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DIFFUSION PROCESS CALCULATIONS FOR MUTANT GENES IN NONSTAYIONARY POPULATIONS

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Diffusion process approximations were introduced into population genetics by Fisher and Wright and perfected by Kimura. Contrary to popular scientific opinion, these pioneers did not solve all of the interesting modeling problems. For instance, none of them has much to say about the stochastic dynamics of recessive disease genes. They are also more or less silent on the stochastic aspects of evolution in the presence of exponential population growth. The current paper uses Itô's formula to derive an infinite hierarchy of integral equations satisfied by the moments of a diffusion process. These integral equations can be converted into an infinite hierarchy of ordinary differential equations and solved either exactly or numerically. We illustrate some of the possibilities for dominant, neutral, and recessive models of inheritance by computing the moments of gene frequencies in the presence of exponential population growth.

1. Introduction. The evolutionary forces governing the distribution and dynamics of human genetic diseases can be modeled in a variety of ways. The earliest and most understandable models are deterministic (Cavalli-Sforza and Bodmer 1971, Crow and Kimura 1970, Ewens 1979, Nagylaki 1992). Later models attempt to capture the more subtle stochastic effects that inevitably come into play. For autosomal dominant or X-linked diseases, branching process models are ideal (Fisher 1930, Haldane 1927, Harris 1989, Skellam 1949). By viewing each new disease mutation as the progenitor of an independently evolving clan of deleterious gene carriers, one can answer a host of interesting population genetic questions (Gladstien and Lange 1978a, Gladstien and Lange 1978b, Lange and Gladstien 1980, Lange 1982). We have recently extended these branching process models to include exponential growth of the surrounding population of normal individuals (Lange and Fan 1997, Fan and Lange 1998).

For recessive diseases, selection occurs when carrier individuals from the same or different clans mate. Thus, the independence assumption of the branching process paradigm breaks down. Although the alternative Wright-Fisher model of evolution eschews the dubious assumption of independently evolving clans, it has yielded, contrary to popular scientific opinion, little insight into the balance between selection and mutation for recessive diseases (Crow and

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