HEART RATE VARIABILITY AND OLIGODENDROGLIOMA

Slade Matthews PhD
Head, Pharmacoinformatics Laboratory
Bosch Institute
Pharmacology, Sydney Medical School.
Automated Morphometric Oligodendroglioma Classification with Machine Learning Algorithms
PAPNET: Neural network driven automated classification

  - PAPNET detected more abnormal PAP smears than manual screening
  - 21,747 Pap smears, PAPNET detected four more true positives than conventional reading
Oligodendrogliomas

* Highest peak seen between ages 35-55 (3:4 males to females)
* Grade-Age correlation: increased risk at +40
* Chemosensitivity increased ~70% resulting from co-deletion of 1p and 19q alleles
* Allelic loss 1p more significant than 19q
How to diagnose?

* Molecular testing
  * Test for 1p/19q co-deletion
  * Test for the TP53 mutation
  * Still in its infancy stages & very expensive

* Histological diagnosis (current “gold standard”)
  * Searching for the morphological indicators
  * Problematic in terms of misdiagnosis
  * Highly subjective from pathologist to pathologist
* Built model on 62 tumours using LR then tested predictive performance on further 20
* Several variables in Scheie model
  * Tumour location
  * Proportion with uniform round nuclei*
  * Vessel shape
  * Tumour cell density (dist btw cells)
  * Also gross pathology features
  * *Found to be most predictive
* Use pathologists not image segmentation
Scheie’s results

* Standardised 10 histological variables for 3 different pathologists
* Multiple logistic regression model constructed
* Results:
  * 80% accuracy obtained when tested on second cohort (20 tumours)
  * variable ‘>50% of cells with round uniform nuclei’, demonstrated strongest association with 1p/19q status.
  * 1p/19q co deletion and TP53 mutation found ‘mutually exclusive’
Fluorescent in-situ hybridisation (FISH)

* Use to detect genotype of cells on a slide

* Gold standard for model development and medical purposes

* Expensive molecular biology technique not available in all countries
1p chromosomal arm deletion
19q chromosomal arm deletion
We analysed 69 images of H & E slides
  * (33/36 split i.e. balanced dataset)
  * FISH data available for all patients
  * Use of automated image segmentation to remove subjectivity (MetaMorph)
  * Machine learning algorithms used to “mine data” for relationship btw 1p/19q co deletion and morphology
Methods

- Histological images → Dako ACIS III auto image acquisition system
- Trace nuclei of the tumour image → METAMORPH
- Define roundness in terms of circularity, curvature and asymmetry – generate data
- Data pre-processing in Microsoft Excel
- Attempt to find relationship in the data using MLAs in the Weka workbench
MLAs used include:

- Multilayer perceptron (MLP)
- Logistic regression (LR)
- J48 decision tree (C4.5)
- Ridor (ripple down rule)
- KStar (IBL)
- Locally weighted learning (LWL)

Histopathology (Co-deletion)
Histopathology (No co-deletion)
Our results so far...

Accuracy for algorithms used in slide means

- LWL algorithm (10-fold cross-validation)
  - AUC 0.704
Slide medians

**KStar algorithm** (10-fold cross-validation)
AUC 0.735

**LWL algorithm** (10-fold cross-validation)
AUC 0.705
Slide Modes

Accuracy for algorithms used in slide modes

- J48
- Logistic
- LWL
- MLP
- Ridor
- KStar

KStar algorithm (10-fold cross-validation)
AUC 0.683
Implications

* Computational method for correlating morphological characteristics with genotype commenced development

* Statistical significance indicates a valuable proof of principle – some signal detected

* Significance found by quantifying just one of 10 potential histological targets
Future Directions

* Improve image segmentation
  * In collaboration with EE (Usyd) PhD project
* Include low power images
  * To assess vascular framework (Chicken wire)
* Fractal analysis of nuclear structures
  * As measure of complexity
* Include re-staining data
* Electrical impedance data
Non-chronotropionic component changes in parasympathetic heart rate variability: a sensitive marker for perceived examination stress in healthy university students.
Introduction

* Exam stress
* Students
* HRV
* Cortisol
Is the stress of examination sufficient to induce a physiological stress response?

Are cortisol levels increased in students during exam time?

Can HRV analysis reveal stress effects in Sydney University students?
The setup
HRV Measures

* NN intervals from Chart (ms) text files imported into Kubios
* Time Domain
  * Mean/SD RR, RMSSD, pNN50
* Frequency Domain (FFT method)
  * VLF, LF, HF
* Non-linear
  * Poincare, Ap En, de-trended fluctuation
Heart Rate Variability Analysis
Settings

* Chart Settings
  * 3 Hz high-pass filter
  * **R Wave Detector Settings**
  * 45 Hz low-pass filter
  * **Position of Event:** Max After Threshold

* Analysis Settings
  * **Interval Classification:**
    * 5 < 600 < 1200 < 2000 ms
  * **Exclude ectopics from analysis**
  * **Frequency Bands:**
    * **VLF:** 0-0.04
    * **LF:** 0.04-0.15
    * **HF:** 0.15-0.4
  * **Interpolation of RR series:** 4 Hz
  * **FFT Spectrum:**
    * **Window Width:** 256 s
    * **Window Overlap:** 50%
## Results

<table>
<thead>
<tr>
<th></th>
<th>Term Time</th>
<th>Exam Time</th>
</tr>
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<tbody>
<tr>
<td>PSS</td>
<td>24.3±1.5</td>
<td>32.1±2.2***</td>
</tr>
<tr>
<td>Cortisol</td>
<td>6.9±3.3</td>
<td>4.7±1.3</td>
</tr>
<tr>
<td>Heart rate</td>
<td>67.1±2.3</td>
<td>75±2.6</td>
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<tr>
<td>LF/HF</td>
<td>1.1±0.3</td>
<td>1.5±0.2*</td>
</tr>
<tr>
<td>Hfnu</td>
<td>54.7±5.1</td>
<td>40.9±3.2**</td>
</tr>
<tr>
<td>Lfnu</td>
<td>40.4±5.4</td>
<td>53.4±3.6**</td>
</tr>
<tr>
<td>A1</td>
<td>0.6±0.1</td>
<td>0.7±0.04</td>
</tr>
<tr>
<td>PNN50</td>
<td>42.4±6.74</td>
<td>23.4±4.38*</td>
</tr>
</tbody>
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Discussion points

* At exam-time
  * Student perceived stress was higher
  * Heart rate not significantly higher
  * LFnu was higher
  * Hfnu was lower
  * PNN50 was lower
  * LF/HF ratio higher
Discussion Points

- SNS and PNS operate at different frequencies
- High fq component HRV (0.15-0.40 Hz)
  - PNS mediated fluctuations
- Low fq component HRV (0.04-0.15 Hz)
  - SNS mediated fluctuations
  - Although substantial PNS presence in signal
- LF/HF ratio shown to increase with PNS withdrawal ➔ sympathovagal balance
HRV provides evidence for stress response in university students at exam-time
Not revealed by salivary cortisol
Type of psychological stress (exam-time) may be more chronic in nature
  reflected by parasympathetic withdrawal (detected through HRV changes)
  not detected with cortisol measurement
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