Multiplicity in a decision-making context

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NB! This presentation is truncated.

The interactive Casino game has been deleted as well as some comments in response to earlier presentations.

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Why alpha=5% ?

Alpha for what

- One trial
- One “dimension” (cf vitamin E, betacarotene?)
- A meta-analysis
- … and the next meta-analyses?
- All you do during your scientific career?

What constitutes one experiment?

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Stat. significance

≠

Truth

Interpretation of data should depend on context

- What is the purpose of the analysis?
- What is known beforehand?

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Some examples of inference based on data with >1 hypotheses:

- Opinion polls
- Industry: tolerances
- Gene finding
- Terrorism: surveillance
- Market research
- Scientific publications (e.g. biology, sociology, medicine, Greek)
- Medical claims based on clinical trials (regulated)

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Different perspectives

- Opinion polls
  - Journalist: Can I write something interesting about this?
  - Me: Do I believe the journalist / commentator?
  - Politician: What's the reaction to my latest move?
  - US president candidate: In which states to run commercials?
  - Financial market: Likelihood of left-wing / right-wing victory

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Pharmaceutical claims based on clinical trials: The regulatory perspective

1. New medicine must have proven efficacy
   - $p<0.05$ in two different clinical trials
2. Should have positive benefit-risk. What does that mean?
   - ? Safety estimate < constant ?
   - ? Safety upper confidence limit < constant ?
   - ? Estimated clinical utility index > 0 ?
3. All claims should be proven
   - FWER < 5%

Are these the best rules?
Regulators are not tied to these;
they put decisions into a context.

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Pharmaceutical claims based on clinical trials: The company perspective

- We have new potential medicine X for obesity. A clinical trial is to be run (in a certain population).
- For simplicity, assume safety to be OK.
- Claims that we would like to make for X:
  - Body weight, BW ↓
  - CV events ↓
  - Mortality ↓
  - BW ↓ more than drug Y
  - Total cholesterol, TC ↓
  - "Good" cholesterol HDL ↑
  - "Quality of life", QoL ↑
- We can make a claim iff it is statistically significant in a multiple testing procedure (MTP) with FWER≤5%.

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Welcome to the
Casino *Multiplicité*

Win amazing prizes!
But first learn the rules,
so listen carefully …

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Should we only learn one thing from each trial?

- One trial = One single objective?
- No, of course not!
- There are many important dimensions to study, e.g.
  - Better effect on primary variable than placebo?
  - Non-inferior effect versus standard treatment
  - Better safety profile?
  - Improved quality of life?
  - Different doses of new drug versus competitor arms

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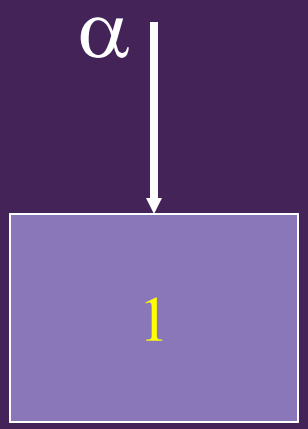
- Several null hypotheses (denoted 1, 2, 3 …)
  - p_k is the raw (unadjusted) p-value for hypothesis k
- Requirement:

  $$FWER = P_\theta(\text{At least one true null hyp is rejected}) \leq \alpha$$
- Want to: Reject as many hypotheses as possible
  - More or less difficult (depending on effect & variability)
  - More or less important to get different claims; Different value of claims

Test mass α = Starting capital at casino



Test of one single hypothesis

Rejected hypothesis = Win at the casino
You win if your bet α is greater than the p-value p_1

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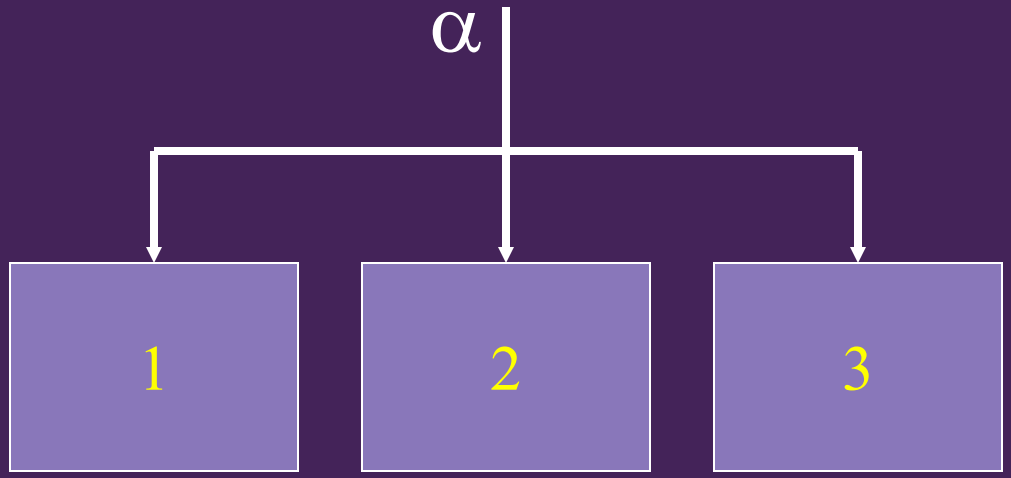
Splitting the test mass

Example: Three hypotheses are tested at level $\alpha/3$ each



Parallel procedure

(= Bonferroni)

You split your casino markers on three games (1, 2 & 3).
Win if bet on a game is greater than its p-value

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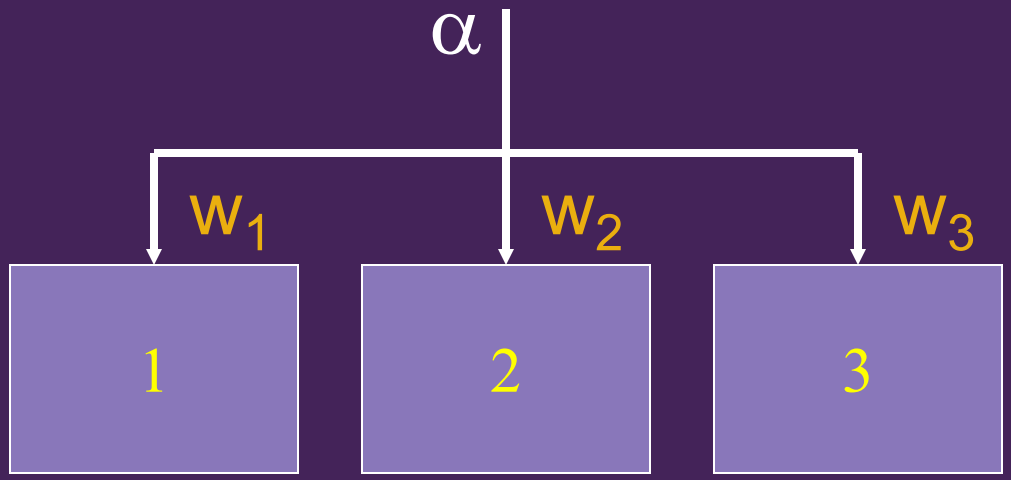
Splitting the test mass in unequal parts



Parallel procedure

(= Weighted Bonferroni)

You split your casino markers on three games (1, 2 & 3).
Win if bet on a game is greater than its p-value

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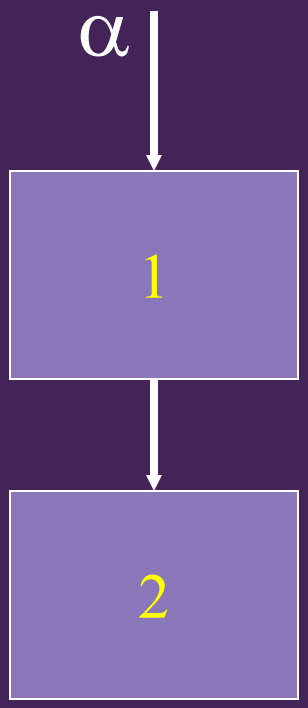
Recycle the test mass

If a hypothesis is rejected, the test mass ”flows” through.

Hypothesis 2 can be tested at level α if and only if hypothesis 1 is rejected



Sequential procedure

If you win a game, you receive a prize (reject the hypothesis). In addition, you get your bet back, and can put it on a new game.

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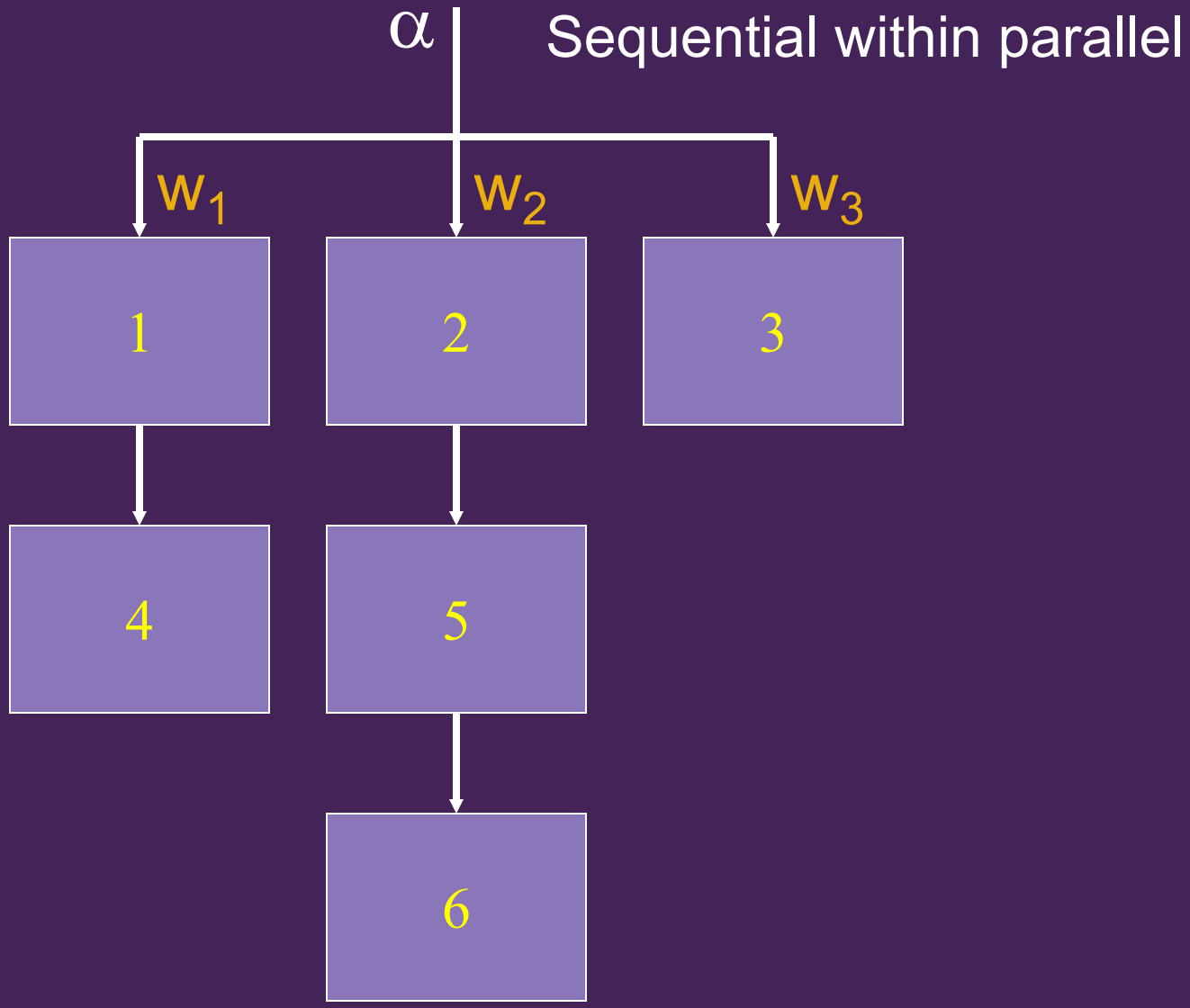
Combine splitting & recycling of test mass



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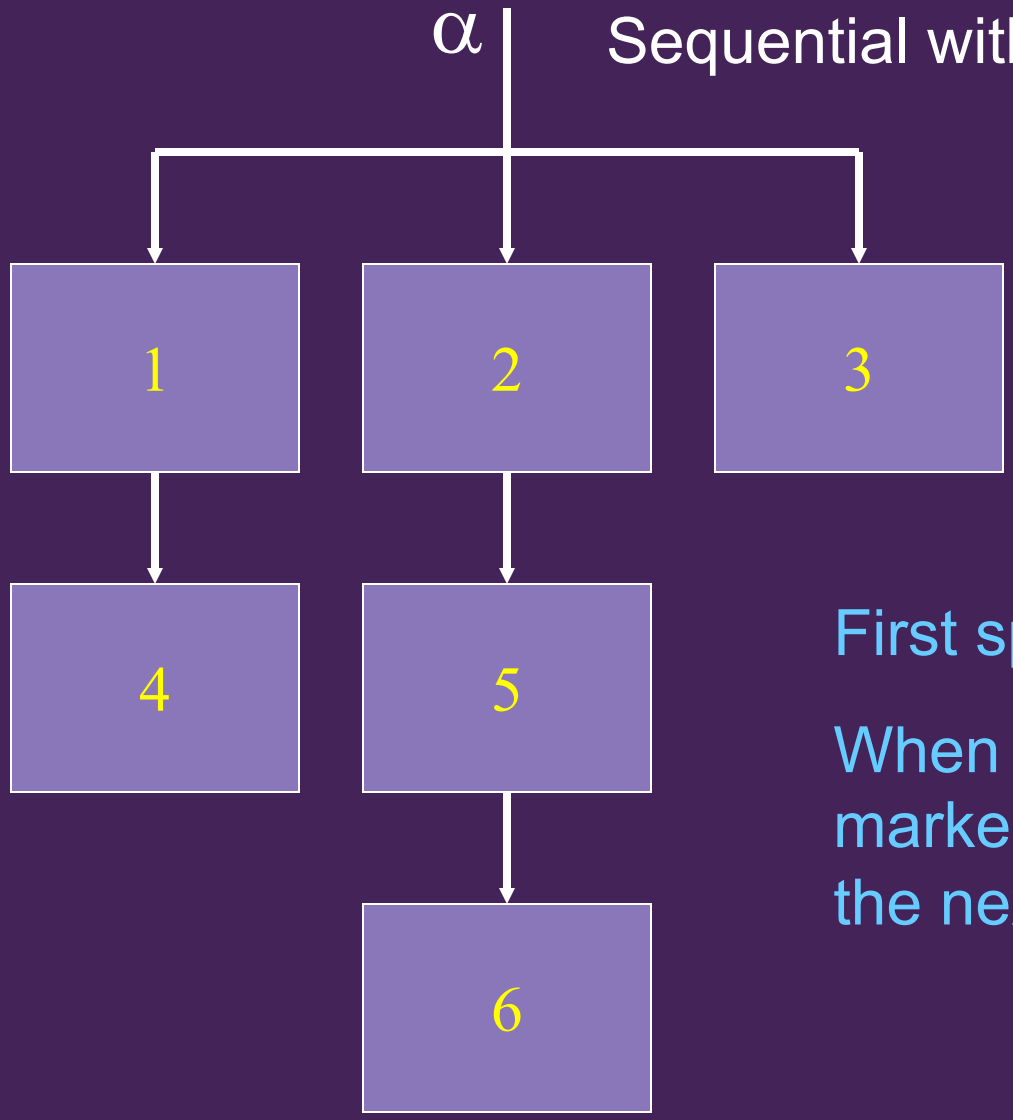
Combine splitting & recycling of test mass



First split the markers on 1, 2 & 3

When you win a game, the markers from that game is put on the next game following the arrow

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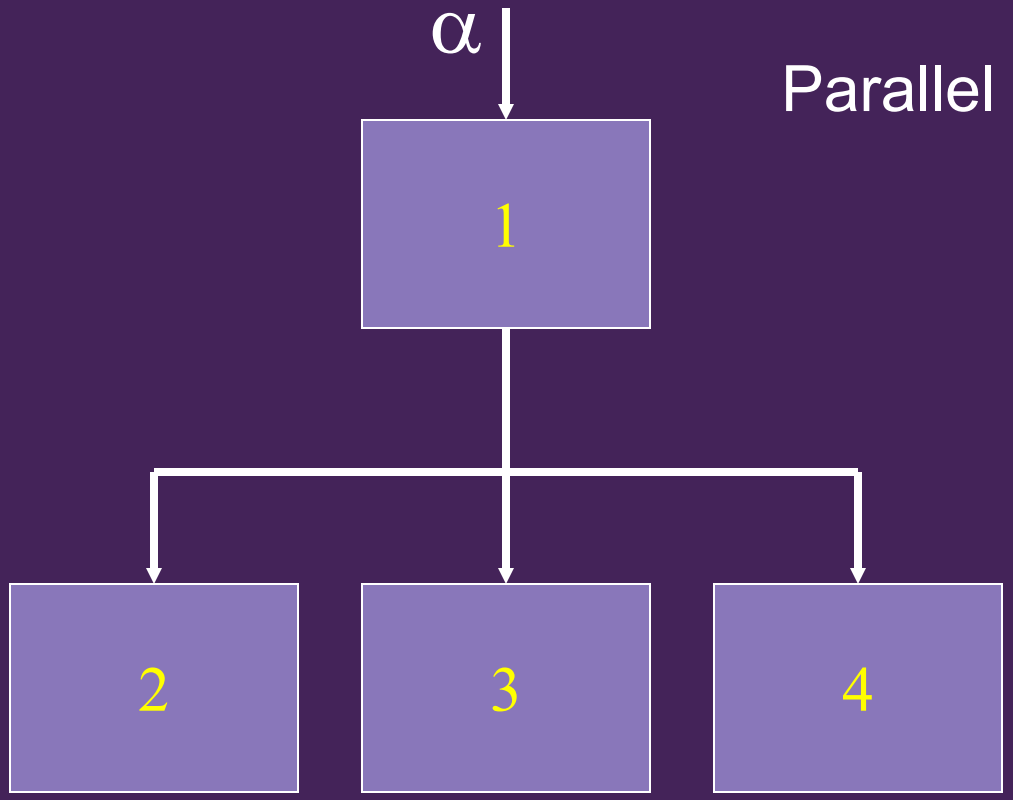
Combine splitting & recycling of test mass



Parallel within sequential

If hypothesis 1 is rejected, Bonferroni over 2, 3 and 4

If you win on game 1, You get all your markers back. They can be split on 2, 3 & 4.

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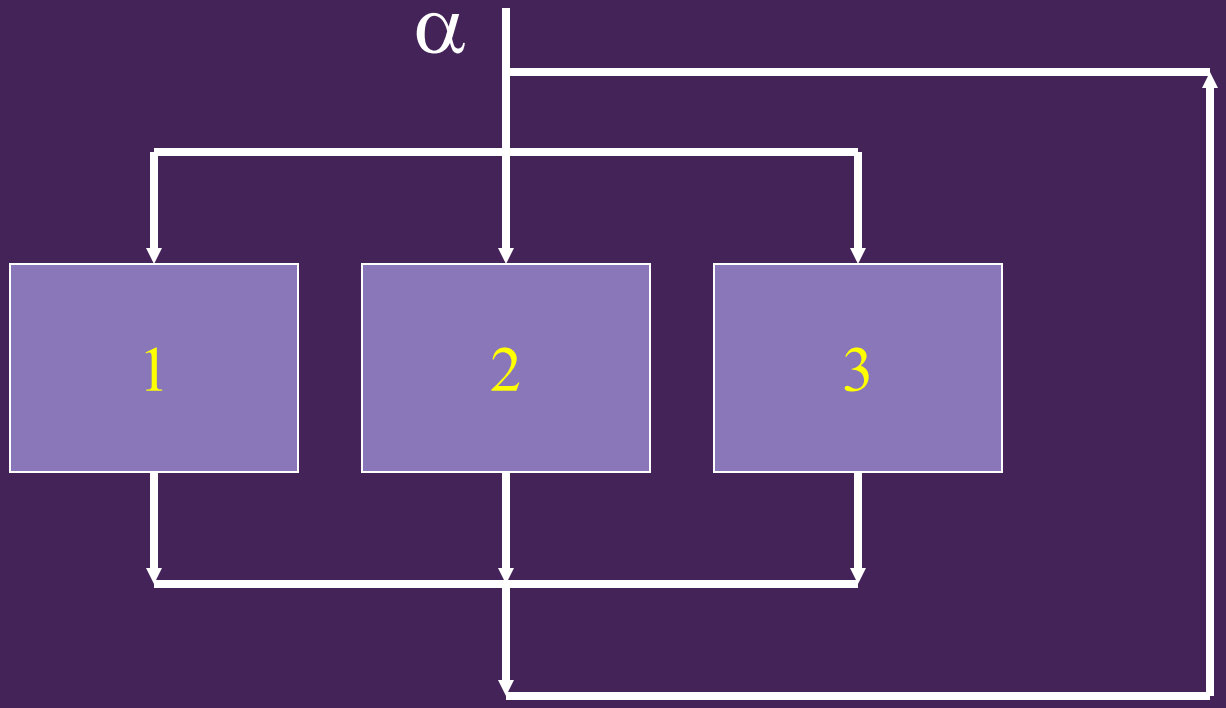
Holm's procedure



If you win on any game ($\alpha/3 \geq p_k$) you get that bet back. Split and add to the old bets. If total mass on a hypothesis now is greater than the p-value, you get a new win and get all these markers back.

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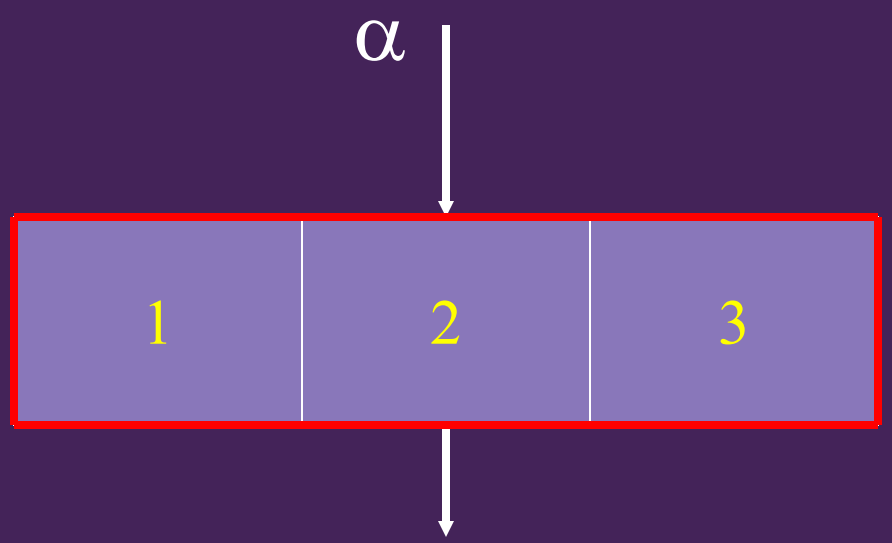
Holm's procedure (simplified notation)



Holms procedure is a *block* in the graph

The red box is just another way of illustrating the previous procedure

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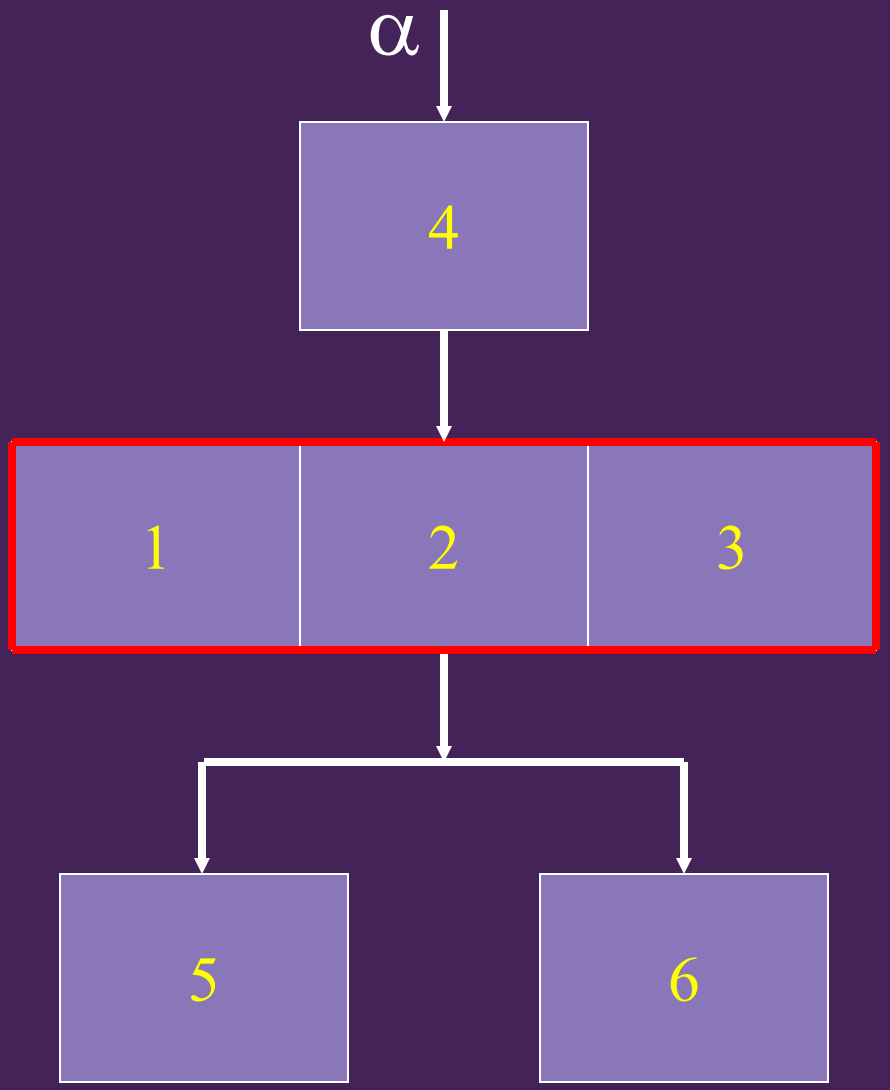
Hypothesis tests
can be combined in sequence or in parallel

We call such a testing procedure ”block”

Block (of hypotheses)
can be combined in sequence or in parallel

A block of blocks is a block

Sequence of single hypothesis 4, Holm(1,2,3) & parallel(5,6)



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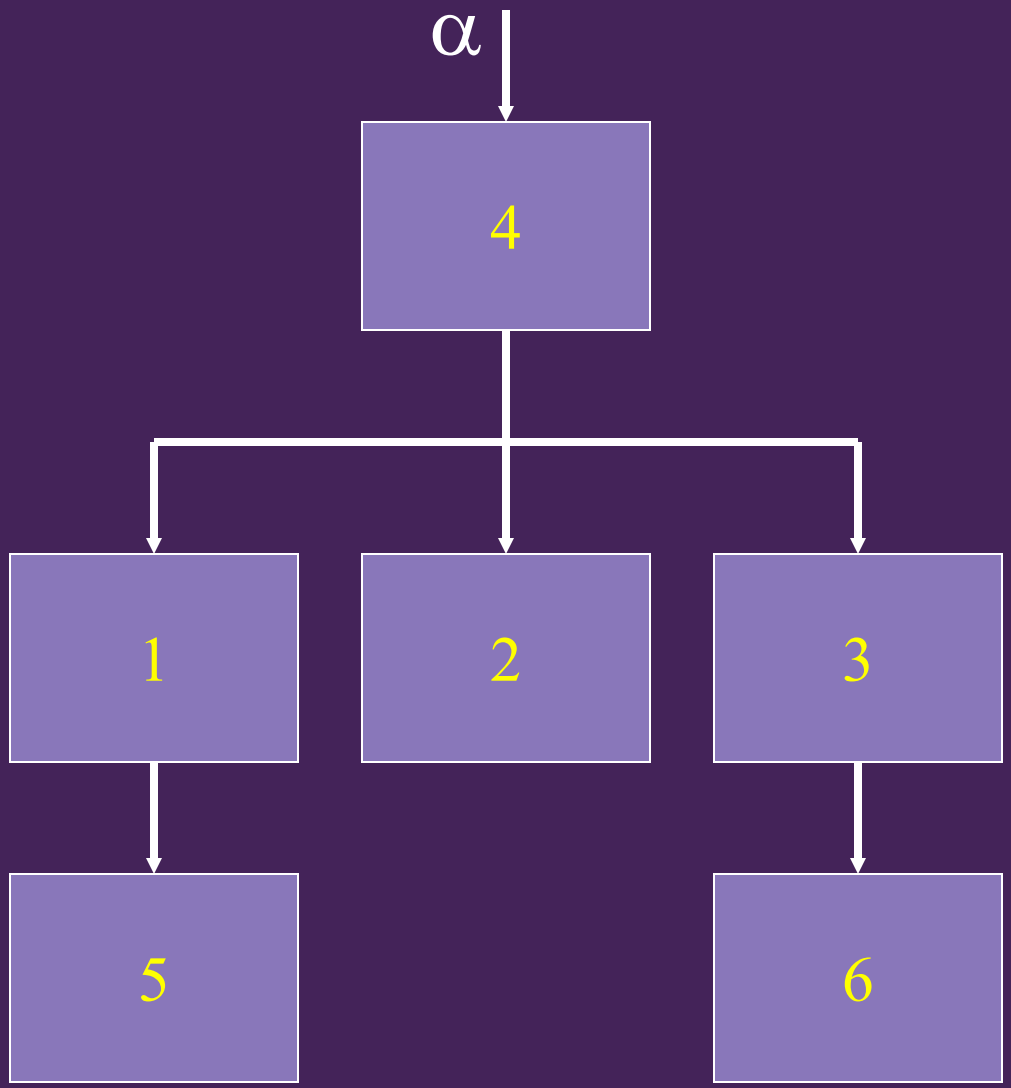
Sequential within parallel within sequential



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Some remarks (1)

- Every casino mark can freely move from between hypotheses in arbitrary order
  - The mark ”knows” which hypotheses it has passed (and helped to reject)
  - It is not allowed to know the exact p-value
  - Snooping on other marks is also forbidden
- The Casino approach is a ”closed testing procedure”

Some remarks (2)

- The test procedures shown are Bonferroni based. These may sometimes be improved by utilising correlations between tests.
- A p-value may be identically zero.
- ”*To infinity, and beyond*”
  - May have infinite loops
  - And then move on if all hypotheses that can be reached in the loop are rejected (e.g. Holm in sequence followed by another block)

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Thank you for you patience …

Now it’s time playing

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How large is the power?

- The following graphs show the distribution for the p-value, given the expected Z-score (normed effect)

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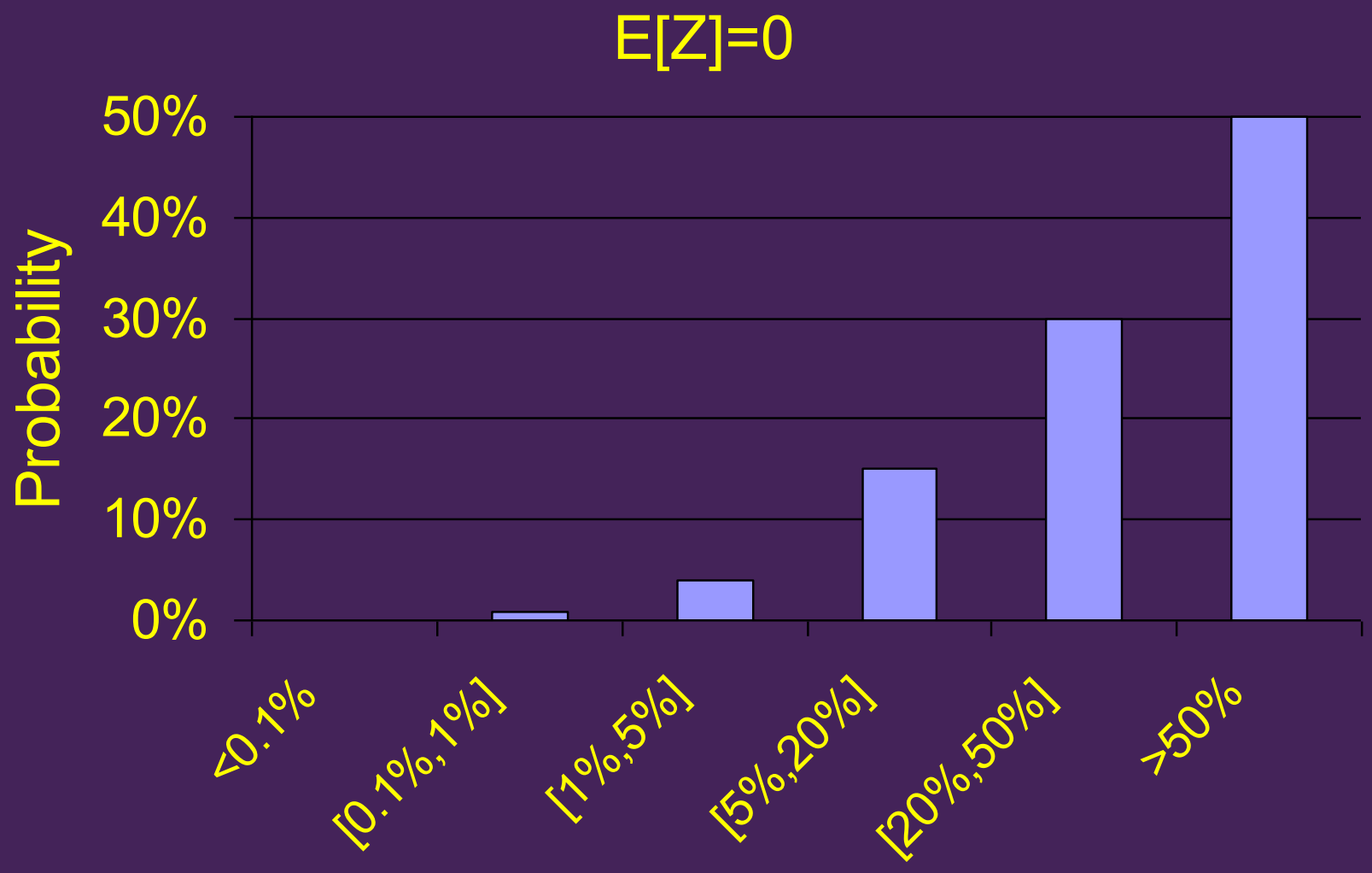

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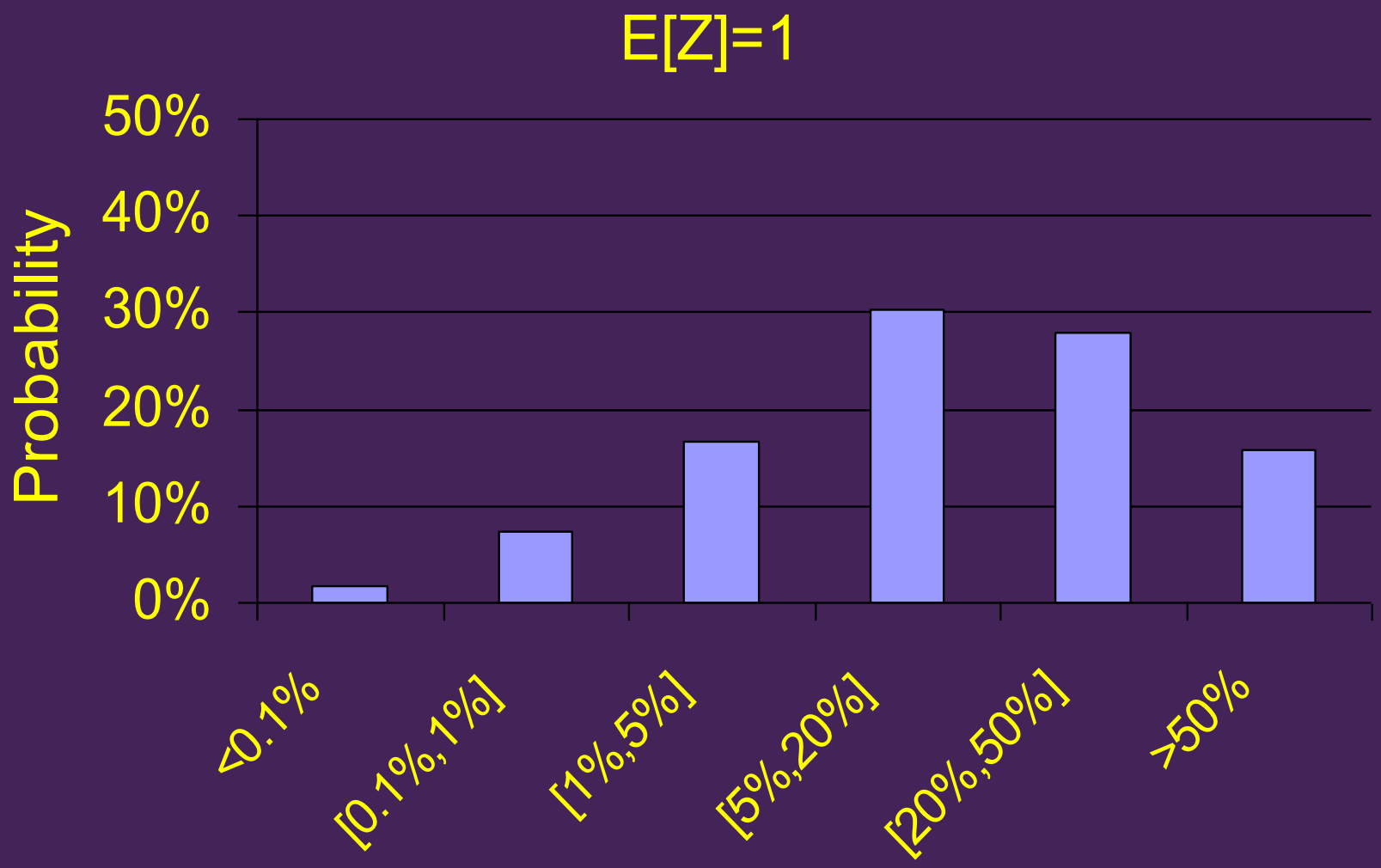

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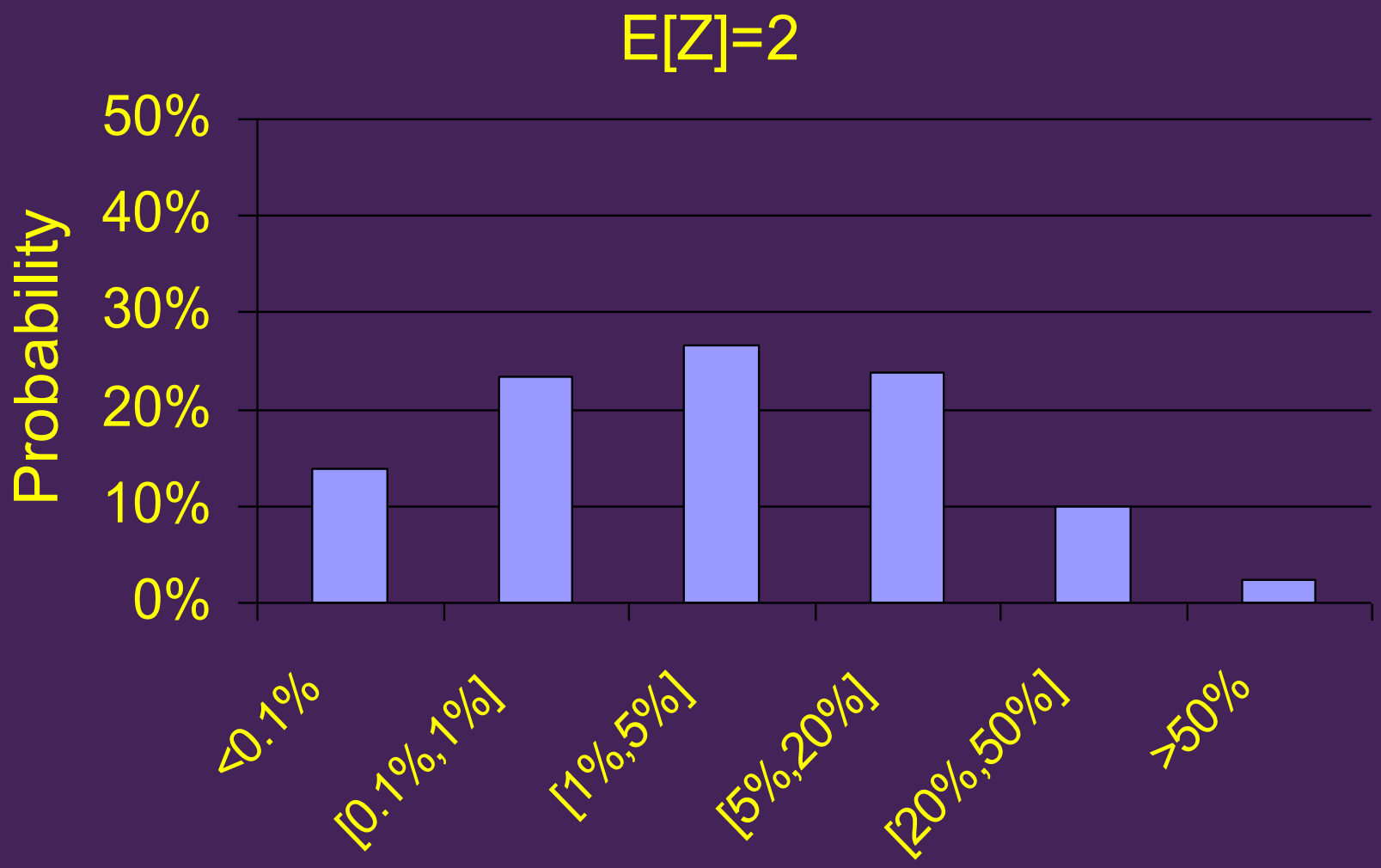

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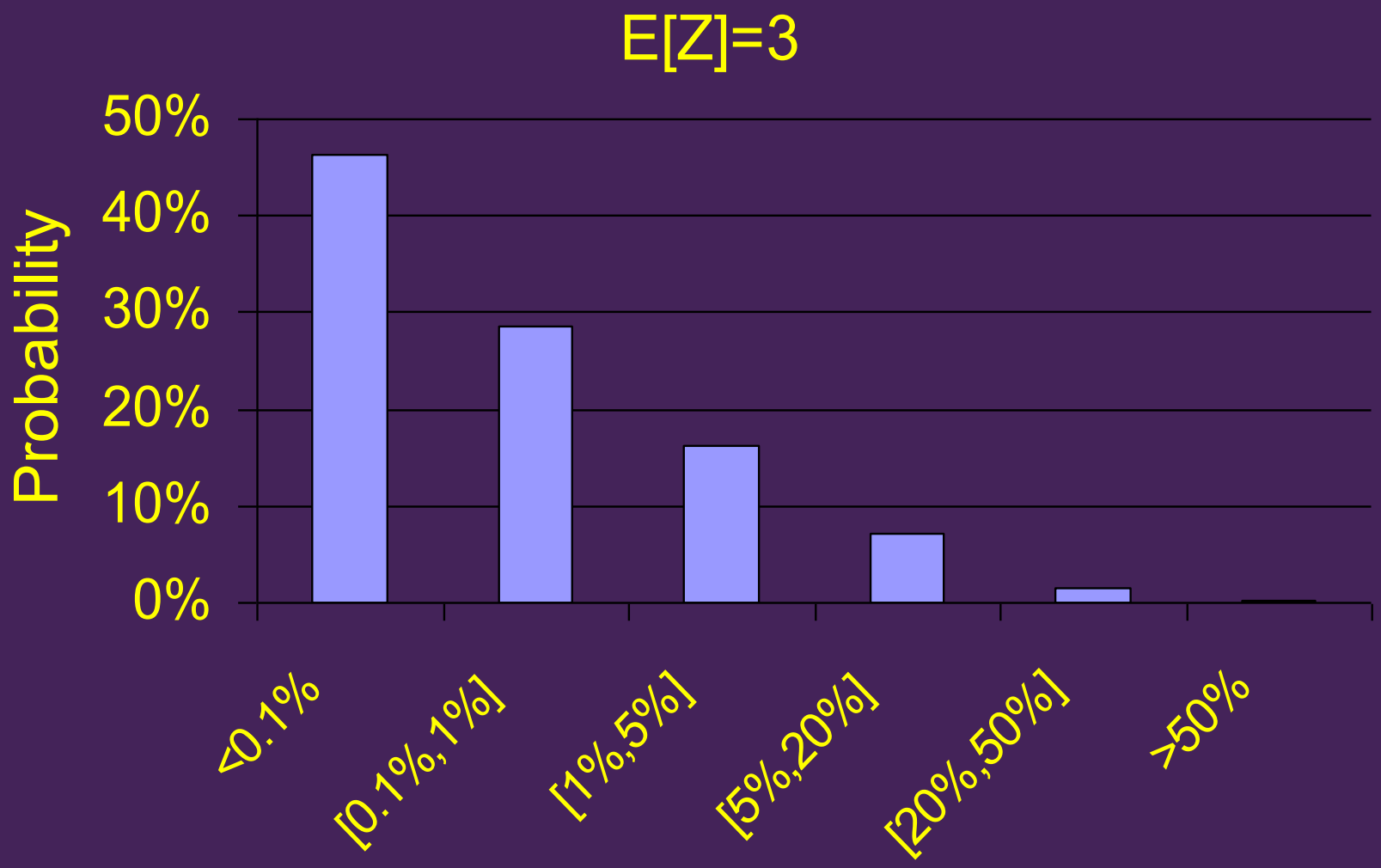

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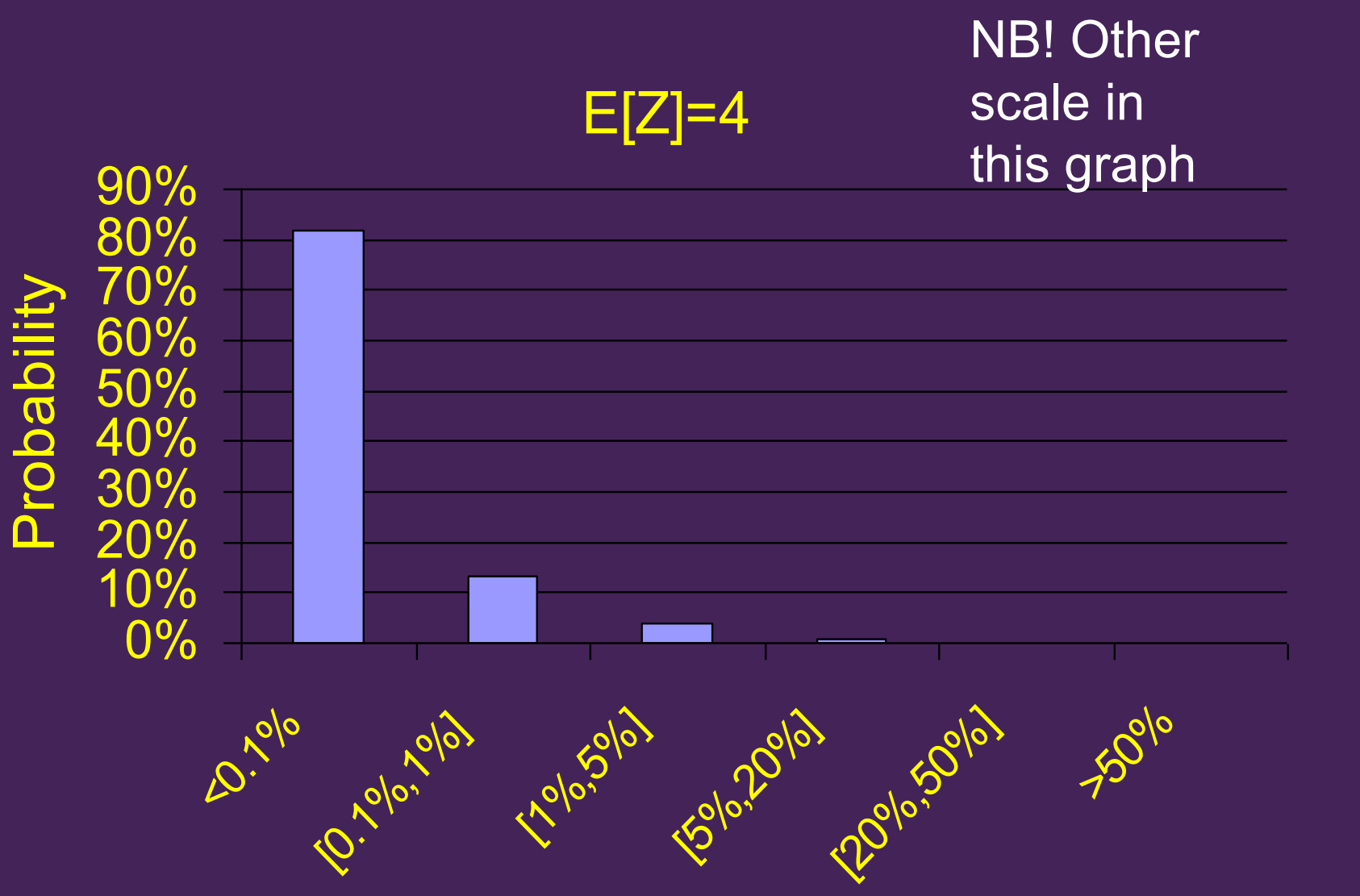

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Commercial Break

Conference on Pharmaceutical Statistics
EMA, ISBS, IBS-GR

- 5 tracks, 400? delegates
- Multiplicity, Adaptive designs, Bayesian, Dose-response, Decision analysis / Go-no go, Non-clinical, Predictive med., Globalisation, Regulatory, Payer, Vulnerable populations, Missing data, New guidance, Personalised healthcare, Meta analyis + Safety, Model-based drug development, Expanding the statistician's role
- www.isBioStat.org

- Berlin 1-3 mars (27-28/2)
- Industry: 500 euro
- Academia: 200 euro
- 5* hotel 125 euro/night
- Air Berlin <1000 SEK
- Courses: Multiplicity / Surveillance / Dose Finding / Non-clin / Intro DD stats / Clin Trial Methodology (S-J Wang, J Hung, FDA)

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Certification of statisticians

?

The board of Statistikerfrämjandet has launched a committee to look at a potential certification of statisticians.
If you want to give input at an early stage, please contact e.g.
Mats Rudholm or Carl-Fredrik Burman

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New books:

Dmitrienko et al. 2009
Bretz et al 2010

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