ADAPTIVE DESIGNS
An Overview

Nancy Flournoy
University of Missouri

Fields Institute
September 26, 2003

CONVENTIONAL EXPERIMENTAL DESIGNS

- All treatments, doses and/or treatment combinations are fixed prior to the study.
- Patients are randomized to the various treatments.
- The chance that any particular treatment will be selected for any particular patient remains constant throughout the study

  (e.g., randomize half of the subjects to an experimental treatment and half to a control).
- Sample size if fixed

ADAPTIVE DESIGNS

- Subjects are treated sequentially, or in (two or more) groups.
- A treatment is assigned to each subject.
- The chance that a subject (group) will get a particular treatment changes as information accrues in the study

REASONS FOR USING ACCRUING EXPERIMENTAL DATA TO CHANGE TREATMENT ALLOCATION PROBABILITIES

→ to improve

power,
efficiency,
safety,
efficiency,
model specification

WHY THE INTEREST IN ADAPTIVE DESIGNS NOW?

- Theoretical advances
- Computational advances

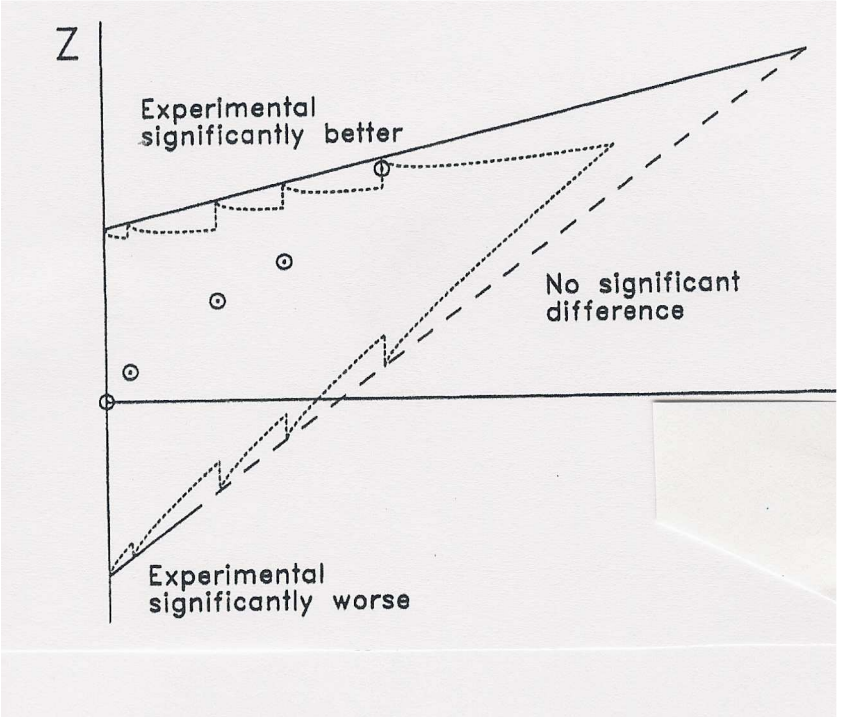
ADAPTIVE DESIGNS OUTLINE

1. CONVENTIONAL VS ADAPTIVE DESIGNS
2. EARLY STOPPING
3. ADAPTING TO BALANCE SUBJECT ALLOCATION BETWEEN TREATMENT GROUPS
4. TWO STAGE DESIGNS
5. BAYESIAN DESIGNS
6. OPTIMAL DESIGNS & APPROXIMATIONS TO THEM
7. AD HOC DESIGNS
   - UP & DOWN DESIGNS FOR TOXICITY ASSESSMENT & PHASE I CLINICAL TRIALS
   - UP & DOWN DESIGNS FOR PHASE I/II TRIALS
   - AN OPTIMIZING URN DESIGN
8. FINAL COMMENTS

EARLY STOPPING
Sequential Analysis

- Subjects arrive sequentially.
- A treatment is assigned to each subject
- The probability that a subject gets any particular treatment remains constant.
- Outcomes are assessed sequentially to determine if the better treatment can be identified with the desired confidence, and the study terminated.

A Triangular Early Stopping Rule



ADAPTING TO BALANCE SAMPLE SIZES BETWEEN TREATMENTS WHILE PRESERVING THE BENEFITS OF RANDOMIZATION

- A biased coin design (Efron, 1971)
- Talk 1. Biased Coin vs Ehrenfest Urn: an analysis of randomness, balance and power

  by Yung-Pin Chen

Balance maximizes power

when groups have equal variances

This is often a reasonable assumption when comparing means.

Let's consider comparing proportions p_T and p_C

1. Risk difference $p_T - p_C$
2. Log odds metric

$$\log (p_T/(1 - p_T) - \log (p_C/(1 - p_C)$$

3. Log risk ratio

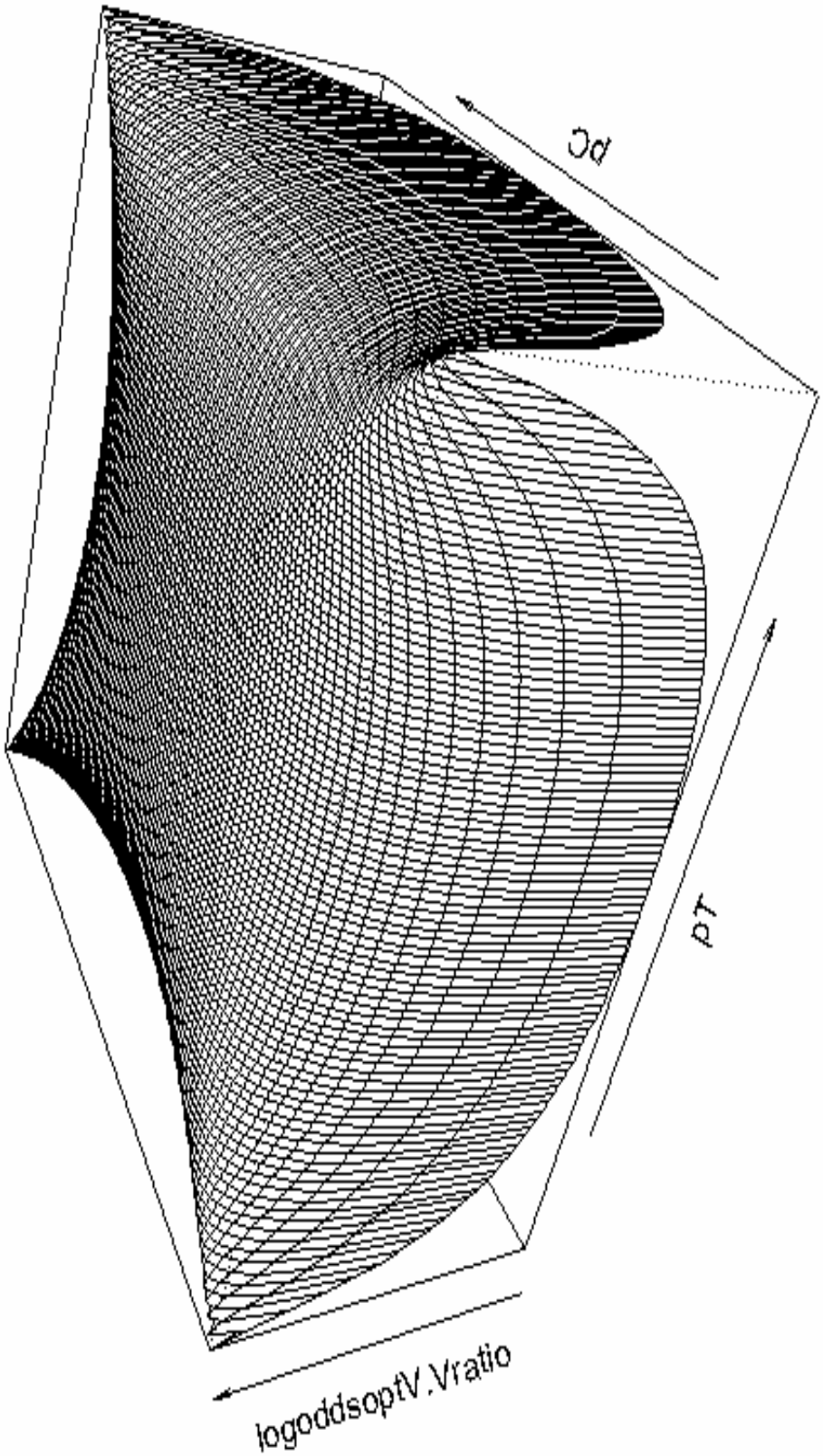
$$\log (p_T) - \log (p_C)$$

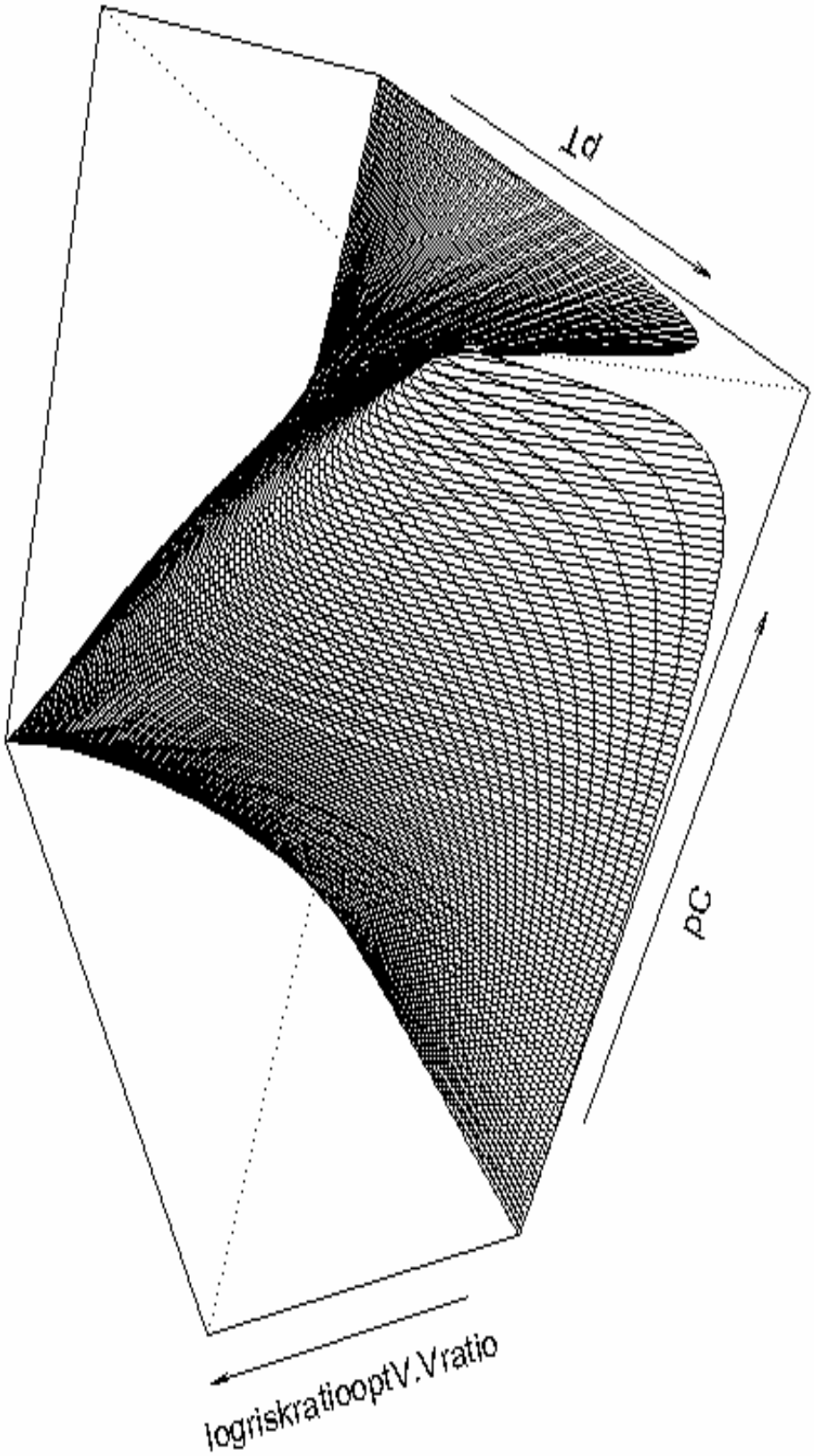
Calculate variance of each metric.

Evaluate each variance at $n_T/n = 1/2$

Find n_T/n for which variances are a minimum, and evaluate variances at these minima

Plot optimal variance / variance at $n_T/n = 1/2$


pC
pT
logoddsoptV.Vratio


1α
pC
logriskratiooptV.Vratio

TWO STAGE DESIGNS

- Talk 2. A Calculus for Design of Two-Stage Adaptive Procedures *by Tatsuki Koyama*

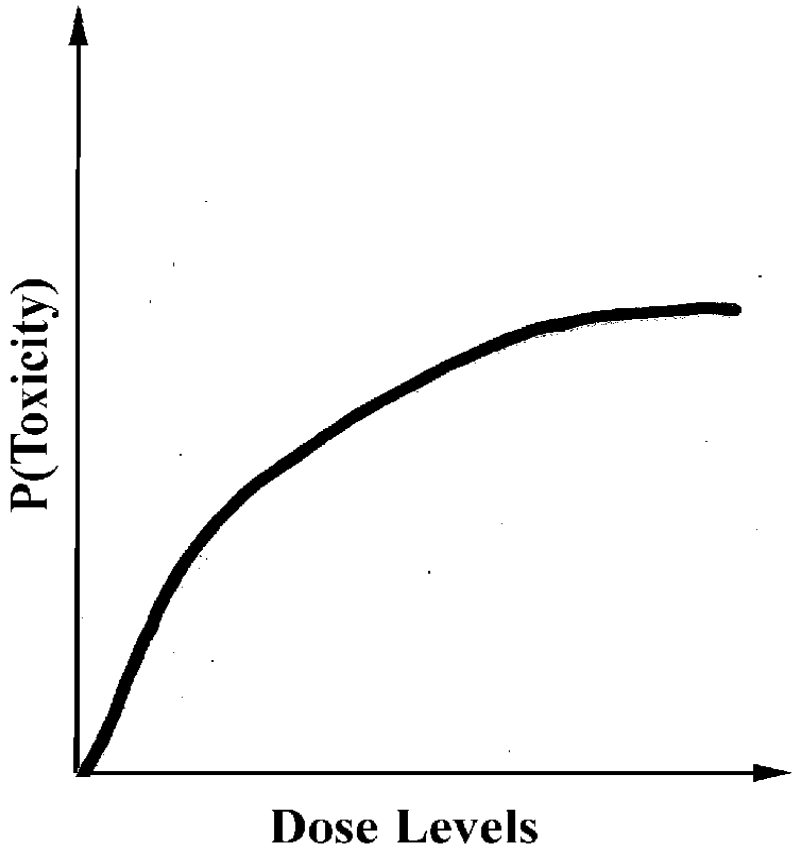
- Talk 3. ADAPTIVE FACTORIAL EXPERIMENTS FOR MODEL IDENTIFICATION *by Subir Ghosh*

RESPONSE - DRIVEN ADAPTIVE DESIGNS

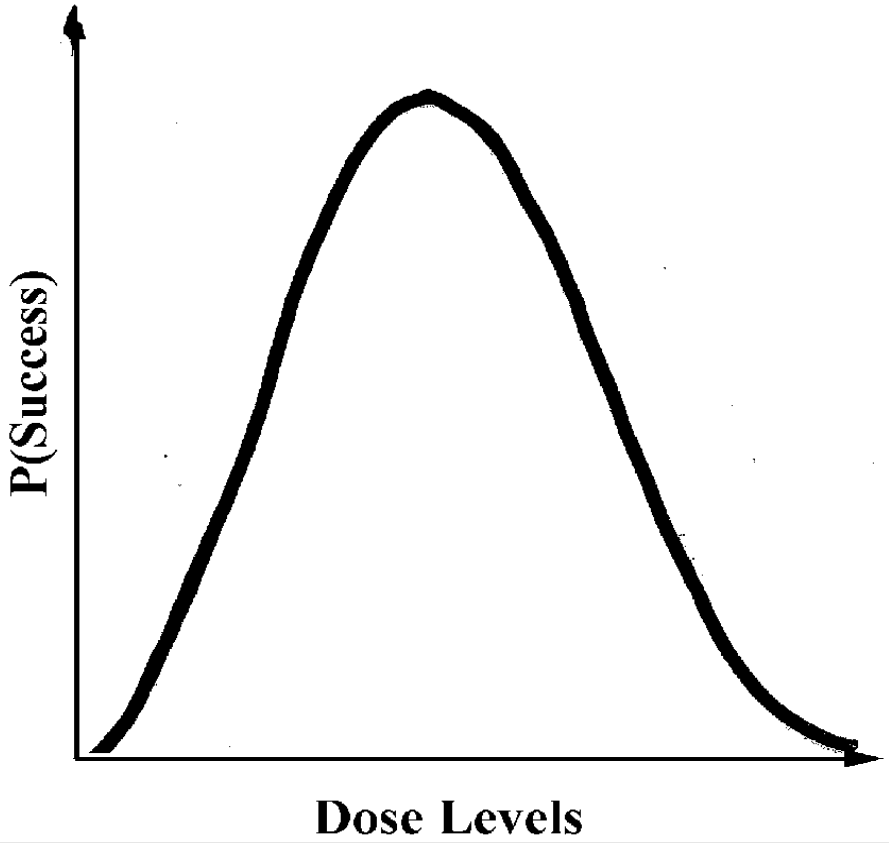
- Bayesian Designs
- Optimal Designs
  (Exact & Asymptotic)
- Ad hoc designs
  Up-and-Down Designs
  Urn Designs
  Stochastic approximation

MOTIVATING APPLICATIONS IN MEDICINE

Increasing Response Function



Unimodal Response Function



BAYESIAN DESIGNS

- Talk 4. Individualized patient dosing in phase I clinical trials

  by Andre Rogatko

- Talk 5. Flexible Bayesian methods for cancer phase I clinical trials

  by Mourad Tighiouart

OPTIMAL DESIGNS

- Talk 7. Optimal allocation in muilt-armed clinical trials

  by Yevgen Tymofyeyev

- Talk 8. Bandit problems and adaptive clinical trials

  by Xikui Wang

- Talk 9. Optimal few-stage designs for clinical trials

  by Janis Hardwick

AD HOC ADAPTIVE DESIGNS

AN URN DESIGN

- Talk 6 Minimized Hellinger distance estimations for randomized play the winner rule *by An-Lin Chen*

AN UP-AND-DOWN DESIGN

- Talk 12. Up-and-down designs for phase I trials; an evaluation of different designs and estimators *by Hon Keung Tony Ng*
- Also Talks 10, 11 & 13?

BIG ISSUES
Estimation and Inference

- Talk 6. Minimum Hellinger distance estimation for randomized play the winner rule

  by An-Lin Chen

- Talk 10. Nonparametric likelihood for response adaptive randomization with delayed response

  by Anand Vidyahankar

BIG ISSUES
efficiency and power

- Talk 1. Biased coin vs Ehrenfest urn: an analysis of randomness, balance and power *by Yung-Pin Chen*

- Talk 9. Optimal few-stage designs for clinical trials
  by Janis Hardwick

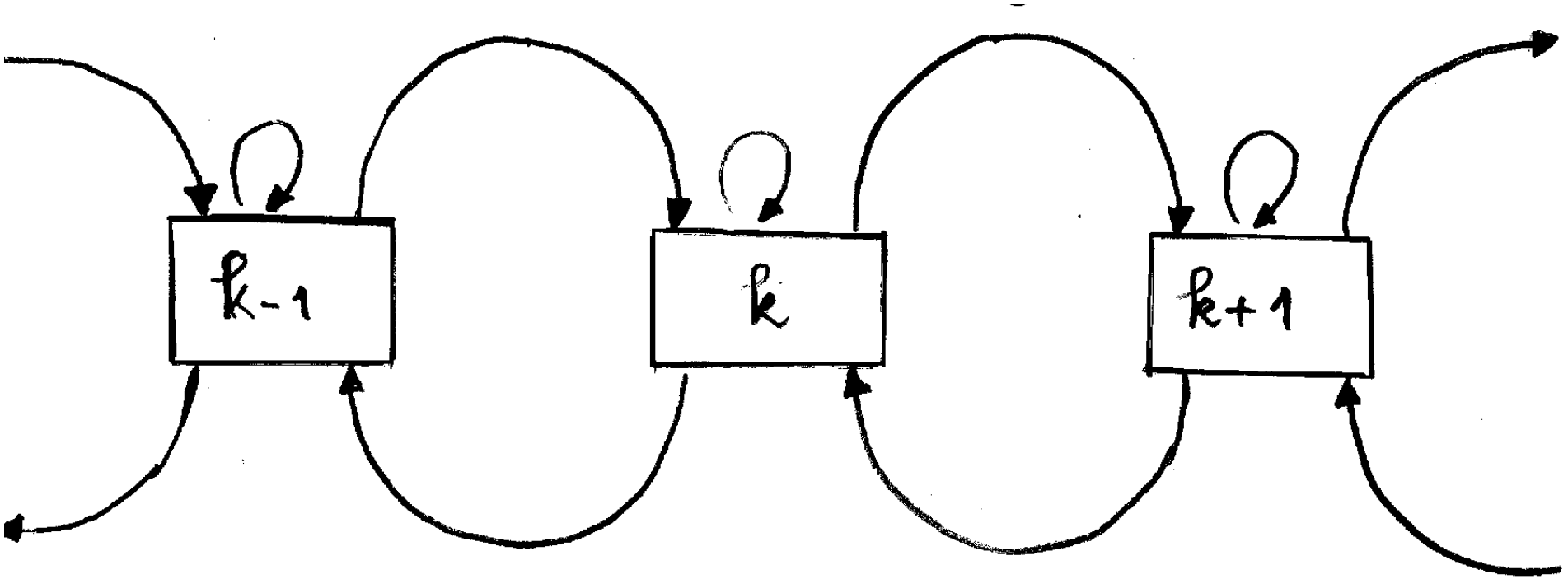
- Talk 11. Response-adaptive designs: ethics and efficiency of estimation
  by Anastasia Ivanova

- Talk 13. Response-adaptive designs: maximizing power and minimizing the expected number of failures
  by Feifang Hu

UP-AND-DOWN DESIGNS

- FOR PRODUCT LABELING
- FOR CONTOLLING TOXICITY
- FOR DOSE-FINDING

UP AND DOWN DESIGN



ADVANTAGES OF UP-AND-DOWN DESIGNS

- **Cluster Doses around an unknown Target Dose**
- Easy to Conceptualize
- Easy to Implement
- Changing Doses is Done Conservatively
  (i.e., no large increments between subjects)
- **No Parametric Model**
- **Exact Distribution Theory Available:**

  - Durham, **Flournoy**, Haghighi (1995). Up-and-down designs II: Exact treatment moments.

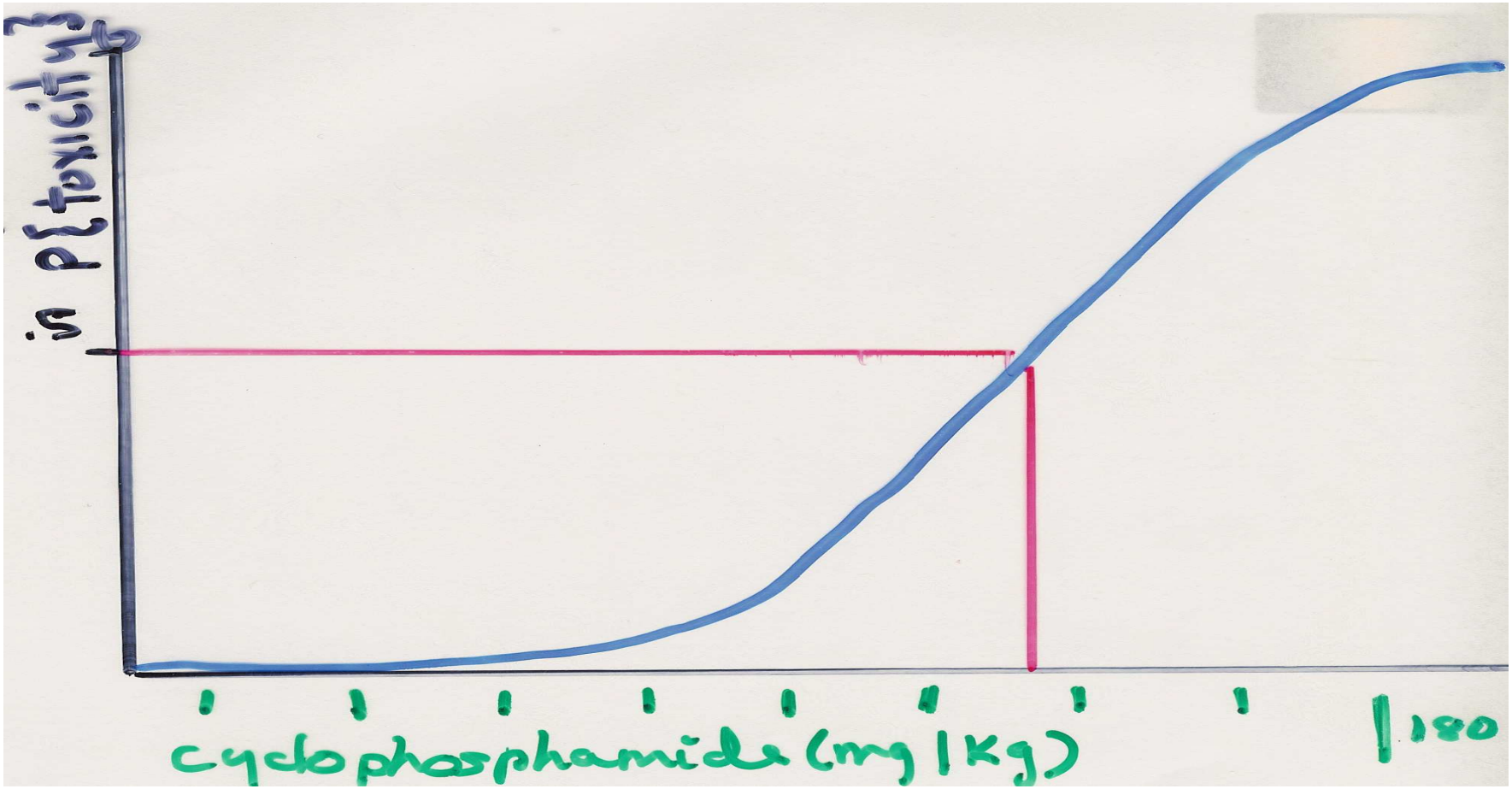
  IMS Monograph

  - Flournoy, Durham, Rosenberger (1995). Toxicity in sequential dose-response experiments. **Sequential Analysis.**

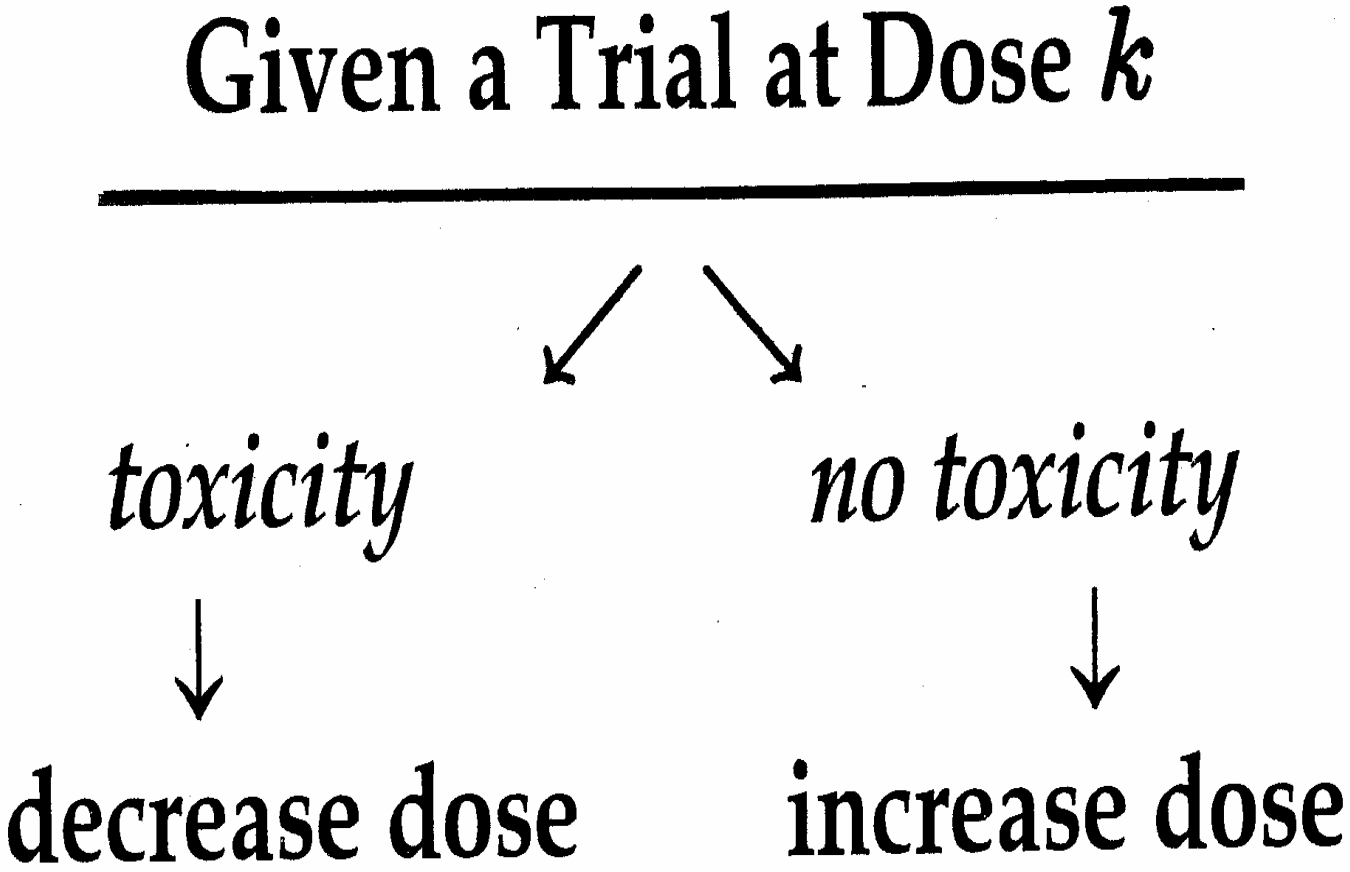
UP-AND-DOWN DESIGNS

WITH SEQUENTIAL ACCRUAL

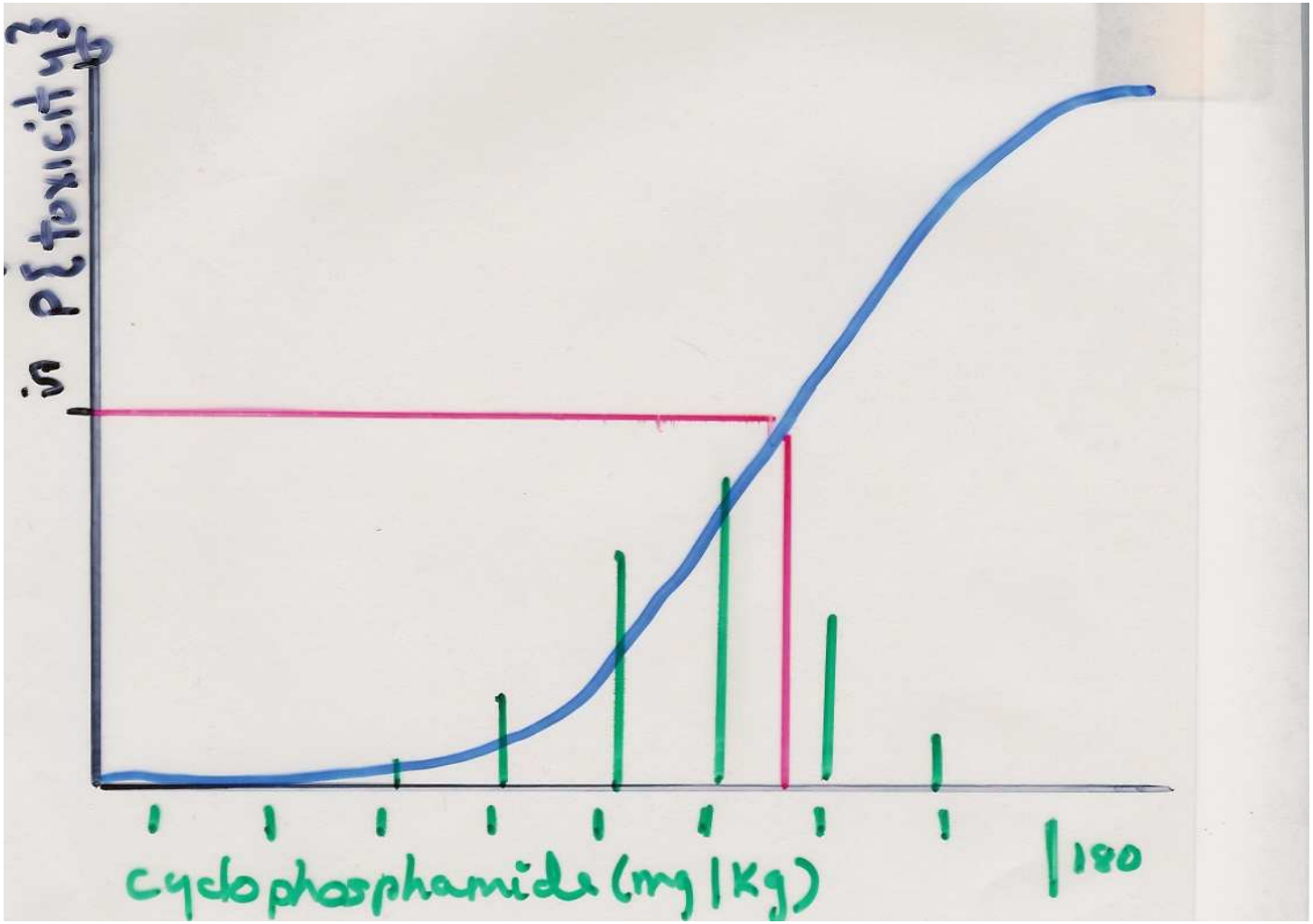
TARGETING THE LD50



DIXON AND MOOD (1948)



ASYMPTOTIC TREATMENT DISTRIBUTION TARGETING THE LD50



THEOREM

For any increasing response function, the asymptotic treatment distribution is unimodal with mode $\hat{\mu}$ less than Δ away from the dose for which $P\{\text{toxicity}\} = .5$

Durham, SD, **Flournoy**, N. (1994). Random walks for quantile estimation. **Statistical Decision Theory and Related Topics V**, 467-476 Springer-Verlag

EPA AND OECD "APPROVED"

UP AND DOWN DESIGN

FOR

PRODUCT LABELING ANIMAL STUDIES

Up-and-Down Procedure for Acute Oral Toxicity Updates and Announcements

http://iccvam.niehs.nih.gov/

U.S. EPA Announces Availability of Revised Final Health Effects Test Guidelines:

Acute Oral Toxicity

Revised December 2002

EPA & OECD "Approved" Up-and-down procedure

Aim: sequential procedure to estimate LD_{50}

Choose initial dose below guess of LD_{50}

Test one animal

death: decrease dose by factor of $\sqrt{10}$ for next animal

survival: increase dose by factor of $\sqrt{10}$ for next animal

Continue until some stopping criterion is met

Estimate LD_{50} using maximum likelihood (assuming β)

obtain confidence interval from profile likelihood

Test Guidelines/Acute Toxicity Acute Oral Toxicity Up-And-Down-Procedure

- User Documentation for the AOT425StatPgm Program

- AOT425StatPgm (This is a self-extracting zip file which will install the program on your computer in two steps…) *Note: This is to confirm that use of the computer program, AOT425StatPgm, developed by Westat for the US EPA , is freely given and there are no licensing restrictions in connection with its use.*
- AOT Test Data Set (This is a zip file which contains 15 test data sets, a result table, and instructions for their use to verify proper installation of the AOT425StatPgm program)

- QA Testing for the AOT425StatPgm Program - (PDF)

- Simulation Results for the AOT425StatPgm Program - (PDF)

- Toxicology Guidance: Performance of the Up-and-Down Procedure - (PDF))
- OECD Test Guideline 425: Acute Oral Toxicity - Up-and-Down Procedure - (PDF)
- OPPTS Harmonized Test Guideline 870.1100 Acute Oral Toxicity (PDF)

Source: http://www.epa.gov/oppfead1/harmonization/

STATISTICAL CONCERNS

UDP SHOULD NOT BE USED FOR

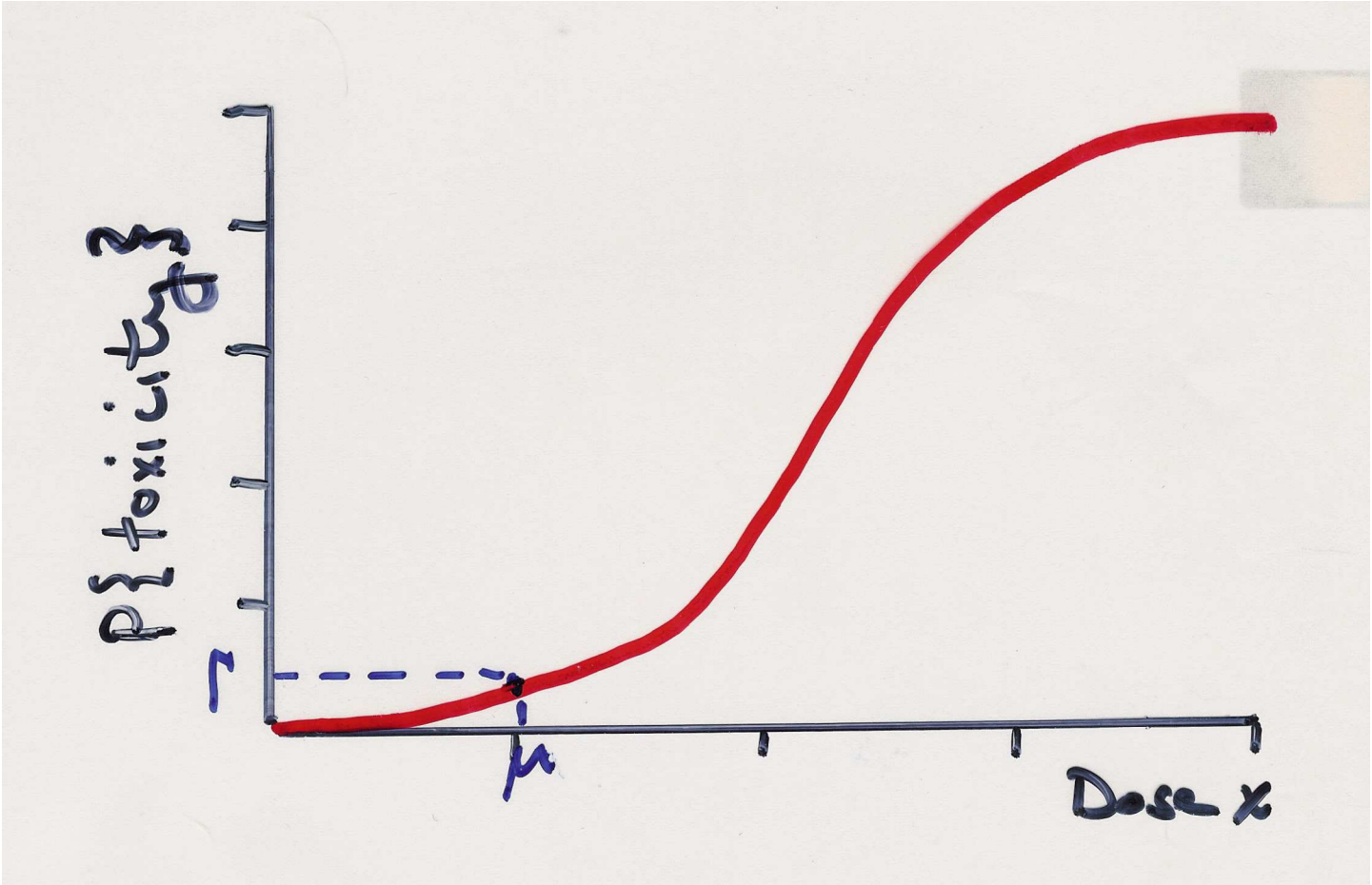
- RISK ASSESSMENT

  Estimate LDp, p possibly small

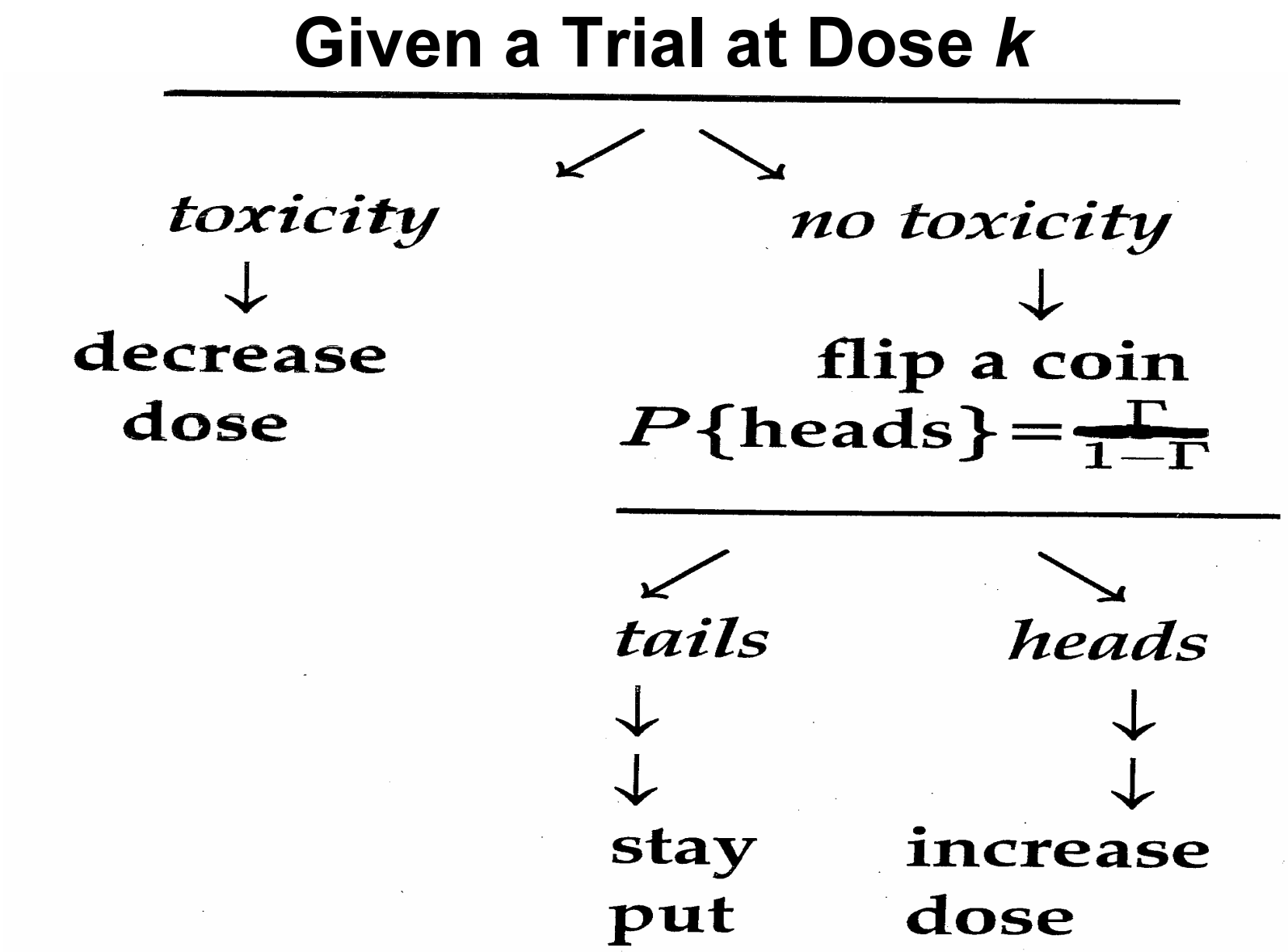
- CONFIDENCE INTERVALS

  FOR THE LD50

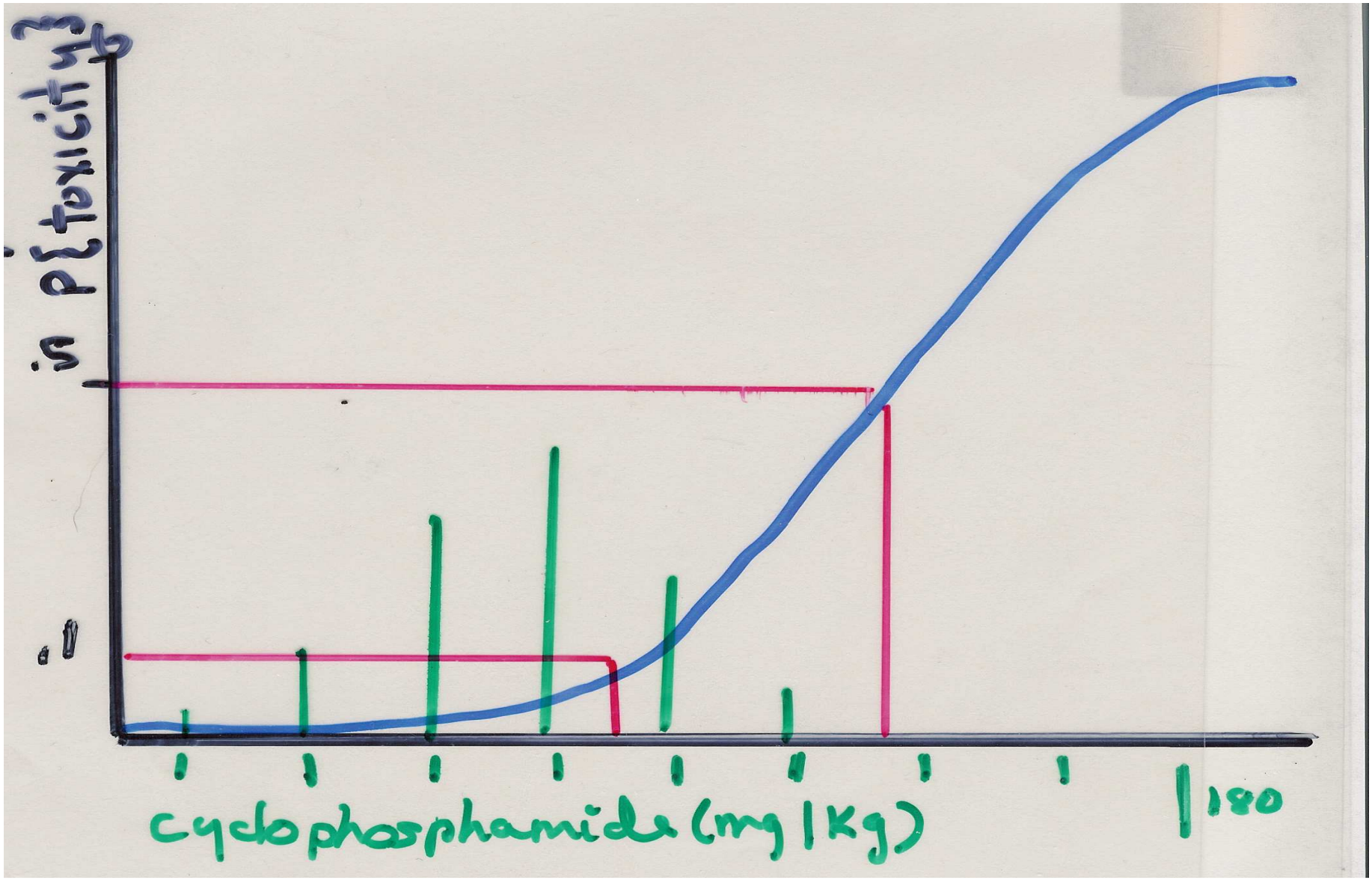
TARGETING THE LDΓ



BIASED COIN
UP-AND-DOWN DESIGN FOR $\Gamma \leq .5$



ASYMPTOTIC TREATMENT DISTRIBUTION TARGETING LDΓ



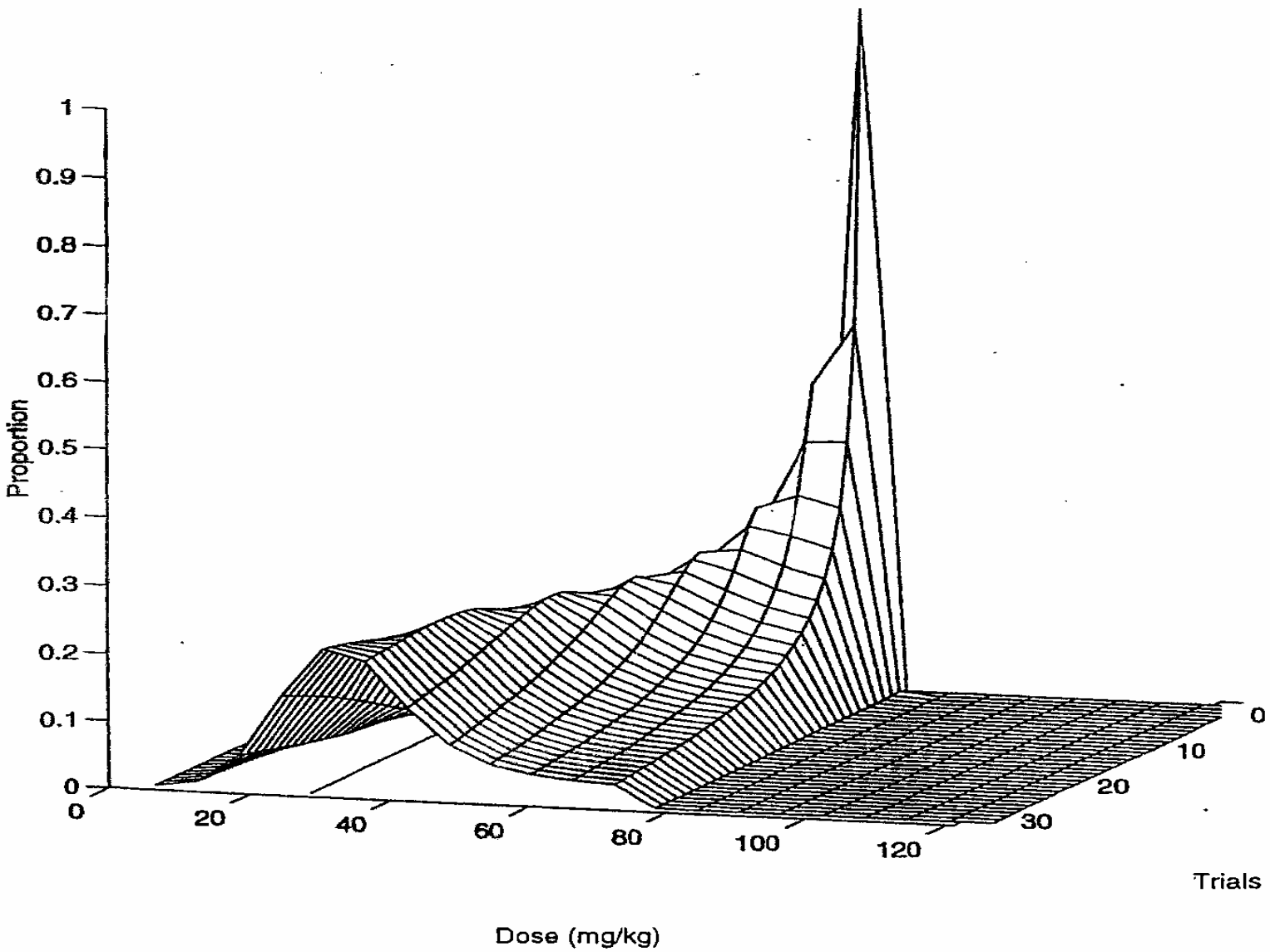
THEOREMS

If treatments are selected according to the Biased Coin Up and Down Design, and the probability of response increases with dose,

Then, asymptotically,

- Treatments assignments are unimodally distributed around the target dose
- Mode of the treatment distribution is the largest dose <= target dose
- |treatment mode - target dose| <= interval between doses

WHAT ABOUT SMALL SAMPLE SIZES?



Expected proportions of subjects allocated at each dose level under the empiric response function. We interpolate between the points that occur at $n = 1, \ldots, 34$ and each possil dose level in x_1.

WE RECOMMEND USING SMOOTHED ISOTONIC REGRESSION TO ESTIMATE THE LDΓ

- Stylianou, M, **Flournoy, N** (2002). Dose finding using isotonic regression estimates in an up-and-down biased coin design. *Biometrics*.

ISOTONIC REGRESSION is NONPARAMETRIC

If observed proportion of responses increase with dose, you are done.

Going from lowest dose toward the highest dose, whenever the empirical proportion of responses drops, average it with the one before.

WHY NOT MLE?

- REQUIRES PARAMETIC MODEL FOR RESPONSE FUNCTION, e.g. logistic
- DESIGN IS NOT GOOD FOR ESTIMATING THE SLOPE PARAMETER OF A PARAMETRIC MODEL
- OFTEN MLE DOES NOT EXIST FOR SMALL SAMPLE SIZES

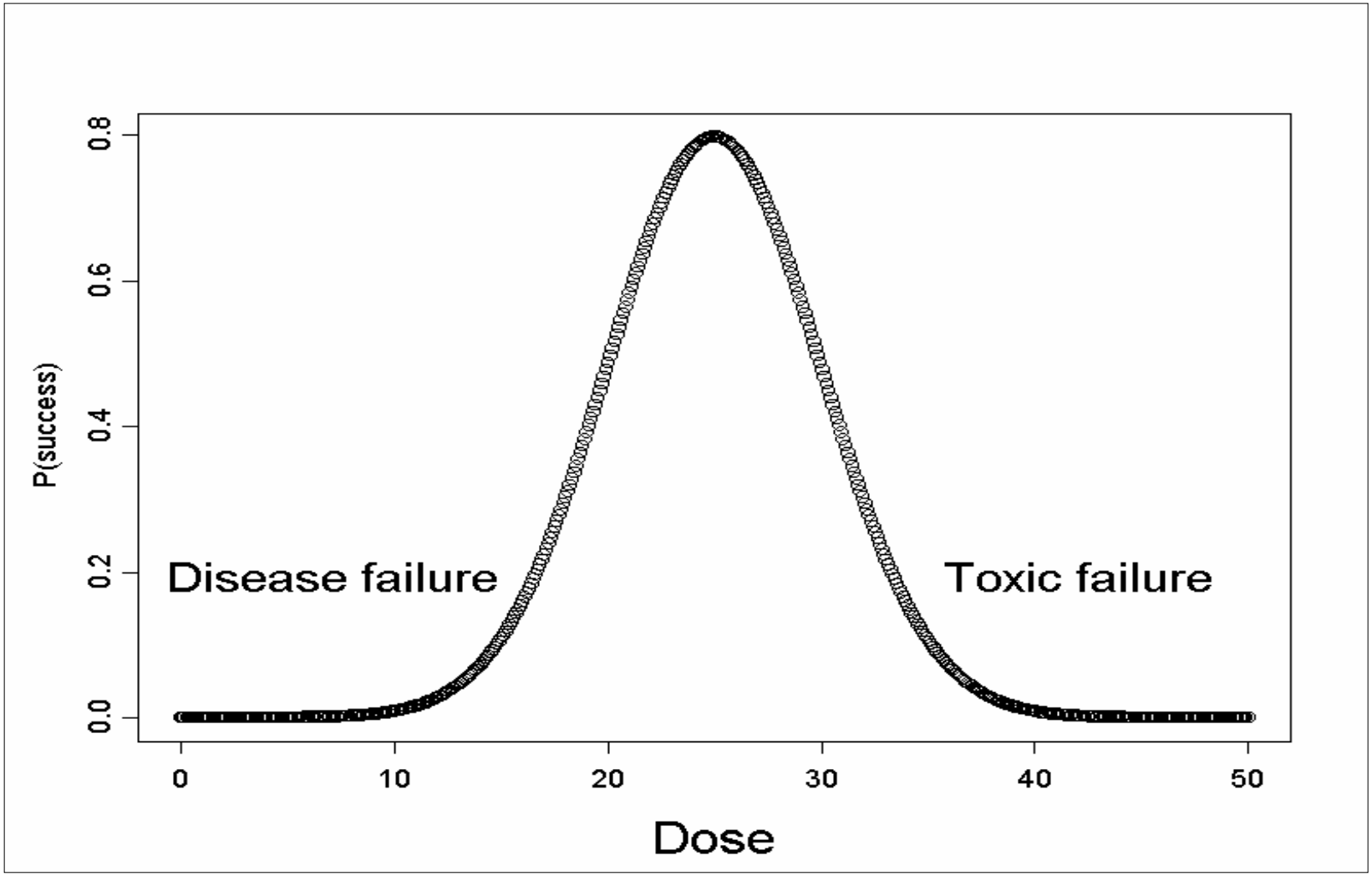
SOME OTHER UP-AND-DOWN DESIGNS

FOR CONTOLLING TOXICITY

- Group up-and-down Designs (Gezmu & Flournoy)
- r-in-a-row (Gezmu & Flournoy)
- Moving Average (Ivanova, Mohanty & Durham)
- Narayana's (Ivanova, Mohanty & Durham)

Talk 12. comparisons *by Hon Keung Tony Ng*

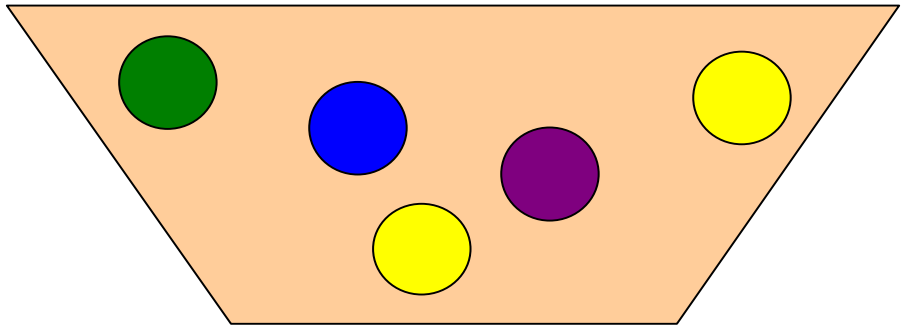
Optimizing Up-and-Down Designs Cluster Subjects Around Optimal Dose



OPTIMIZING URN DESIGNS

PURE BIRTH URN DESIGN

Li, Durham & Flournoy



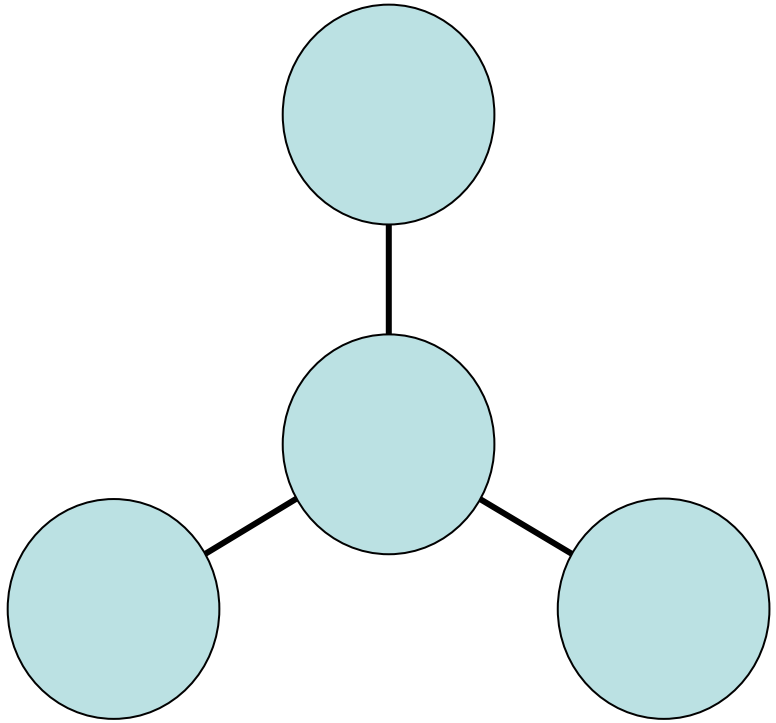
- Draw a ball and replace it.
- If ball is color *i*, give treatment *i.*
- If that treatment is successful,

  add another color *i* ball.
- If that treatment is a failure, do nothing.

PURE BIRTH URN DESIGN

- Suppose the best treatment corresponds to the green balls.
- Green balls will proliferate

  until virtually all the balls are green.



$\alpha_k = P\{\text{success given treatment } k\}$

THEOREM

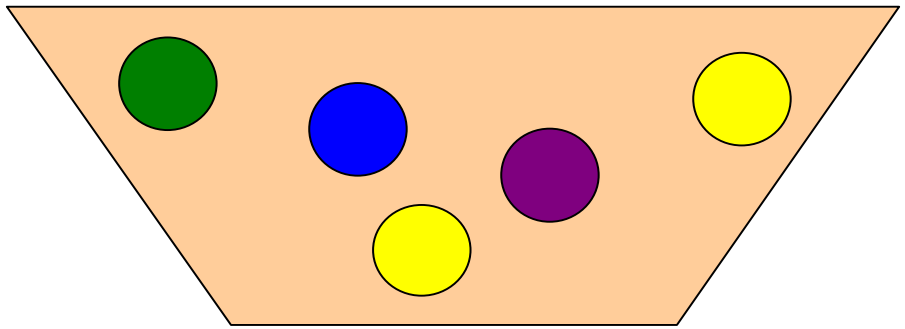
If $\max\{\alpha_1, \ldots, \alpha_K\} = \alpha_i$,

the proportion of type i balls $\rightarrow 1$

wp 1 as $n \rightarrow \infty$

PURE DEATH URN DESIGN

Ivanova

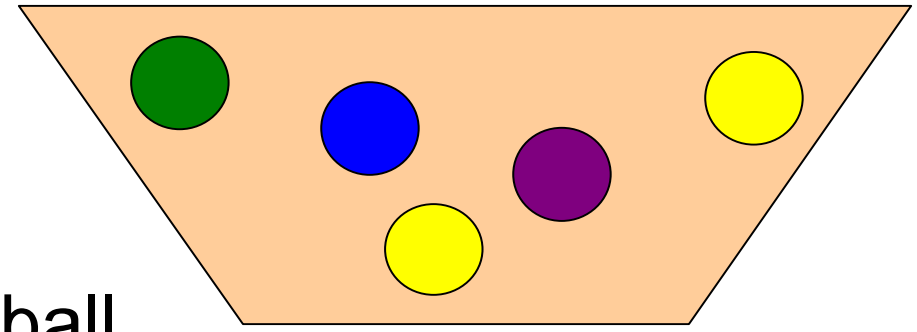


- Draw a ball and replace it.
- If ball is color *i*, give treatment *i.*
- If that treatment is successful,

  replace the drawn ball.
- If that treatment is a failure, do not replace the drawn ball.

BIRTH AND DEATH URN DESIGN

Ivanova, Rosenberger, Durham & Flournoy



- Draw a ball.
- If ball is color *i*, give treatment *i.*
- If that treatment is successful,
  add another color *i* ball.
- If that treatment is a failure,
  do not replace the drawn ball.

RANDOMIZED PLAY THE WINNER

Does it have a future?

Talk 6 (others?).

ADAPTIVE DESIGNS
OUTLINE

1. CONVENTIONAL VS ADAPTIVE DESIGNS
2. EARLY STOPPING
3. ADAPTING TO BALANCE SUBJECT ALLOCATION BETWEEN TREATMENT GROUPS
4. TWO STAGE DESIGNS
5. BAYESIAN DESIGNS
6. OPTIMAL DESIGNS & APPROXIMATIONS TO THEM
7. AD HOC DESIGNS
   - UP & DOWN DESIGNS FOR TOXICITY ASSESSMENT & PHASE I CLINICAL TRIALS
   - UP & DOWN DESIGNS FOR PHASE I/II TRIALS
   - AN OPTIMIZING URN DESIGN
8. FINAL COMMENTS

BIG ISSUES

POWER

EFFICIENCY

ESTIMATION

INFERENCE