Inferring Where and When Replication Initiates from Genome-Wide Replication Timing Data

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Based on an analogy between DNA replication and one dimensional nucleation-and-growth processes, various attempts to infer the local initiation rate $I(x, t)$ of DNA replication origins from replication timing data have been developed in the framework of phase transition kinetics theories. These works have all used curve-fit strategies to estimate $I(x, t)$ from genome-wide replication timing data. Here, we show how to invert analytically the Kolmogorov-Johnson-Mehl-Avrami model and extract $I(x, t)$ directly. Tests on both simulated and experimental budding-yeast data confirm the location and firing-time distribution of replication origins.

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DNA replication is an essential genomic function responsible for the accurate transmission of genetic information through successive cell generations. Although it is clear that some sites consistently act as replication origins in most eukaryotic cells, the mechanisms that select these sites and the sequences that determine their location remain elusive in many cell types. Furthermore, even less is known about the mechanisms that regulate their firing time [1–4]. Despite recent experimental efforts to map replication origins in higher eukaryotes, the concordance between different studies is generally very low, even when the same technique is employed (e.g., see Ref. [5] for the human genome). Thus, the reliable detection of individual origins is still a very delicate experimental task. This contrasts

$$s(x, t) = e^{-}$$

notice in Fig. 2(a) that the origin O_7, detected by the numerical inversion, does not correspond to a local minima of the unreplicated fraction. About one origin in three in the multiple-initiator model is not associated with a local minimum in the unreplicated fraction data [13]. It is sometimes assumed that origins whose positions are well defined correspond to local minima in the mean RT or the unreplicated fractions [21]. Such methods would fail to detect the well-positioned origin O_7.

Passive replication can strongly affect both the replication kinetics at a locus and the observed efficiencies of replication origins and can lead to misinterpretation of RT data [11–13]. For a potential origin that is rarely passively replicated, we expect the RT to be equal to the intrinsic firing time of the origin. That is, its RT distribution $P(x, t)$ should be similar to the intrinsic firing time distribution $\phi(x, t)$. Since, in such cases, the firing time corresponds to an observed initiation event, we also expect the observed density of initiations $n(x, t)$ to be similar to the intrinsic firing time distribution $\phi(x, t)$. Indeed, in Fig. 3(c), we see that the early-firing origin O_6, which Fig. 2 shows is unlikely to be passively replicated, has $P(x, t) \sim n(x, t) \sim \phi(x, t)$. These approximations do not hold when the potential origin is passively replicated. For instance, the RT distribution of potential origin O_7, which is often passively replicated by a fork originating from O_6 (Fig. 2), clearly differs from its intrinsic firing time distribution [Fig. 3(d)]. Indeed, the RT distribution of O_7 is close to that of O_6, delayed by the time (7 min) necessary for a fork to propagate from O_6 to O_7 ($x_7 - x_6 = 14$ kbp and $v = 2$ kbp/min). At the onset of S phase ($t < 16$ min), the origin O_7 is unlikely to be passively replicated, since only a few forks coming from O_6 reach O_7 in time, and the observed density of initiations at O_7 is very similar to its intrinsic firing time distribution [Fig. 3(d)]. At later times,

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