EXTINCTION OF VIRAL INFECTIVITY THROUGH LETHAL DEFECTION

Jaime Iranzo[1] and Susanna C. Manrubia[2]. Centro de Astrobiología, CSIC-INTA (Ctra. de Ajalvir km. 4, 28850 Torrejón de Ardoz, Madrid, Spain). E-mail: [1]iranzosj@inta.es, [2]cuevasms@inta.es.

Introduction: RNA viruses are characterized by high mutation rates, providing them with a high variability that makes them able to get easily adapted to changing environments. The heterogeneous nature of these viral populations has been studied by means of quasispecies theory, one of its most remarked predictions being the extinction of the virus if the mutation rate rises above certain critical value. The idea of an extinction threshold for the mutation rate is the basis for the treatment of viral infections with mutagenic agents, what has been called "lethal mutagenesis" [1, 2].

However, besides crossing an error threshold, there are other possible ways by which mutagens can induce viral extinction. Therefore, although increased mutagenesis is a robust experimental way to produce the loss of viability of a viral population, a current matter of concern is to determine what mechanism is really acting behind.

It has been reported that also mild increases in the mutation rate (below the error threshold) can cause extinction of infectivity in viruses. Experiments with persistent infections of lymphocytic choriomeningitis virus (LCMV) treated with a small amount of mutagen revealed that the virus eventually loses the ability to produce infective particles, while replicative ability is not affected [3]. This result cannot be explained within the framework of present quasispecies theory, since it requires considering the fitness as composed by two traits. On the one hand, replicative ability governs competition among viral genomes inside each cell, selection favoring individuals with higher replication rates. On the other hand, infectivity is necessary for entering new cells and starting the infection, but it remains free of selection once the intracellular replication cycle has been established. In persistent infections, the virus stays inside the cell for long periods before being released and required to infect new cells. During those periods, infectivity behaves as a neutral trait that can accumulate random mutations, this resulting in a loss of infectivity in the long run. It was conjectured that the role of the mutagen is to enhance the appearance of a class of defective mutants, able to replicate but unable to infect susceptible cells. This parasitic subclass eventually induces the extinction of the whole population. The extinction of viral infectivity through the action of defective, non-infective genomes is a novel mechanism, referred to as "lethal defection" [3].

Here we introduce a simple model for the evolution of a population whose individuals are characterized by two traits subject to positive and neutral selection pressures, respectively. It shows lethal defection as a purely stochastic phenomenon that is likely to occur whenever the population is smaller than a certain size.

Results and discussion: We have considered a viral population of a fixed maximum size N replicating inside a cell, whose individuals are defined by two phenotypic traits: replicative ability (fast and slow replicators) and infectivity (viable and defective). We assume that viable forms maintain the integrity of their genomes and correctly code for the proteins that permit replication and infection. Once produced, these proteins are shared, conferring no particular advantage to the viable genome that codified it. As a result, intracellular competition among the four resulting subclasses depends only on the replication rate, while the viability constitutes a neutral trait. Moreover, the extinction of viable individuals implies the extinction of the whole population, as no more functional proteins for replication and infection can be produced. When replicated, individuals can suffer mutations that change their phenotype (e.g. from viable to defective, or from fast to slow replicator). Beneficial mutations or reversions are also permitted. The model has been analyzed both analytically and by means of numerical simulations [4].

It is shown that there are two different regimes for the population dynamics. When the size of the population is large the behavior is well described by the mean-field solution of a system of deterministic equations. In this situation all subclasses can coexist and extinction by lethal defection is not observed. In contrast, for a small population the dynamics is driven by stochastic fluctuations. In this case, intermittent outbreaks of defective individuals can take over the population causing its extinction. The transition between both regimes has been characterized, and the size for which it occurs estimated. The results imply that stochastic extinction is a common event in conditions consistent with biological ones.

The model here presented shows how simple evolutionary mechanisms can cause the extinction of populations of fast mutating pathogens under environmental changes, and strongly suggest that one could devise strategies to take advantage of those mechanisms in fighting viral infections.

References:

[1] Eigen M. (2002) *Proc. Natl. Acad. Sci. USA, 99,* 13374–13376. [2] Bull J. J. et al. (2007) *J. Virol., 81,* 2930–2939. [3] Grande-Pérez A. et al. (2005) *Proc. Natl. Acad. Sci. USA, 102,* 4448–4452. [4] Iranzo J. and Manrubia S. C. (2009) *Europhys. Lett.,, 85,* 18001.