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of replication are stochastic

of the independent origin hypothesis is that, if too simple, it may fail to describe experiments accurately or that implausible coincidences of parameters may be required to fit the data.

In a second scenario, the initiation of an origin, although still stochastic, is linked to the state of the genome in its vicinity. For example, observations of origin clustering [12–14] have led several authors to hypothesize that the presence of a replication fork can increase the firing rate of nearby origins, for instance, the 'next-in-line' model [15] and the 'domino-cascade' model [16,17]. We refer to this second scenario in general as the correlated origin hypothesis.

Previously, there was considerable debate as to whether replication was stochastic and whether origins are independent. At present, it is generally accepted that all models

on replication timing in yeast. Second, the intrinsic parameters characterizing each origin have values that are independent of their neighbors, again suggesting that the initiation of each origin is an independent stochastic event [8]. Studies in fission yeast have also led to the conclusion that local initiation models suffice to explain the available experimental data [30,31]. However, several biologically different scenarios can lead to similar overall timing patterns [32], and more complicated mechanisms, such as trans-acting regulators of origin activity and chromosome structure, can affect origin timing [33,34]. Clearly, further iterations of modeling and experiment will bc4ls

the replication timing of replication domains has led

A scenario comprising stochastically firing origins with different firing probabilities naturally leads to a reproducible replication-timing program [66].

fire early. Although the periodic distribution of such groups of origins would be an efficient way to replicate the genome, mechanisms that could achieve this global order are not clear, at present.

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The hypothesis that replication is largely controlled by the local rate of initiation has received wide support from recent experiments and analyses. Models based on local replication rates I(x,t)

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