Genetics and prehistory of the periodicity of lymphatic filariases: geometrical approach, simulation and cellular automaton.

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The lymphatic filariases, the extreme manifestation of which is elephantiasis, are cosmotropical mosquito-borne diseases, due to the Nematodes *Wuchereria bancrofti* and *Brugia malayi*. In the major part, their embryos or microfilariae (mf) only appear in the human peripheral blood at night, when their mosquito vectors (mainly rural *Anopheles* and urban *Culex*) are active, and concentrate in the lungs during the day. This form is called "periodic". At the individual level, the life history of a mf is a compromise (Hawking, 1967). It seems to follow a 12h/12h-switch process. During the day, it actively remains at the entrance of the lung to avoid oxygen concentration. During the night, it lets passively carry itself by the blood stream, where it has to withstand some oxygen, but can be ingested by the mosquito and continue its life-cycle. Giving some stochasticity to the moving time, the summation of many individual migrations can be fitted correctly by a sinus curve, the peek-hour of which (acrophase) is k=0h and the relative (semi-) amplitude (a/m) of which is close to 1.

In several foci of Southeast Asia and the Pacific, mf are said "sub-periodic": mf are detectable in the peripheral blood at any time. Periodicity exists, but the relative amplitude is generally less than 0.5. Phase and amplitude vary from a focus to another. It was thought that that subperiodicity was an adaptation to the absence of nocturnal vectors. On direct and indirect evidence, Pichon (1979) suggested that subperiodicity was due to a mixture of strictly periodic biorhythms.

As the most parsimonious hypothesis, we propose that subperiodicity is genetically determined by only two alleles, n (for night) and d (for day), the phenotype [nn]=0h representing the nocturnally periodic biorhythm. Knowing the amplitude and phase averages of a population, it is possible to find geometrically the solution(s) [dd] and [nd] if the frequency p of the n gene in a population is fixed.

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For p varying between 0 and 1, we obtain for each population a diagram of the solution points ([dd], [nd]). We observe that all of the 7 diagrams intercept at the same point (14h, 14h). The hypothesis of a simple genetic determinism is thus ruled out. Moreover, as [dd]=[nd]=14h, we can conclude that, by definition, the d gene is dominant over the n gene.

Taking into account the biting cycle of the mosquitoes, simulation is in accordance with this finding. After 1000 parasite generations (5000 years), both genes coexist (subperiodicity) if the only vector is an *Aedes* (diurnal), but if the vector is an *Anopheles* (nocturnal), the d gene will irreversibly disappear in 4 generations (20 years). This explains the "success" of the nocturnally periodic parasite. A cellular automaton explains the geographical distribution of the periodic and subperiodic parasites. From the initial focus, somewhere in insular Southeast Asia, selection by Anopheles would rapidly eliminate the d gene and the subperiodic form. The d gene can only be maintained and expanded Eastward due to the intervention of Austronesian (pre-Polynesian) people whose canoes contain durable and salt-tolerant eggs of *Aedes* mosquitoes , mainly represented by *Ae. polynesiensis*, a diurnal (crepuscular) mosquito the irregular habits of which maintained the genetical diversity of the parasite biorhythms.

References

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