Course Syllabus:

Adaptive Randomized Trial Designs
140.850, 4th Quarter, 2011
Johns Hopkins Bloomberg School of Public Health

Instructor: Michael Rosenblum
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http://csail.mit.edu/~mrosenblum/Teaching/adaptive_designs_2011.html

Dates: March 28, April: 1, 4, 11, 15, 18, 22. (Note April 8 is excluded.)
Time: 10:30AM-11:50AM.
Room: W2009

3 credits
(All are invited to attend, even if not taking for credit.)

Summary:
The course will give an overview of adaptive randomized trial designs. The aim of the course is to familiarize students with the advantages, limitations, and open problems in adaptive randomized trial designs.

Assignment: There will be a single assignment for those taking the course for credit—to complete one of the following:
1) Conduct simulations comparing two or more existing adaptive designs.
2) Propose a novel adaptive design and compare to existing designs,
(where comparison is via simulation or asymptotic results, you choose).
3) Use the clinical trials database http://clinicaltrials.gov to investigate how often different adaptive design types are used, and under what settings. E.g. searching under the term "adaptive design" yields 42 clinical trials; you could classify these by type of adaptation, Phase of the trial, and condition type.

The project is not meant to be onerous, just a chance to experiment with the ideas we discuss. It should be written up in at most four pages, single spaced, 12 point font.

Readings (The date below indicates when the papers will be discussed.):

All papers are available on the course website given above.

March 28: Overview of Adaptive Randomized Trial Designs: Some Skeptics' Perspectives

[N.B. There is no expectation that the following two papers will be read before the first class meeting.]

Wittes, J., and Lachenbruch, P. (2006) Discussion: Opening the Adaptive Toolbox. *Biometrical Journal.* 4, 598-603. DOI: 10.1002/bimj.200610240

Fleming, T. R. (2006) Standard versus adaptive monitoring procedures: a commentary. *Statistics in Medicine*. 25: 19. 3305-3312. DOI: 10.1002/sim.2641

April 1: U.S. FDA Guidances. Adapting Randomization Probabilities

U.S. F.D.A. (2010) Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

April 4: Adapting Randomization Probabilities

Feifang Hu, William F Rosenberger. (2004) Maximizing power and minimizing treatment failures in clinical trials*. Clinical Trials*. 1:141. http://ctj.sagepub.com/cgi/content/abstract/1/2/141

[Here's the more theoretical version of above paper:]
Feifang Hu, William F Rosenberger. (2003, September) *Journal of the American Statistical Association.* 98(463): 671-678. doi:10.1198/016214503000000576.

April 11: Adapting Sample Size

Scharfstein DO, Tsiatis AA, Robins JM (1997). Semiparametric efficiency and its implication on the design and analysis of group sequential studies. *Journal of the American Statistical Association.* 92(44): 1342-1350.

Anastasios A.Tsiatis and Cyrus Mehta. (2003) On the inefficiency of the adaptive design for monitoring clinical trials. *Biometrika.* 90(2):367-378; doi:10.1093/biomet/90.2.367

April 15: Seamless Phase II/III Designs

Jennison C, Turnbull BW. (2006) Confirmatory seamless phase II/III clinical trials with hypothesis selection at interim: opportunities and limitations. *Biometrical Journal.* 48:650–655.

Jennison, C. and Turnbull, B.W. (2007) Adaptive seamless designs: Selection and prospective testing of hypotheses. J. Biopharmaceutical Statistics, 1135-1161; doi: 10.1080/10543400701645215.
http://people.bath.ac.uk/mascj/papers/JBS07.pdf

Tim Friede and Nigel Stallard. (2008) A Comparison of Methods for Adaptive Treatment Selection. *Biometrical Journal*. 50 5, 767–781 DOI: 10.1002/bimj.200710453

April 18: Adapting Hypothesis Tested

Gerhard Hommel. Adaptive Modifications of Hypotheses After an Interim Analysis *Biometrical Journal.* 43 (2001) 5, 581–589

Rosenblum and van der Laan. (2009, April) Optimizing Group Sequential Designs that Allow Pre-planned Changes to the Population Sampled Based on Interim Data. *Proceedings of the 57th Session of the International Statistical Institute.* Durban, South Africa.

April 22: Bayesian Designs

Barker, AD, Sigman, CC, Kelloff, GJ, Hylton, NM, Berry, DA, and Esserman, LJ (2009), I-SPY 2, An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

Berry, DA, Mueller, P, Grieve, AP, Smith, M, Parke, T, Blazek, R, Mitchard, N, Krams, M (1999)
Adaptive Bayesian Designs for Dose-Ranging Drug Trials

Rosner, GL, and Bekele, BN
Bayesian Designs in Clinical Trials

Giles, FJ, Kantarjian, HM, Cores, JE, Garcia-Manero, G, Verstovsek, S, Faderl, S et al. (2003)
Adaptive Randomized Study of Idarubicin and Cytarabine Versus Troxacitabine and Cytarabine Versus Troxacitabine and Idarubicin in Untreated Patients 50 Years or Older With Adverse Karyotype Acute Myeloid Leukemia

Zhou, X, Liu, S, Kim, ES, Herbst, RS, Lee, JJ (2008)
Bayesian adaptive design for targeted therapy development in lung cancer-a step toward personalized medicine