Bioinformatics Analysis of Intragenomic Interactions of Polyomaviruses

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Background

Alternative splicing and Bridging Sequence Model (BSM)

- Alternative splicing is a process where multiple types of RNA transcript are produced from a single DNA gene.
- The exact mechanism of alternative splicing is still not known.
- The Bridging Sequence Model (BSM) by Burnett is a hypothetical model to explain the mechanism of alternative splicing [1].
- The model hypothesized the existence of Bridge or anti-Bridge nucleotide sequences that bind to sequences around the splice sites (Fig 1).
- The bridges and anti-bridges control the version of genes expressed by promoting/blocking certain splice sites.

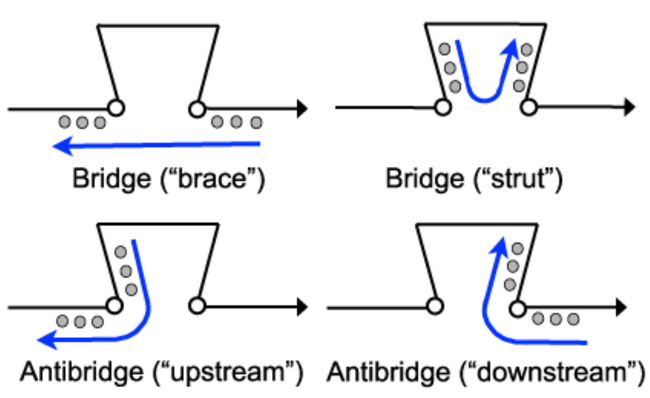


Fig. 1. The different types of bridging sequence as described in the Bridging Sequence Model. Adapted from [1]

Polyomaviruses

- These are small, circular, double stranded DNA viruses known to cause chronic infections and tumours.
- Simian Vacuolating virus 40 (SV40), JC virus (JCV) and BK virus (BKV) are the first three polyomaviruses found to cause disease in immunocompromised humans.
- An understanding of the biology of these viruses – in particular, the synthesis of the oncogenic T-antigen proteins – is important for both virology and cancer biology.

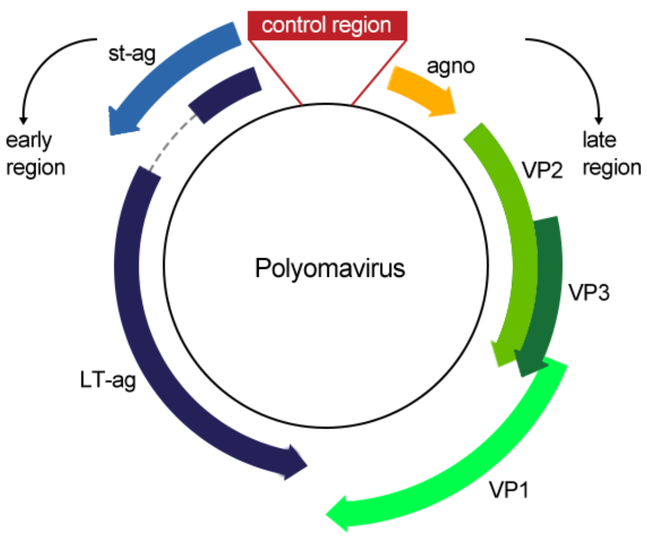


Fig. 2. Common genomic organisation of SV40, JCV and BKV. The coloured arrows illustrate the approximate genomic locations of the major Polyomavirus gene. Derived from [5]

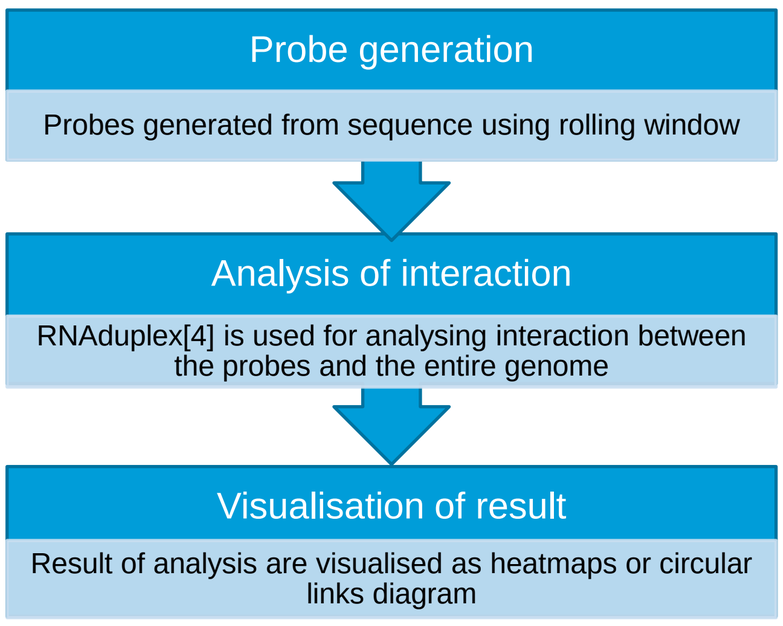
Motivation

- Early work by Burnett shows that the regulation of the T-antigen synthesis in SV40 can be explained by the Bridging Sequence Model (BSM) [1, 2].
- A recent review by White et al. highlighted that the three primate polyomaviruses have similar properties [3].

Aim

To test the hypothesis that the BSM is applicable to the general primate polyomaviruses by comparing *in silico* the regulatory networks of SV40, JCV and BKV polyomaviruses

Method



Results

- Circular links diagram (produced using visualization tool by A. Rosado, a fellow Honours student) shows a high degree of similarity of interactions between the viral ‘control regions’ and the rest of the genome.
- A high resolution analysis performed using heatmaps annotated with important genomic landmarks shows the presence of potential bridges and anti-bridges.

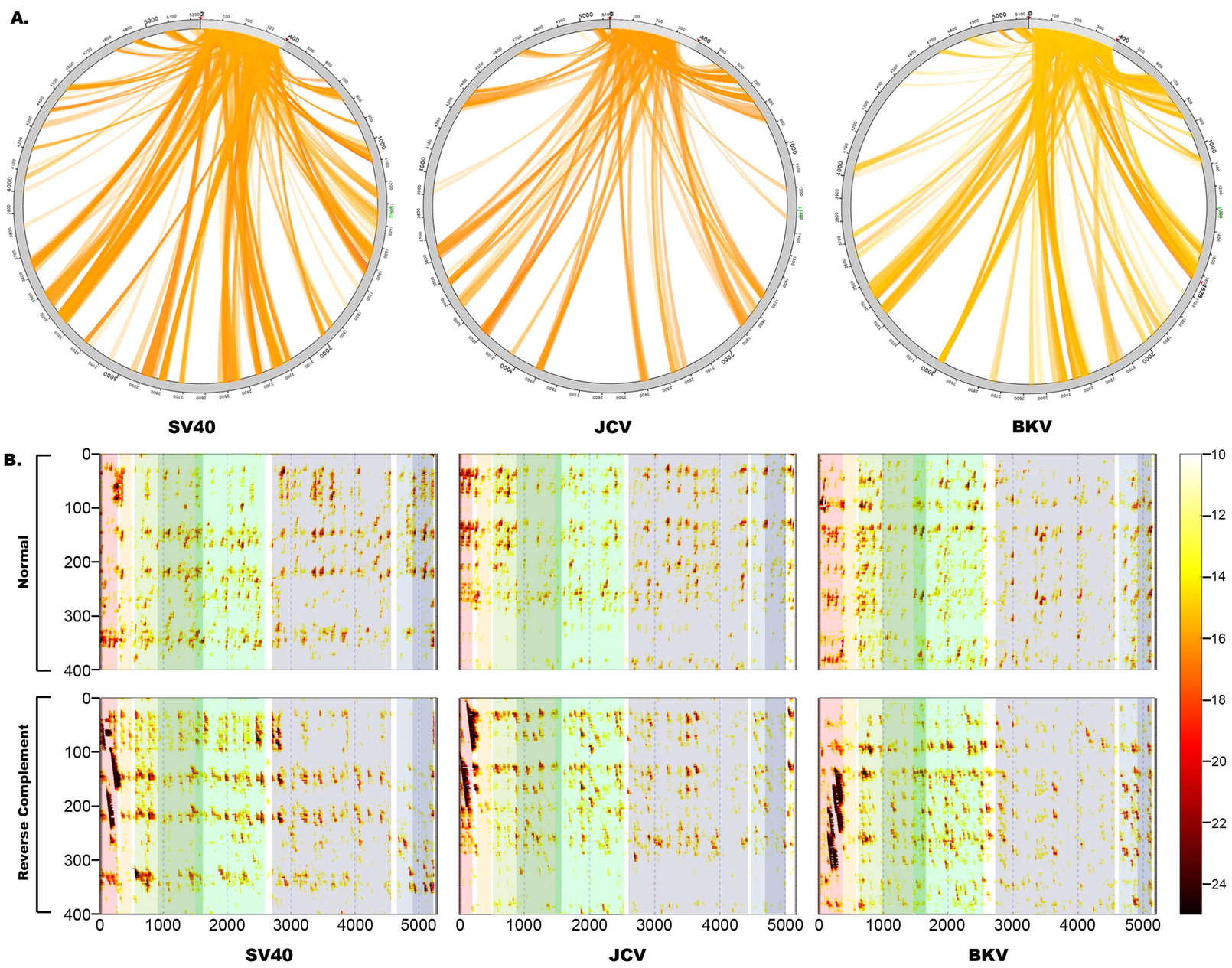


Fig. 3. Result of the genome-wide RNA interaction analysis of SV40, JCV and BKV visualised as circular links diagrams (A) and heatmaps (B). The links diagrams highlight interaction between the viral ‘control regions’ (top of circle) and intragenomic targets, while the heatmaps shows a high resolution interactions between the ‘control regions’ (Y-axis) and the total genome (X-axis). Both links diagrams and heatmaps are colour coded, with black/red indicating strong, high-energy interactions and yellow/white indicating weaker, low-energy interactions. The coloured bands in the heatmaps correspond to genomic features shown in Fig. 2. Combinations of particular of these highlighted sites of interactions, where their locations correspond to sites at which alternative splicing is known to occur, represent potential half-bridging sequences, which in SV40 and JCV could combine to form potential bridges and antibridges.

Conclusion

- Presence of bridges in the SV40 and JC virus shows that the BSM may explain alternative splicing in polyomaviruses.
- Analysis of the viral ‘control regions’ of SV40, BKV and JCV shows high degree of similarity in the pattern of intragenomic interactions of the three species.

Future Work

We will:

- Perform full genome comparative analysis on SV40, JCV and BKV, focusing on important genomic landmarks such as the alternative splice sites of the late and early genes.
- Perform full analysis on other members of the polyomavirus family
- Perform full analysis on other genes, such as human and mouse globin loci and bim/bax genes
- Determine the validity of the BSM to explain alternative splicing in other gene systems

References

[1] L. Burnett, “A model for the mechanism and control of eukaryote gene splicing.,” Journal of theoretical biology, vol. 97, no. 3, pp. 351–66, Aug. 1982.
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[3] M. K. White et. al., “Regulation of gene expression in primate polyomaviruses.,” Journal of virology, vol. 83, no. 21, pp. 10846–56, Nov. 2009.
[4] R. Lorenz et. al., “ViennaRNA Package 2.0.,” Algorithms for molecular biology : AMB, vol. 6, p. 26, Jan. 2011.
[5] M. V. Ghelue and U. Moens, “Merkel Cell Polyomavirus: A Causal Factor in Merkel Cell Carcinoma, Skin Cancers - Risk Factors, Prevention and Therapy, Prof. Caterina La Porta (Ed.), InTech, Available from: http://www.intechopen.com/books/skin-cancers-risk-factors-prevention-and-therapy/merkel-cell-polyomavirus-a-causal-factor-in-merkel-cell-carcinoma