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ABSTRACT

Motivation: Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text.

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1 INTRODUCTION

The past 6 years have seen the development of methodologies to identify genomic variation within a fetus through the sequencing of maternal blood plasma. These novel non-invasive methods are based on the observation that maternal plasma contains a fraction of DNA (typically 5-15%) originating from the fetus (Lo *et al.*, 1997). The key advantage of non-invasive methods is that they pose no associated risk to the pregnancy. In contrast, invasive methods like chorionic villus sampling or amniocentesis (sampling of amniotic fluid from around the developing fetus) have estimated procedure-related fetal loss rate of 0.6% to 1%, Douglas *et al.* (2007). Non-invasive methods have already been used, mainly for the detection of whole-chromosome events like trisomy of chromosome 21 (Down syndrome) (Chiu *et al.*, 2008; Fan *et al.*, 2008), and to a more limited extent for smaller (typically several megabases long) Copy Number Variants (CNVs) (Chen *et al.*, 2013; Srinivasan *et al.*, 2013; Rampasek *et al.*, 2014). Methods utilizing genome-wide detection of sub-chromosomal CNVs are highly desired, to enable prenatal screening for diseases like DiGeorge syndrome (3Mb deletion), Prader-Willi syndrome (4Mb deletion), and other, associated with a mid to large sized CNV. In addition to CNV detection, a successful proof-of-concept for non-invasive genome-wide fetal genotyping has been published (Kitzman *et al.*, 2012). This is the only work (to our best knowledge), in the field of maternal plasma analysis for fetal variation detection, with available data set.

In this project we will work on a new method for non-invasive fetal CNV detection given paternal genomes and deep sequencing of maternal plasma cell free DNA (cfDNA). We will build on (Rampasek *et al.*, 2014), seeking to addresses several of its current modelling drawbacks. Foremost, we will employ a discriminative model like a Conditional Random Field to focus on the classification goal and to better incorporate multiple dependant data features. We plan to investigate multiple ways of such CRF application, analysing the advantages and limitations of such models compared to Hidden Markov Model used in (Rampasek *et al.*, 2014). We will use the *in silico* simulated CNV data set by (Rampasek *et al.*, 2014) based on sequencing samples of (Kitzman *et al.*, 2012).

In the following sections, we give a brief description of the methods published so far, provide motivation for employing CRF rather than HMM for the CNV detection task, and outline the project goals.

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2 APPROACH

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3 METHODS

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4 DISCUSSION

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5 CONCLUSION

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