

The University of Manchester

Christopher Robert Lockwood

PhD

Can Gains and Losses of Transcription Factor Binding Sites be Related to What Occurs Elsewhere in the Regulatory Region?

2008

ABSTRACT

Background: This thesis asks whether a transcription factor binding sites (TFBSs) tend to evolve together with other TFBSs located in nearby DNA. Other studies suggest this occurs, but the present study asks if it occurs frequently.

Results: Starting from a database of known TFBSs, a computer analysis produced a sample of TFBSs that seem to be conserved (eg within a human-mouse comparison), and another sample of TFBSs that seem to have diverged. The conserved TFBSs were flanked by DNA which was well conserved, whereas the diverged TFBSs were flanked by DNA which was less well conserved. The difference was typically 11%. The thesis considers if this difference could be produced by faulty data, or by TFBSs that have no effect on fitness, but shows this is unlikely by analysing a set of fictional TFBSs. Two possible explanations are: (i) correlated evolution, in which the loss of a TFBS is accompanied by the loss of several other TFBS within 50 bases; or (ii) a site-density effect, where the probability that a TFBS is lost/gained varies with the number of TFBSs in nearby DNA. To decide between these, a method was devised and implemented; it required gain-of-TFBS to be distinguished from loss-of-TFBS. This produced tentative evidence that “losses” are flanked by DNA that is more highly conserved than the DNA flanking “gains”. Such a result is difficult to explain using a “turnover” model or a “site-density” model, but can be explained by a “correlated-evolution” model.

Conclusions: It was found that “correlated-evolution” best explained the data, but this was a tentative conclusion, given the statistical significance levels. If true, the implication is that a common event in TFBS evolution is the simultaneous loss of several nearby TFBSs.