DAGs) can allow one to use standard statistical tools but still make causal interpretations of the data.
- In this problem, use of the DAGs clarified the research questions and gave the right direction for modelling.
- As always in science, you must understand your problem before your look at the data, as your models are only as good as the quality of the things you measure and the non-existence of the things that you don't.

Summary

- Thanks to the organizers and the CRM
- Laura Stone, Alex Danco, Sean Bohun