Stochastic Simulation to Obtain the Exact Solution of the Two-Stage Clonal Growth Model

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Multistage clonal growth models (CGM) are used to predict tumor incidence in support of cancer dose-response assessments. Several groups have described analytical expressions for the exact solution of the 2-stage CGM for time-constant parameters. However, solutions derived for time-constant parameters sometimes fail to give good approximations when the parameters are time-dependent. Moolgavkar and co-workers solved the forward Kolmogorov equations to calculate the exact solution of the 2-stage CGM with piecewise-constant parameters. Recently, a new method of solution based on the backward Kolmogorov equations had been developed for the case of time-dependent parameters. In this report we describe an alternative, though computationally intensive, method to obtain the exact incidence for the 2-stage CGM for time-dependent parameters. Poisson random numbers are used to describe mutation of normal cells, the birth-death process of the initiated (1-mutation) cells is described using binomial random numbers, and the mutation of initiated cells is described using either binomial or Poisson random numbers. A model run proceeds until a tumor arises. The model is then restarted. Several thousand runs provide incidence curves that agree well with the exact solution calculated by solving the backward Kolmogorov equations. The current implementation of this model in vectorized MATLAB code achieves about 100 runs/minute on a desktop PC. This approach is much slower than the method that solves the backward Kolmogorov equations, and would therefore have little value for applications involving statistical optimization. The approach may in the future be more useful as computer power increases and as more complicated biochemical signaling networks are incorporated into CGM. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*

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Notes for Sandra:

Conolly and Clewell are full members of SOT
Crump is not a member of SOT