Math in Dose Escalation

- Modified Fibonacci Sequence

Modified Fibonacci Sequence

Fibonacci Sequence

The classic Fibonacci sequence is defined by the linear recurrence equation:

Which goes like 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, ... In another words, the next number in the sequence is equal to the sum of its two predecessors.

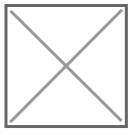
The ratio of successive Fibonacci number tends rapidlly to a constant 1.618.

Extend for Mathematical Prove

It is known that,

So that,

Let,



Hence,

When n approaches to infinity,

Then,

Solve the equation,

The ratio is positive,

Modified Fibonacci Sequence

However, the modified Fibonacci sequence commonly used in dose escalation (over 2, 1.67, 1.50, 1.33 and so on) is not identifed and almost never cited.

Marvin Schneiderman, a statistician at the National Cancer Institute, seems to have been the first to propose in writing a scheme of decreasing increases for drug testing.

Later, Hansen gave increasing doses of lomustine to subsequent sets of patients, saying that they used “escalation in decreasing steps” and that “the dose was escalated with a modification of the Fibonacci search scheme” citing Schneiderman’s article, but they don’t elaborate.

Professor George A. Omura of Medicine in the Hematology/Oncology Division at UAB had clearly justified and suggested that "It might be best, for the sake of clarity, to label decreasing increment schemes as such, specifying the increments, without invoking Fibonacci".

Reference

1. Omura, G. A. Modified Fibonacci Search. JCO 21, 3177–3177 (2003).

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3. Penel, N. & Kramar, A. What does a modified-Fibonacci dose-escalation actually correspond to? BMC Med Res Methodol 12, 103 (2012).

4. Schneiderman, M. A. MOUSE TO MAN: STATISTICAL PROBLEMS IN BRINGING A DRUG TO CLINICAL TRIAL.