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Interim Report **IR-05-069**

The Greater than Two-fold Cost of Intergration for Retroviruses

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The Greater than Two-Fold Cost of Integration for Retroviruses.

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Sexual reproduction, typically conceived of as a puzzling feature of eukaryotes, has posed an extraordinary evolutionary challenge in terms of the two-fold replicative advantage of asexuals over sexuals [11]. Here we show mathematically that a greater than two fold cost is paid by retroviruses such as HIV during reverse transcription. For a retrovirus replication is achieved through RNA reverse transcription and the effectively linear growth processes of DNA transcription during gene expression [2]. Retroviruses are unique among viruses in that they show an alternation of generations between a diploid free living phase and a haploid integrated phase [12]. Retroviruses engage in extensive recombination during the synthesis of the haploid DNA provirus [8]. Whereas reverse transcription generates large amounts of sequence variation, DNA transcription is a high fidelity process. Retroviruses come under strong selection pressures from immune systems to generate escape mutants [9], and reverse transciption into the haploid DNA phase serves to generate diversity followed by a phase of transcriptional clonal expansion during the restoration of diploidy.

The Darwinian theory of evolution makes the average rate of replication of an organism a measure of competitive status. The greater the rate of replication, the greater the frequency of genes placed back in the population gene pool. Endogenous mechanisms that increase this frequency are typically deemed adaptive, whereas those that decrease this frequency are deemed maladaptive. Sexual reproduction according to this simple definition, is maladaptive, as rather than allowing each genome to place two copies back into the gene pool as it could if asexual, it only allows a single copy to be placed back into the gene pool. This feature has been called, the two-fold cost of sex, the cost of males and the cost of meiosis [11]. The fundamental feature of sexual reproduction in contrast to asexual replication, according to measurement by gene frequencies, is the halving of the intrinsic growth rate. This preference for reduced rates of growth in a wide range of eukaryotes, has been considered one of the more puzzling traits observed in nature.

Here we show that this trait is not restricted to sexual reproduction or to eukaryotic organisms, but is a prominent feature of the life cycles of the retroviruses, such as Human Immunodeficiency Virus (HIV) and T-cell leukemia virus (HTLV) [2]. Retroviruses are RNA viruses which integrate a copy of their genome into the DNA genome of their host. This is achieved through the action of an RNA-dependent-DNA polymerase, called reverse transcriptase (RT) [14]. Reverse transcription proceeds when a retrovirus specific tRNA binds to a complementary region of the virus RNA called the primer binding site (PBS). A DNA segment is extended from the bound tRNA in the 3' to 5' direction through the action of the polymerase. The underlying replicated genome is then removed by the RNase H activity of RT. The newly synthesized sequence, thus liberated, then binds to the complementary 3' sequence and extends in the 5' direction to complete synthesis of the proviral DNA genome with an accompanying break down of the remaining RNA genome. The virus encoded protein integrase, then inserts the virus genome into the host DNA genome.

Most RNA viruses replicate their genomes using an RNA-dependent-RNA polymerase in the cytoplasm. Each new genome synthesized in this way serves indirectly as a template for another round of replication. With retroviruses replication disappears to be replaced by transcription. In other words, for a retrovirus replication has become a modified form of host gene expression. We model the intracellular dynamics of the virus life cycle as follows:

Let $p(t)$ be the probability that a viral genome is integrated into the host genome by a time t following infection:

$$\dot{p} = \lambda(1-p).$$

The parameter λ is the rate of integration in a unit time interval. From an integrated provirus, the genomic RNA (G) and viral messenger RNAs are produced:

$$\dot{G} = m_H f_G \, p.$$

The parameter m_H is the rate of (host-transcriptase-dependent) transcription from the integrated DNA and f_G is the fraction of viral genomic RNA in the total transcripts (the remaining fraction $f_P = 1 - f_G$ are to be translated into viral proteins). The initial conditions are $p(0) = 0$ and $G(0) = 0$ This gives $p(t) = 1 - e^{-\lambda t}$ and

$$G(t) = m_H f_G \int_0^t p(s)ds = m_H f_G \left[t - \frac{1}{\lambda}\left(1 - e^{-\lambda t}\right) \right].$$

For $t \gg 1/\lambda$,

$$G(t) \approx m_H f_G \left(t - \frac{1}{\lambda} \right). \tag{1}$$

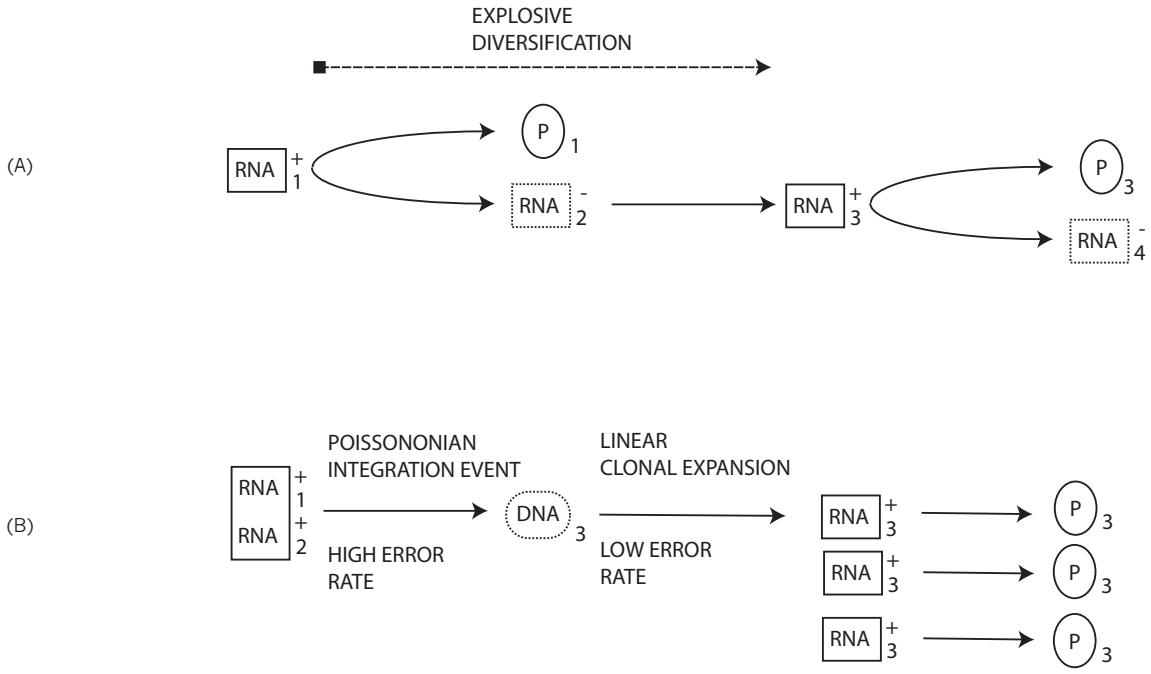

FIG. 1: Logic of virus life cycles. (A) Positive strand RNA virus of strain type 1 infects cell. RNA is translated into polyprotein 1 and replicated with error into strain 2. Process repeats. Growth is explosive (greater than exponential) as both new genomes and additional replicatory proteins are synthesized throughout the life cycle (B) Diploid, heterozygous, retrovirus infects cells . Proviral genome of strain type 3 is synthesized during reverse integration after a poissonian waiting time. Genomes of type 3 are transcribed at high fidelity at a linear rate and translated into proteins producing an effectively clonal population of new retroviruses of strain type 3. While we have not show it, coinfection with multiple virus strains can produce heterozygous diploids at the final segregation stage of the life cycle.

That is the viral genomic RNAs accumulate linearly with time after a grace period $1/\lambda = 8 \sim 12$ h for integration.

Now we compare this with the corresponding rate of genomic RNA accumulation in a model describing a positive strand RNA virus [7] (e.g. Flavi- and picornaviruses). We focus on the rate of genomic RNA accumulation in an infected cell. Because genomic RNA G^+ of positive strand RNA virus and negative strand RNA G^- is templated from G^- and G^+ respectively assisted by

viral RNA replicase P,

$$\dot{G}^+ = m_V G^- P, \tag{2}$$

$$\dot{G}^- = m_V G^+ P. \tag{3}$$

Here m_V is the rate of viral RNA-dependent transcription. As genomic RNAs (G^+) also act as messenger RNAs for viral proteins, RNA polymerases (P) are translated with the rate

$$\dot{P} = kG^+ - \mu P,$$

where k is the rate of translation and μ is the degradation rate of replicase. The initial conditions are $G(0) = G_0$ and $P(0) = 0$, where G_0 corresponds to the concentration of a viral genome packaged inside the infected virion. Assuming quasi-equilibrium for the production and degradation of P's (i.e. $\dot{P} = 0$), we find after some algebra that

$$G(t) = G_0\sqrt{1 + \tan^2(aG_0 t)}, \tag{4}$$

which diverges to infinity at

$$t_c = \frac{\pi}{2aG_0},$$

where $a = m_V k/\mu$. Thus the number $G(t)$ of genomic RNA explodes in a finite time $t = t_c$. The rate of growth of genome copy numbers will eventually approach zero, as a result of depletion of nucleotides, and energy and space limitations. This threshold implies that a very large number of genomes accumulate around the critical time t_c. Moreoever this rate of growth near t_c produces a greater than two-fold advantage over the retrovirus life cycle. In classical evolutionary models of sex, the rate of replication of an asexual is held constant; hence its population growth rate is kx where k is a rate constant and x population density. With a positive strand RNA virus, the rate is accelerating since the replication rate is proportional to the product GP. This can be thought of as a simple form of niche construction, whereby the virus synthesizes components of its environment (in this case P) which feedback positively to increase its net rate of replication. With coinfection, each virus strain benefits from the polymerase synthesized by homologous strains.

In summary, for a retrovirus the number of genomic RNAs accumulates only linearly with time after a long grace period following integration (see (1)), whereas copy numbers explodes in a finite time t_c (as in (4)) for a positive strand RNA virus. Though the initial production rate of virus genomes is small for an RNA virus as a result of a dependency on low copy numbers of

viral RNA transcriptases, the integration of the retroviral genome depends in a similar way on the reverse transcriptases packaged inside the infected virion. Overall, retroviruses are expected to suffer significant opportunity costs of replication by virtue of interposing a DNA phase in the positive-strand RNA life cycle.

A retrovirus genome is a diploid genome comprising two positive sense, single stranded RNAs. During reverse transcription of the virus genome, the DNA polymerase switches back and forth between the two RNA templates, in a process of homologous recombination, producing a recombinant provirus with sequence information derived from both parental RNAs [5]. Furthermore reverse transriptase has a high error rate, with approximately 1 in every 2000 bases being a misincorporation [10]. Thus retroviruses, just like sexual eukaryotes, exploit diploidy and recombination as a means of generating genomic variation [4]. As the fidelity of reverse transcriptase is low, there is a comcomitant increase in the rate of mutation during the recombination process.

The questions therefore arises, why not have evolved recombination with a diploid RNA genome and forgo the DNA phase in the life cycle? This strategy would serve to circumvent the greater than two-fold cost and render a significant growth rate advantage? There are two possible sets of answers to this question. The first is mechanistic and relates to recombination in RNA viruses, and the second is functional and relates to the fidelity of replication through DNA transcription.

Consider the first reason. The retroviruses are the only diploid positive strand RNA viruses. As a result, homologous genomes are always in close proximity and potentially physically linked. Whereas a number of RNA viruses have been observed to engage in recombination through copy choice mechanisms – including coronaviruses and picornaviruses – recombination involves collisions between free viral RNAs concentrated at membranes [8]. For a retrovirus recombination rates are limited by mechanisms of template switching, for a positive strand RNA virus, recombination rates are limited by the multiplicity of coinfection and template switching. Furthermore, it seems that RNA-dependent DNA polymerase is more efficient at template switching than RNA-dependent RNA polymerase based on rates of recombination in in-vitro experiments. Why this should be the case remains unknown. One possibility is that the protracted selection pressure on RNA-dependent DNA polymerase by virtue of the persistently diploid state of retroviruses, has lead to more effective mechanisms of homologous recombination.

Consider the second reason. Retroviruses are able to simultaneously exploit reverse integration to generate high levels of diversity, and as a mechanism for generating a DNA genome from which

genomic transcripts are generated with very high fidelity during transcription. Thus after a phase of recombination and hypermutation during the synthesis of the provirus, the virus mutation rate drops effectively to zero, and new genomes are produced through transcriptional clonal expansion (see Figure 1b). This is not true for ordinary RNA viruses, which experience a very high rate of diversification during every round of replication (see Figure 1a). Hence retroviruses have discovered a unique means of mitigating mutational-error accumulation while simultaneously producing very variable genomes. A cell infected by retroviruses presents a very diverse ensemble of clonal populations of virus, where each population in the ensemble is the transcriptional progeny of a single integration event.

Traditionally, three forms of explanation have been provided to account for the evolutionary persistence of sex in eukaryotes: (1) sexual recombination generates diverse progeny to occupy diverse environments (tangled bank hypothesis - TB [1]), (2) sex allows hosts to generate sufficient antigenic diversity to evade parasites (parasite-host coevolution hypothesis - CE [3]), and (3) recombination promotes efficient purging of deleterious mutations from the population (Synergistic mutation hypothesis - MH [6]). Empirical evidence has been used in support of each of these hypotheses [13]. Somewhat surprisingly, similar if not identical arguments can be applied to reverse integration by retroviruses. We examine the explanatory power of each of these theories.

Under the TB retroviral diversification becomes a function of the diversity of host niches which the virus population finds itself in. Immune memory establishes a diversity of niches negatively by excluding virus epitopes for which their exists complementary T cell receptors. Furthermore, during the course of a single HIV infection following inoculation with a single train, variants emerge that are specialists for different tissue types. The pattern of virus evolution in different tissues can proceed at very different rates, and can favor different amino acid subsitutions. Since the infection bottleneck for a retrovirus can be very small, it might be important that sufficient diversity can be generated over the course of a single infection to allow for maximum population growth. However, it is unclear whether such high rates of virus mutation are necessary given that host genomes associated with tissues are highly conserved. Furthermore, many positive strand RNA viruses are able to exploit a diversity of host niches over the course of infection, without recourse to recombination and hypermutation during reverse integration. For these comparative reasons, the TB hypothesis is somewhat weakened.

Under the CE, pressure from the host adaptive immune system favors mechanisms by which the virus can quickly generate variable epitopes promoting immune evasion. It is well known that

viruses such as HIV are under very strong selection pressures for diversification, and that reducing virus mutation rates promotes more effective clearance. Circumstantial evidence also comes from escape variants that mutate away from drug target sequences thereby restoring high rates of replication. The adaptive immune system is the only antagonistic host response to a virus that can evolve on a comparable time scale to the virus and therefore imposes strong and variable selection pressures on mechanisms of diversification. Excessive mutation can lead to loss of heredity. The DNA phase serves to damp down mutation and promotes a phase of transcriptional clonal expansion analogous to the clonal expansion of immune effector cells of the adaptive immune system. In this way the retrovirus can enjoy the benefits of recombination and hypermutation, with the possibility of exploiting strong genotypes repeatedly by creating clonal pools through transcription of DNA.

Under the MH recombination becomes a means of parcelling groups of mutations among the members of a virus population. Recombination allows that some genomes will harbor large numbers of deleterious mutations, whereas others will have very few to none. Assuming that selection works more efficiently in genomes with larger numbers of mutations, then recombination can be favored. Unlike the TH and CE hypotheses, the MH hypotheses for reverse transcription does not favor a DNA phase, as it could work just as well for a non-integrating diploid RNA virus that is capable of recombination. Indeed it would be preferable, as the additional hypermutation associated with generating the provirus could be avoided. It seems therefore that we can rule out the MH hypothesis as an explanation for the greater than two-fold disadvantage of reverse integration.

The two-fold cost is not restricted to sexual reproduction as much of the evolutionary literature would seem to imply. The two-fold or greater than two-fold cost, is a more fundamental property related to the tradeoff between diversity-promoting mechanisms, and those mechanisms promoting replication. Retroviruses are an ancient evolutionary lineage that have elected to solve their replication-diversity problem, in much the same way as complex, multicellular eukaryotic lineages. Interestingly, the most plausible explanation for why retroviruses reverse transcribe, is a mirror image of one of the dominant theories for why sexual eukaryotes produce males. For the retrovirus, the greater than two-fold cost pays for diversity capable of escaping immune detection,

whereas for the eukaryotes, the two-fold cost pays for diversity required to clear virus infection.

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