Title: Inferring genome replication dynamics from DNA abundance in asynchronous populations
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The evolutionary fitness of many single-cellular organism crucially depends on the ability of cells to replicate their genome quickly and accurately. By studying the dynamics of replisomes (the biochemical machines responsible for replication) and their interaction with other essential processes like transcription we can thus gain insights into the evolutionary pressures faced by a species and its response. Recently, sequencing-based Marker Frequency Analysis (MFA) has emerged as an experimentally convenient tool for studying replisome dynamics of single-cellular organism. In MFA, the distribution of DNA abundance as a function of genomic location is measured in a large, exponentially growing population through high-throughput sequencing. This data is then used to infer dynamical properties of the replication process. Recently, MFA was used successfully to show that replisome speed in E. coli fluctuates along the genome (Bhat et al., 2022. eLife 11 e75884).

However, while MFA is experimentally convenient because it does not require replication to be synchronised between individual cells, inferring properties of the replication program from MFA data is non-trivial. To improve the situation, we present a coherent and elegant mathematical framework that links the replication programs of individual cells to the population-wide DNA abundance observed in MFA experiments. To show the universality of our framework, we apply it to wide range of situations; from deterministic to diffusing replisomes and from bacteria with a single origin of replication to eukaryotes with many potential origins which fire stochastically. By solving the inference problem for these cases, we demonstrate that our mathematical framework makes MFA a viable tool for studying the spatio-temporal replication programs.

Finally, we apply our framework to the study of the fork-trap system in Ecoli. Fork traps are an example of a system with unclear evolutionary benefit; they exist to ensure a consistent meeting point of the two replisomes working in opposite direction, yet disabling the system does not seem to affect fitness. We show that our framework allows us to infer the dynamics of replisomes with and without active fork traps, and discuss possible implications for the evolutionary benefit of this system.