Adaptive Dose Insertion for Early Phase Clinical Trials

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We propose to adaptively insert new doses during the course of a dose-finding trial when none of the prespecified doses in the trial are acceptable, e.g., have tolerable toxicity. Our procedure uses an activation rule to determine whether a new dose is needed and an inverse dose-response algorithm to estimate new doses to be inserted into the trial. The proposed method can be applied to both one-agent and two-agent trials. In application to a Phase I trial about advanced ovarian cancer, our method selected a new dose that is better than all prespecified doses in at least 44% simulations. The effectiveness of the procedure was also demonstrated in a simulation study. We believe that with the added adaptive dose insertion, traditional dose-finding trials will have better chances of locating desirable doses. In addition, by allowing for dose insertion, unnecessary trial suspension due to lack of acceptable doses can be avoided.