Journal of Theoretical Biology 265 (2010) 278–286

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Error threshold in RNA quasispecies models with complementation

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ARTICLE INFO

Article history:
Received 22 December 2009
Received in revised form
26 April 2010
Accepted 14 May 2010
Available online 21 May 2010

Keywords:
Complementation
Defective interfering particles
Error threshold
Quasispecies theory
RNA viruses

ABSTRACT

A general assumption of quasispecies models of replicons dynamics is that the fitness of a genotype is entirely determined by its sequence. However, a more biologically plausible situation is that fitness depends on the proteins that catalyze metabolic reactions, including replication. In a stirred population of replicons, such as viruses replicating and accumulating within the same cell, the association between a given genome and the proteins it encodes is not tight as it can be replicated by proteins translated from other genomes. We have investigated how this complementation phenomenon affects the error threshold in simple quasispecies mean field models. We first studied a model in which the master and the mutant genomes code for wild-type and mutant replicases, respectively. We assume that the mutant replicase has a reduced activity and that the wild-type replicase does not have increased affinity for the master genome. The whole pool of replicases can bind and replicate both genomes. We then analyze a different model considering a more extreme case of mutant genomes, the defective interfering particles (DIPs) described in many cases of viral infection. DIPs, with a higher replication rate owed to their shorter genomes, do not code for replicase, but they are able of using the replicase translated from the master genome. Our models allow to study how the probability of interaction between the genomes and the whole pool of replicases affects the error threshold. In both systems we characterize the scenario of coexistence between master and mutant genomes, providing the critical values of mutation rate, μ_c, and the critical interaction rate between master genomes and replicases, γ_c, at which the quasispecies enters into error catastrophe, a situation in which the mutant genomes dominate the population. In both cases, we showed that the error-threshold transition is given by transcritical-like bifurcations, suggesting a continuous phase transition. We have also found that the region in the parameter space (μ,γ) in which the master sequence survives is reduced when DIPs are introduced into the system.

1. Introduction

RNA viruses are the most important pathogens infecting plants and animals, and they are also a continuous source of emerging infectious diseases. The extremely short generation time, large population size and high mutation rates make RNA viruses excellent tools for experimental evolution and for testing basic principles of Evolutionary Theory (Elena and Sanjuán, 2007). RNA viruses are characterized as highly polymorphic populations which are usually assimilated to quasispecies by many virologists (Nowak, 1992; Domingo and Holland, 1997; Domingo et al., 2001). The quasispecies population structure arises as a consequence of fast replication coupled with high mutation rates (Domingo et al., 1978, 1988; Domingo and Holland, 1994; Domingo, 2000). The mathematical quasispecies theory (Eigen, 1971; Eigen et al., 1988, 1989; Bull et al., 2005) describes populations of replicons as a collection of a master genome and a diverse cloud of mutants, which all together contribute to the phenotypic properties of the entire population. Under this view, the entire quasispecies, rather than individuals, is the target of natural selection (Eigen, 2003; Biebricher and Eigen, 2005). A remarkable result of the quasispecies theory is the prediction of the existence of a phase transition at a critical mutation rate, μ_c, the error-threshold, beyond which the master sequence is lost and the quasispecies is dominated by the mutant genomes. Roughly speaking, the critical mutation rate can be obtained as $\mu_c \approx \nu^{-1}$, being ν the sequence length. The theory predicts that replicons with mutation rates $\mu > \mu_c$, might enter into the so-called error catastrophe regime, involving the out-competition of the master sequence by the pool of mutant genomes. Hence, genomic information is lost as the population enters into a drift phase (Eigen, 1971; Schuster, 1994).

The standard quasispecies mathematical model assumes that the fitness of any particular genotype entirely depends on its genome, without specifically distinguishing between effects at the genotypic and protein (phenotypic) levels. However, this

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doi:10.1016/j.jtbi.2010.05.018

assumption is highly unrealistic, because the fitness of a genome would depend on the functionality of the proteins it encodes. Furthermore, as master and mutant genomes coexist and both may contribute to the pool of proteins, it is conceivable that wild-type proteins may, for instance, act over mutant genomes, replicating and/or encapsidating them and vice versa, in a clear case of functional trans complementation (Wilke and Novella, 2003). Henceforth, the phenotype of a genome may not reflect its genotype, a situation which in the case of viruses is known as phenotypic mixing and hiding (Novick and Szilard, 1951; Brenner, 1957; Huang et al., 1974; Holland et al., 1989). Moreover, a substantial amount of evidences, gathered with viruses as different as the murine cytomegalovirus (Cicin-Sain et al., 2005), foot-and-mouth disease virus (García-Arriaza et al., 2004) or tobacco mosaic virus (Fraile et al., 2008), give support to the fact that deletion mutants can be replicated in cells coinfected with the full-genome helper viruses.

Several mathematical models have been proposed that take into consideration trans interactions between different viral genomes with different fitness properties (Gao and Feldman, 2009). For instance, studying the dynamics of defective interfering particles (DIPs) as an extreme case of complementation (Bangham and Kirkwood, 1990; Szathmáry, 1992, 1993; Kirkwood and Bangham, 1994; Frank, 2000). DIPs are mutant viruses that lack most of the viral genome and cannot complete the infectious cycle by themselves (Holland et al., 1976; Damayanti et al., 1999) (see also Marriott and Dimmock, 2010 for a review). However, they can be replicated and encapsidated by the proteins translated from a helper virus coinfecting the same cell. The mechanisms ensuring the survival and persistence of DIPs are not entirely clear, as they behave as hyperparasites and usually get involve in an arms race with the full virus (Horodyski et al., 1983; DePolo and Holland, 1986; DePolo et al., 1987). It is possible that the emergence of genomes shortened by deletions might confer an advantage in terms of replication speed compared with the full virus (García-Arriaza et al., 2004). Furthermore, there is also evidence of a stronger form of interference whereby the DIPs genome competes more successfully for the viral replicative machinery (DePolo and Holland, 1986; Pattnaik and Wertz, 1991).

As previously mentioned, several authors have theoretically investigated the dynamics of full viruses replicating together with DIPs. For example, Szathmáry (1992) analyzed simple models based on mass action kinetics considering standard viruses and DIPs. In Szathmáry (1992), structured deme models where developed to provide a description of the coexistence of virus segments considering standard virus and DIPs, sensitive and resistant viruses together with DIPs, covirus pairs (i.e., virus that exist as two or more separated particles all of which must be present for the complete replication cycle of a virus to occur), and virus–covirus systems. A deeper analysis of the model with standard virus and DIPs was later developed by Szathmáry (1993) considering cell populations infected by particles differing in number. Several different coexistence situations were shown to be possible by means of stable equilibria governed by fixed points or periodic orbits; also evidence was found of stable coexistence out of equilibrium governed by strange attractors.

Later, Kirkwood and Bangham (1994) developed a differential equations model to analyze a system formed by host cells, wild-type virions and DIPs. Such a model was able to explain several dynamic behaviors found in experiments, especially the fluctuations in virus titers on successive passages. Their model also gathered some interesting dynamical phenomena such as self-curing, which involves the extinction of the full virus together with the DIPs, and that had been previously observed to occur in vitro (Jacobson et al., 1979). They found that self-curing was associated to transient chaos, which might arise due to the presence of chaotic saddles in phase space.

More recently, Wilke and Novella (2003), analyzed a simple model of complementation with differential fitness between master and mutant viruses due to an impaired ability to infect cells. The model studied by these authors predicted a strong influence of phenotypic mixing and hiding on population dynamics of viruses at high multiplicity of infection as well as important effects on the mutation-selection balance at low multiplicity of infection.

None of the aforementioned models, and to the extend of our knowledge no one else, explores the effect of complementation on the error threshold predicted by the standard quasispecies theory. Therefore, neither the parametric regions in which the master sequence survives nor the bifurcations causing the error threshold have been characterized for systems of replicons in which complementation between mutant and master genomes may occur. We sought to cover this hole by studying two simple quasispecies models taking into account complementation during replication between master and mutant genomes.

The model studied in Section 2 considers that both master and mutant genomes encode, respectively, for wild-type and mutant replicases, with the mutant replicase having a lower catalytic activity. Hence, the fitness landscape is included at the replicase level and is given by the Swetina–Schuster (1982) fitness landscape. However, since both types of replicases contribute to the cellular pool of proteins, both can replicate the master and mutant genomes. From a more biologically relevant perspective, the model can also give insights on the population dynamics of master and mutant viruses replicating within the same cell and may help to understand under which conditions master genomes can survive in the population.

The second model, developed in Section 3, considers a problem of relevance in virology: the production of DIPs by some viruses and the effect they may exert on the full-length virus. In this model DIPs do not encode for replicase and have a faster replication rate and/or higher effective interaction with the wild-type replicase. Such a model will also provide some insights into the effect of competition between master genomes and DIPs, as well as into the possible persistence scenarios of the master sequence under the presence of DIPs. In both systems, replication is governed by a nonlinear, density-dependent growth. Actually, this system is equivalent to a two-member hypercycle with replicase-mediated replication (see Fig. 1). Some models of hypercycles coding for a replicase able to instruct the synthesis of other replicators can be found in Eigen and Schuster (1979).

2. Quasispecies model with complementation

We analyze the effect of complementation in the dynamics of RNA viruses with a simple quasispecies mean field model that describes the replication-mutation dynamics of RNA macromolecules in a flow reactor (see Fig. 1). Hence we study an unstructured model that only gathers the replication kinetics with a constant population, obviating the details of viral intracellular amplification. This is a standard method used in replicator theoretical models (see e.g., Tarazona, 1992; Campos and Fontanari, 2000; Silvestre and Fontanari, 2008). For mathematical convenience we studied the Swetina-Schuster (1982) single peak fitness landscape, where mutations are assumed to be largely deleterious and all mutant genotypes have identical low fitness. For simplicity we will not consider beneficial or neutral mutations. Our model considers the simplest scenario dividing the population of genomes into two types of sequences, the master and the mutant genomes, which are grouped into an "average" mutant sequence. The relative