1 Abstract

- Abstract: high throughput sequencing is not unbiased. It is definitely more comprehensive than microarrays.

I have re-worded the original sentence:

"Traditionally, transcriptome profiling has relied on microarray technologies but with the advent of high-throughput sequencing, the ability to profile transcripts accurately and in an unbiased manner has transformed the study of transcriptomes."

into

"Traditionally, transcriptome profiling has relied on microarray technologies but with the advent of high-throughput sequencing, the ability to profile transcripts the ability to profile transcripts accurately and in an unbiased manner has transformed the study of transcriptomes."

- Abstract: last sentence needs rephrasing

- Nederlandse samenvatting: tissue –¿ weefsel

2 Chapter 1

- The description of SAGE is a bit inaccurate as the sequences in the early SAGE method were indeed always 9-10 bp long but the tag is usually said to also contain the restriction enzyme site so the total length is 13-14 and therefore better able to discriminate transcripts than a 9-10 bp tag. Also, the tag is not at the ultimate 3-end as the text suggests.

- The CAGE figure could be clearer. Currently it is not clear that only capped RNAs are measured, and it is not clear the endonuclease cuts downstream of its recognition site.

- Section 1.5.4: spliceosomal RNAs aid protein translation?

- Section 1.8: the research goal is very broad. It would be good to set a few more specific goals related to the different chapters

3 Chapter 3

- I would advise to include supplementary data files. For example: Suppl Figures 22 and 23 are probably key figures for Chapter 3 generated by Dave but not included in the thesis.

4 Chapter 5

- I miss a discussion on the non-capped RNAs that may also be . I also miss whether you observe clear CAGE peaks / start sites for these lncRNAs (like for protein-coding RNAs) or multiple distinct start sites or an even more even coverage pattern.

- I miss also an analysis what kind of sRNAs are derived from these different repeat elements. Given the previous chapter, I would at least assume that you checked for Piwi RNAs, but I assume as well that most of these sRNAs are not capped so I am still a bit unclear what this enrichment in sRNAs actually means.

5 Chapter 6

- I would reference to the specific chapter instead of to the paper (Chapter 6 instead of Tang et al 2013).

- Title 6.0.3: MecP2: strange use of capitals and lower case.

- 6.0.3: when you refer to the gene, use Italics.