

Case Study B

Pain Relief Medication

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Case statement

- ▶ 20 experiments on mice with combinations of marijuana and morphine, of which:
 - ▶ 1 control experiment;
 - ▶ 5 experiments with marijuana only;
 - ▶ 8 experiments with morphine only;
 - ▶ 6 experiments with both drugs.
- ▶ 10 mice used per experiment;
- ▶ Each mouse undergoes a tail flick test.

The tail flick test assesses the effect of drugs on the mouse.

In each experiment, the proportion of mice not flicking their tail can be interpreted as a **measure of the effect of the drug** for the chosen experimental dosage.

First objective

*Determine the minimum dosage amount of the drugs that achieves **efficacy**.*

The dosage of a drug is said to be **efficient** if at least 50% of the subjects are responding.

Second objective

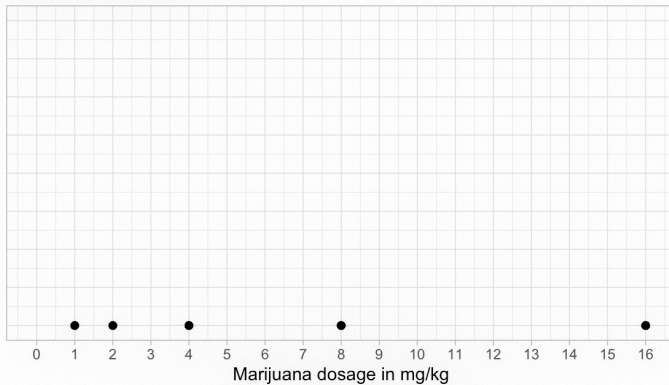
*Detect whether a **synergy** exists between the two drugs.*

If the combined efficacy of the two drug dosages is greater than the sum of the individual efficacy of each drug for its respective dosage, there is **synergy**.

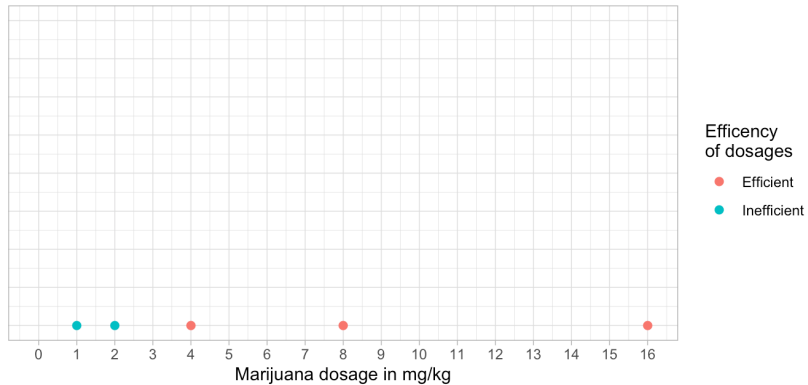
Identifying synergy with the isoboles method

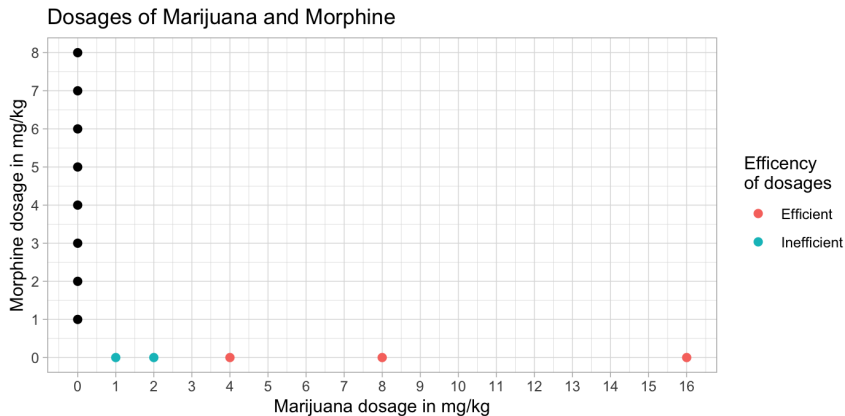
The isoboles method is a graphical representation which allows to identify synergy and helps to better understand the concept.

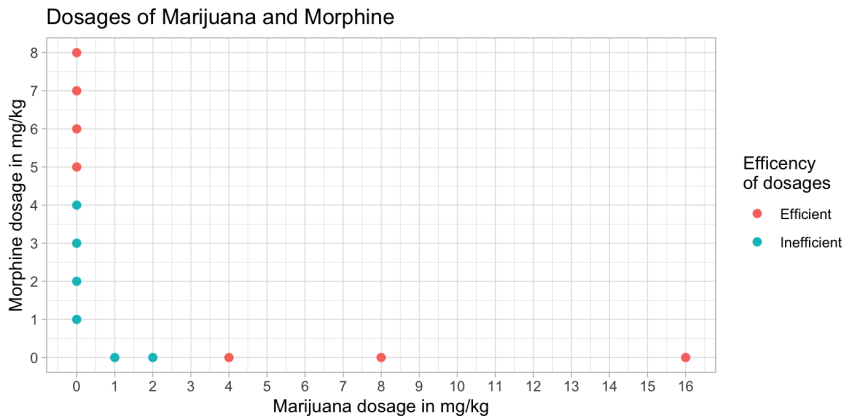
Dosages of Marijuana

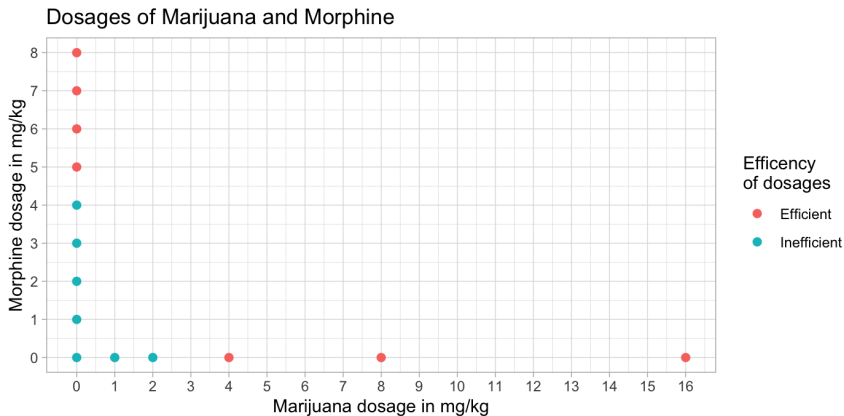


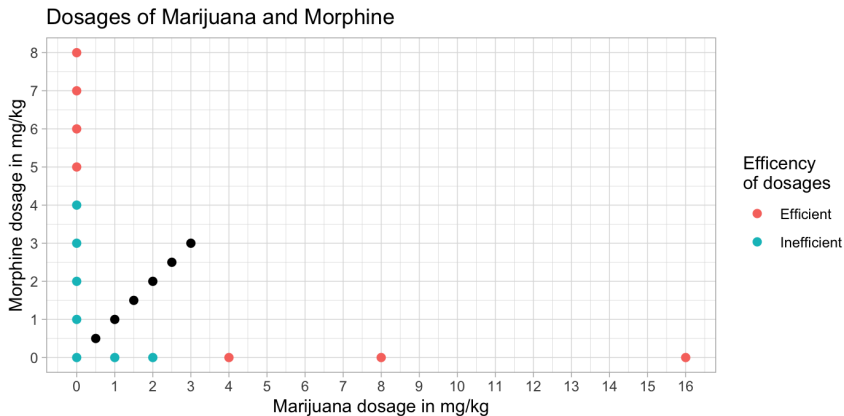
Dosages of Marijuana

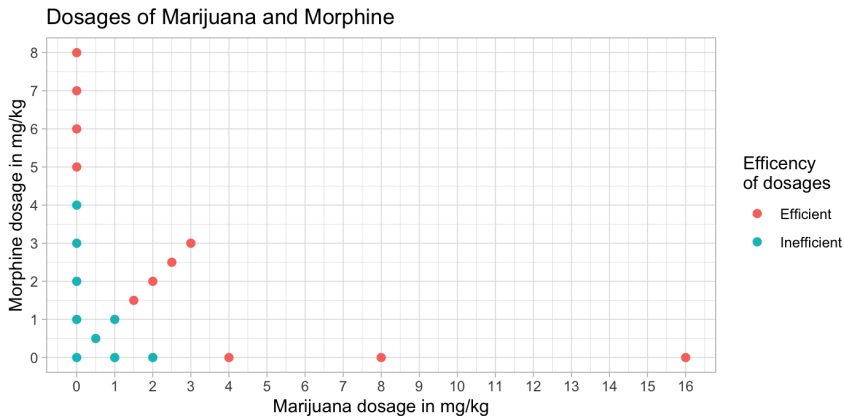


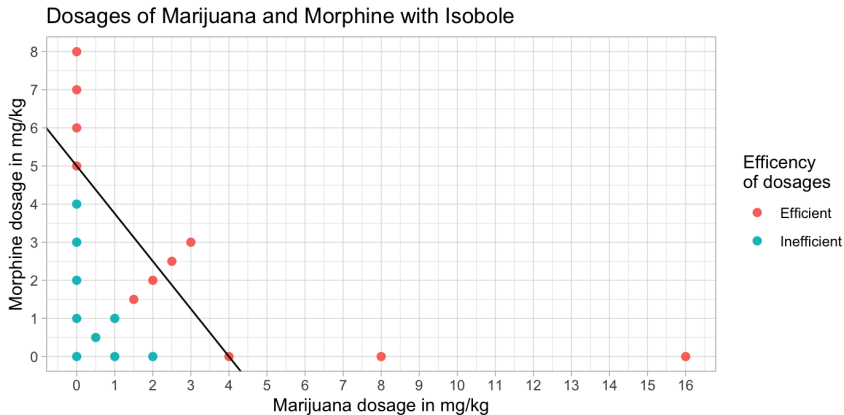












Isobole insights

- ▶ Using 4 mg/kg of marijuana gives an equivalent effect ($\geq 50\%$ of mice responding) to using 5 mg/kg of morphine.
- ▶ Combined dosages of the two drugs which are on the isobole have an equivalent effect to the ones mentioned above.
- ▶ A combined dosage which is under the isobole but is still efficient is synergic.

Isobole conclusion

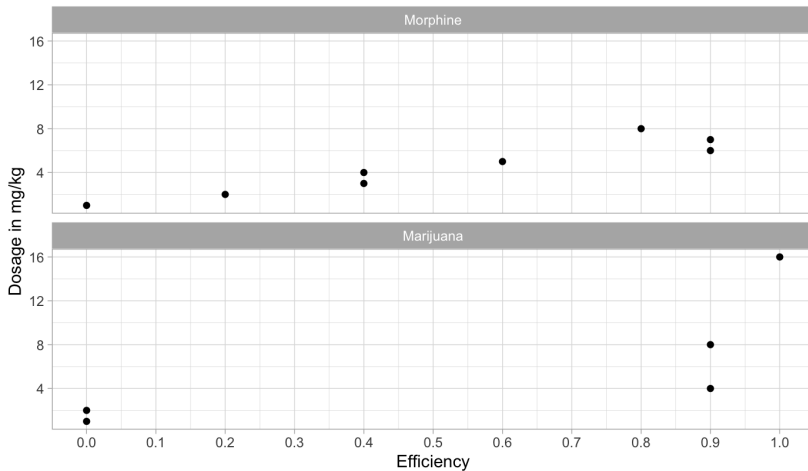
- ✓ **First objective, minimal efficient dosage:**
 - ▶ 4.0 mg/kg for marijuana alone;
 - ▶ 5.0 mg/kg for morphine alone;
 - ▶ 1.5 mg/kg of each for both drugs.
- ✓ **Second objective, synergy:**

Dosages of 1.5 mg/kg and 2.0 mg/kg each are synergic.

Isoboles method assumption

The ratio between dosages of morphine and marijuana when they give the same efficiency level is constant.

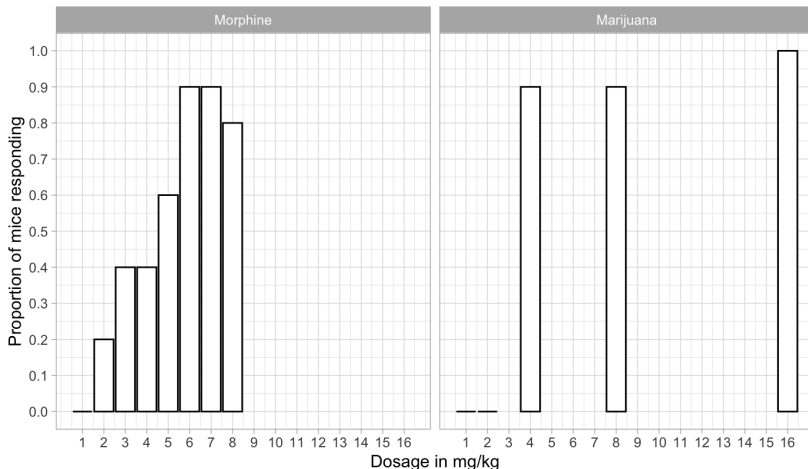
Dosages of Marijuana and Morphine vs Efficiency



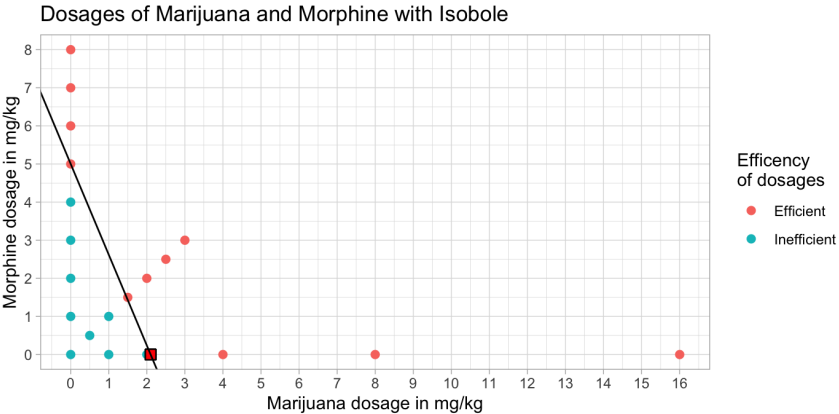
- ▶ Only two common efficiency levels, 0.0 and 0.9
- ▶ This is not enough to verify the assumption for this experiment.
- ▶ This weakness is due to dosage choices for marijuana.
- ▶ However, the linear isobole method is used in multiple experiments which are extremely similar.

Dosage choices for marijuana

Proportion of mice responding per dosage of drug



- ▶ The choice of dosages for marijuana does not allow for precise exploration of the minimal efficient dosage.
- ▶ A better minimal efficient dosage could be found between 2.0 and 4.0 mg/kg.
- ▶ This could change the isobole in a drastic way, making it more strict towards the synergic dosages.



Recommendations

- ✓ **Complete the experiment with trials for at least 3 or 4 dosages of marijuana between 2.0 and 4.0 mg/kg.**
- ✓ Experiment with more dosages of morphine between 4.0 and 5.0 mg/kg.
- ✓ As of now, the best minimal efficient dosage is 1.5 mg/kg of marijuana and morphine combined.