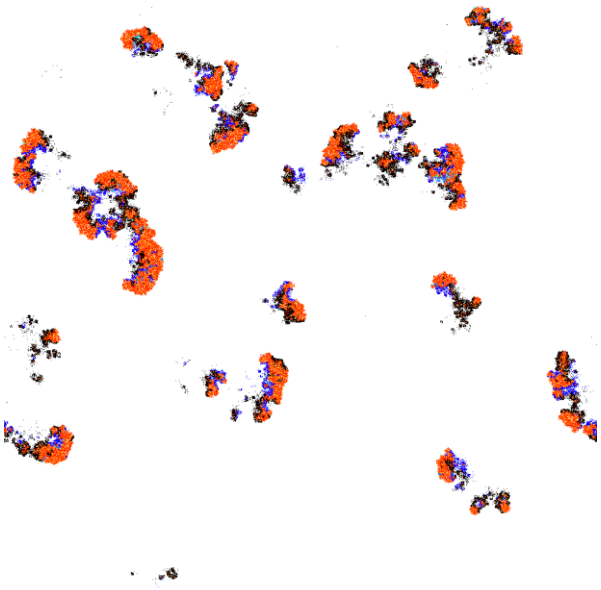
ERROR THRESHOLDS FOR RNA REPLICATION IN THE PRESENCE OF BOTH POINT MUTATIONS AND PREMATURE TERMINATION ERRORS. Andrew S Tupper and Paul G Higgs, Origins Institute, McMaster University, Hamilton, Ontario L8S4M1, Canada. (tuppea2@mcmaster.ca, higgsp@mcmaster.ca).

Introduction: We consider a spatial model of replication in the RNA World in which polymerase ribozymes use neighbouring strands as templates. Errors in the fidelity of replication create sequences with point mutations which act as parasites. These parasites have the same length as the polymerase, and hence the same replication rate. We have shown previously [1] that spatial clustering allows survival of the polymerases as long as the error rate is below a critical error threshold. Here, we consider errors where a polymerase prematurely terminates replication before reaching the end of the template, creating shorter parasites that are replicated faster than the functional polymerase. We are motivated by well-known experiments where Qβ RNA is replicated by an RNA polymerase protein. In that case, virus RNA is rapidly replaced by very short non-functional sequences. If the same thing were to occur when the polymerase is a ribozyme, this would mean that termination errors could potentially destroy the RNA World.

Results: Initially we consider the worst-case scenario where parasite replication rate varies inversely with length. Parasites shorter than a certain minimum length are lethal. Addition of a tiny fraction of these short parasites destroys the polymerases. Surprisingly, however, when there is continued generation of parasites of all lengths by premature termination, the system can survive up to a finite error threshold. Moderate length parasites coexist with the polymerase and cause the system to split into spatial structures that move like travelling waves. Short parasites, which would be lethal on their own, cause extinction of local clusters, but do not destroy the whole system. The error threshold for termination errors is much lower than for point mutations; hence termination errors are still important, but they do not lead to the inevitable destruction of the RNA World by short parasites. We also consider a more realistic model in which the time for replication of a strand is the sum of a time for binding of the polymerase, and a time for replication. In the limit where the binding time is dominant, replication rates are equal for all lengths. The error threshold for termination is then the same as for point mutations. When the replication time is dominant, we have the worst-case scenario discussed above. The general case is intermediate between these limits. Thus, when the binding step is considered, termination errors are less serious than in the worst case.

References:

[1] Kim YE. and Higgs PG. (2016). Co-operation between Polymerases and Nucleotide Synthetases in the RNA World. *PLoS Comput Biol*, *12*(11), e1005161.



The figure shows travelling wave patterns that arise in a two-dimensional surface model of RNA replication when when an RNA polymerase and its complement (red and orange) are replicating in the presence of a mixture of parasitic templates of different lengths (blue and black) that are produced by premature termination errors.