Mixed-Effects Modeling of Tumor Growth in Animal Xenograft Experiments

When basic science research suggests a new possibility for a cancer treatment approach, pre-clinical studies are performed to obtain preliminary assessments *in vivo* of the biological response of human tumors to that treatment. Such translational research often relies on tumor xenograft experiments in animal models (e.g., mice). [Morton & Houghton, 2007; Richmond & Su, 2008] These data come from such an experiment but have been edited to highlight certain issues for pedagogical purposes. There are various issues relevant to the design, implementation, and data analysis of animal xenograft experiments. [Hanfelt, 1997]. This teaching resource introduces the mixed-effects regression approach for the analyses of such data.

Cells from a human glioma cell line were implanted in the flank of n=37 nude mice and a subcutaneous tumor (xenograft) was allowed to grow. When a tumor grew to around 40-60 mm^3, the animal was assigned to one of 4 experimental groups (day 0): 1) Control (CTR, n=8); 2) Drug only (D, n=10); 3) Radiation only (R, n=10); and 4) Drug + Radiation (D+R, n=9). The main outcome in xenograft experiments is the size (volume) of the tumor over time. In this study, tumor size was typically measured every work day (excluding weekends and holidays, and occasional skipped days) for up to 4 weeks. An animal was euthanized if it appeared distressed or moribund, or when its tumor grew to about 2 cm^3.

The study's two main **scientific aims** were to assess whether:

a. The drug has an effect on tumor growth.
b. The administration of the drug before radiation enhances the effect of the latter on tumor growth.

Mixed-effects modeling approaches were used to address these aims. Mixed-effects linear regression is an extension of ordinary linear regression that accounts for the within-animal correlation of the repeated measurements over time and for missing data (intermittent measurements and uneven follow-up due to animal death). Non-linearity of tumor growth and the potential confounding effect of variations in tumor size at the start of the experiment were also considered.

References:

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