USE OF FUZZY LOGIC / ARTIFICIAL NEURAL NETWORK IN PEDIATRIC HYPERTENSION

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Goals & Disclosure

- Introduce fuzziness to a crisp view on blood pressure
- Outline the potential of artificial neural network
- Use BP classification in adolescents as an example
- **Proof of concept of the methodology**
- Food for thought
- Stimulate discussion
- Get your opinion / ideas
What you see is not always what you get
• Biological data (blood pressure) are highly variable and (may be) imprecise
• Traditional approach: to apply exact statistical methods for analysis of imprecise data

Can we use less exact methods for analysis of imprecise data?
Fuzzy logic

• Introduced in 1965 by Lofti A. Zadeh, professor at University of California
• Precise logic of imprecision and approximate reasoning
• Attempt to formalize human capabilities

Make decisions in an environment of imprecise information

Zadeh LA. Information Sciences 2008;178:2751
Traditional / strict BP definition

- Variations of BP by 5-15 mgHg due to:
  - BP measurement accuracy
  - BP device selection (ausc/oscill)
  - BP device algorithm
  - BP method (attended, unattended)
  - BP variability subsequent measurements
  - BP normative data
  - Use / non-use of normative data
  - Age/height related normative data
  - Seasonal, temperature, stress variations
Fuzzy systolic BP – degrees of membership
Fuzzy BP (systolic) definition

Fuzzy blood pressure (systolic) definition

mmHg

α

L

N

H

μ(L,N,H)=(0,0.1,0.9)

μ(L,N,H)=(0,0.5,0.5)
**BP in adolescents**

**Europe (ESH)**
- Age $\geq 16$ years
- Normotension: $< 130/85$
- HN BP: 130-139/85-90
- HTN: $\geq 140/90$
- Stage 1 HTN: 140-159/90-99
- Stage 2 HTN: 160-179/100-109

**USA (AAP)**
- Age $\geq 13$ years
- Normotension: $< 120/80$
- HN BP: 120-129/80
- HTN: $\geq 130/80$
- Stage 1 HTN: 130-139/80-89
- Stage 2 HTN: $\geq 140/90$

Should the BP be managed as in adults? At what age? By which guidelines?

Lurbe E et al, J Hypert 2016;34:1887 (ESH)
Flynn JT et al, Pediatrics e20171904:140 (AAP)
Brady TM et al, Ped Nephr 2019;34:405
Study goal

• To compare the **classification of office BP** (normal, high normal, stage 1 and 2 HTN) in adolescents based on:
  1. European Society of Hypertension 2016 (ESH)
  3. Fuzzy rules (FR)

• To assess performance of ESH, AAP and FR classification in **prediction of ABPM hypertension** and **left ventricular hypertrophy** (LVH)
Definition of fuzzy BP sets
(normal, high normal, stage 1 HTN, stage 2 HTN)

Thresholds at approx: 124 135 149 82 88 95
Fuzzy Inference System (FIS)

1. Conversion of crisp BP numbers to fuzzy numbers (degrees of membership)
2. Processing of fuzzy BP numbers / confrontation with knowledge base/rules
3. De-fuzzification of results to crisp output (BP classification)
Fuzzy BP rules & Output

Rules:
```r
rule <- matrix(c("no", "and", "no", "->", "1",
"no", "and", "hino", "->", "2",
"no", "and", "hi1", "->", "3",
"no", "and", "hi2", "->", "4",
"hino", "and", "no", "->", "2",
"hino", "and", "hino", "->", "2",
"hino", "and", "hi1", "->", "3",
"hino", "and", "hi2", "->", "4",
"hi1", "and", "no", "->", "3",
"hi1", "and", "hino", "->", "3",
"hi1", "and", "hi1", "->", "3",
"hi1", "and", "hi2", "->", "4",
"hi2", "and", "no", "->", "4",
"hi2", "and", "hino", "->", "4",
"hi2", "and", "hi1", "->", "4",
"hi2", "and", "hi2", "->", "4"),
nrow=16, byrow=T)
```

Output:
- 1 = normal BP
- 2 = high normal BP
- 3 = stage 1 HTN
- 4 = stage 2 HTN

Input:
BP 120/80
Patients & Methods

• 323 office BP records from adolescents >= 16 years of age (2012-2018)
• Pts referred for primary and secondary HTN
• ABPM done within 90 days from office BP
• Echocardiography done within 180 days from office BP
• Median age = 17 yrs (16.01 – 20.28)

• Fuzzy Rule Based System (FRBS) package in R, v.3.1.0
• Comparison of proportions by propensity test
• Kruskal Wallis test to compare groups
• Agreement between methods assessed by kappa statistics
• Prediction of ABPM hypertension and LVH by ROC (AUC) analysis
Office hypertension

Agreement (kappa coefficient):
- ESH vs AAP: 0.48 (moderate)
- AAP vs FR: 0.71 (substantial)
- ESH vs FR: 0.73 (substantial)

Kappa:
0 - 0.2 = slight agreement
0.2-0.4 = fair agreement
0.41-0.6 = moderate agreement
0.61-0.8 = substantial agreement
0.81-1.0 = almost perfect agreement
Classification of office HTN

Agreement (kappa coefficient):
- ESH vs AAP: 0.04 (slight)
- AAP vs FR: 0.47 (moderate)
- ESH vs FR: 0.48 (moderate)

Kappa:
- 0 - 0.2 = slight agreement
- 0.2 - 0.4 = fair agreement
- 0.41 - 0.6 = moderate agreement
- 0.61 - 0.8 = substantial agreement
- 0.81 - 1.0 = almost perfect agreement
ABPM – 24h systolic BP
Systolic 24h BP is significantly higher in pts classified of HTN1 by ESH.
Prediction of ABPM

Prediction of ABPM hypertension

- ESH: AUC=0.667
- AAP: AUC=0.674
- Fuzzy: AUC=0.663
LVMi in pts with office HTN Stage 1&2

No difference in LVMi among pts classified by various guidelines
Prediction of LVH

Prediction of LVMi>=38.6 g/m^2.7

- ESH: AUC=0.59
- AAP: AUC=0.59
- Fuzzy: AUC=0.58
• Fuzzy rules:
  – **user** defined (based on expert opinion)
  – **computer** defined (fuzzy regression)
    • Central tendency=101+1.76*age
    • Lower boundary=101+1.1*age
    • Upper boundary=104+2.0*age
Fuzzy regression of 95th percentiles - boys

Fuzzy linear regression - SBP boys

Fuzzy ULN
Fuzzy LLN
Screening BP

ULN = 104 + 2*age (yrs)

Fuzzy linear regression - DBP boys

Fuzzy ULN
Fuzzy LLN
Screening BP

ULN = 64 + 1.5*age (yrs)
Fuzzy regression $95^{th}$ percentiles – girls (height)
From simply complex to fuzzy simple?

Upper fuzzy limit of normal BP (mmHg):

**SBP boys** = \(104 + 2 \times \text{age}\)

**DBP boys** = \(64 + 1.5 \times \text{age}\)

**SBP girls** = \(106 + 1.7 \times \text{age}\)

**DBP girls** = \(67 + 1.2 \times \text{age}\)
Fuzzy logic for BP classification - summary

- Poor agreement between ESH and AAP in the classification and grading of office BP in adolescents

- Pts classified by ESH have a higher BP on ABPM but:
  - Similar predictions (ROC) of ABPM hypertension by office BP
  - Similar predictions (ROC) of increased LVM by office BP

- Fuzzy regression allows for “simple” prediction or upper (and lower limits) of normal BP (for age and height) across all age categories

- Fuzzy rules (FR) classification allows for a softer / less crisp classification of office BP and a better differentiation between HN and Stage 1 HTN ABPM values
FR classification as a bridge between EU and US hypertension guidelines

ESH classification

AAP classification

Fuzzy BP rules classification

Which classification is better / closer to CV risk based classification?
The 2018 European Society of Cardiology/European Society of Hypertension and 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines More Similar Than Different

Despite their similarities, the guidelines take a different position in several areas. The most apparent is in classification of BP. The definition of hypertension in the European guideline is unchanged, reflecting the level of BP (≥140/90 mm Hg) at which drug treatment is recommended for all patients. In the US guideline, hypertension is defined by an average systolic BP of at least 130 mm Hg or diastolic BP of 80 mm Hg or higher, based on an interpretation of risk and treatment effect. This results in a different approach to treatment of adults with a systolic BP of 130 through 139 mm Hg or diastolic BP of 80 through 89 mm Hg, who are classified as having stage 1 hypertension in the US guideline and high-normal BP in the European guideline. The US guideline recommends nonpharmacological therapy for all adults with stage 1 hypertension and additional antihypertensive drug therapy for the approximately 30% in this highly prevalent BP category who are deemed to be at high risk for atherosclerotic CVD (10-year risk of atherosclerotic CVD≥10%). In contrast, the European guideline predominantly recommends lifestyle interventions, with consideration of antihypertensive drug therapy only in adults at very high risk, i.e., with established CVD, especially coronary artery disease.

“Use CV risk estimation, in addition to BP levels, for therapeutic decision-making.”

Whelton et al. JAMA 2018;320:1749
Can we use CV risk estimates from adults for office BP classification in children?
### Framingham database (n=4240)

557/3658 developed CHD within 10 years
Can we predict it?

| Coefficient | std err | t     | P>|t| | [0.025] | [0.975] |
|-------------|---------|-------|------|--------|--------|
| Intercept   | 0.5763  | 0.079 | -7.303 | 0.000  | -0.731 | -0.422 |
| male        | 0.0574  | 0.012 | 4.604  | **0.000** | 0.033  | 0.082 |
| age         | 0.0071  | 0.001 | 9.17   | **0.000** | 0.006  | 0.009 |
| education   | -0.0056 | 0.006 | -0.990 | 0.322  | -0.017 | 0.006 |
| currentSmoker | 0.0081 | 0.018 | 0.447  | 0.655  | -0.027 | 0.044 |
| cigsPerDay  | 0.0022  | 0.001 | 2.764  | **0.006** | 0.001  | 0.004 |
| BPMeds      | 0.0459  | 0.035 | 1.324  | 0.186  | -0.022 | 0.114 |
| prevalentStroke | 0.1368 | 0.075 | 1.816  | 0.069  | -0.011 | 0.285 |
| prevalentHyp | 0.0283 | 0.017 | 1.622  | 0.105  | -0.006 | 0.063 |
| diabetes    | 0.0258  | 0.044 | 0.584  | 0.559  | -0.061 | 0.113 |
| totChol     | 0.0001  | 0.000 | 0.956  | 0.339  | -0.000 | 0.000 |
| sysBP       | 0.0025  | 0.000 | 4.987  | **0.000** | 0.002  | 0.003 |
| diaBP       | -0.0012 | 0.001 | -1.437 | 0.151  | -0.003 | 0.000 |
| BMI         | 7.9e-05 | 0.002 | 0.051  | 0.959  | -0.003 | 0.003 |
| heartRate   | -0.0004 | 0.000 | -0.729 | 0.466  | -0.001 | 0.001 |
| glucose     | 0.0011  | 0.000 | 3.786  | **0.000** | 0.001  | 0.002 |
Linear model vs ANN

• Linear model
  – CHD risk = -0.58 + 0.06*male + 0.006*age + 0.002*cigs per day + 0.002*SBP + 0.001*gluc
  – Need to select significant parameters for predictions
  – Assumes linear relationship between variables
  – Extreme values of age, blood pressure etc.

Is there a more flexible / more accurate model?
Artificial Neural Network (ANN)
ANN

Machine Learning

Input → Feature extraction → Classification → Output
Car
Not Car

Deep Learning

Input → Feature extraction + Classification → Output
Car
Not Car

Age, sex, SBP, DBP
Framingham database
CHD risk estimation
Framingham (modified) ANN

Confusion Matrix and Statistics

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<th>1</th>
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<tbody>
<tr>
<td>0</td>
<td>955</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>122</td>
<td>33</td>
</tr>
</tbody>
</table>

Accuracy : 0.8591; 95% CI : (0.8377, 0.8787)
Kappa : 0.2224
Mcnenar's Test P-Value : 1.966e-10
Sensitivity : 0.45205
Specificity : 0.88672
Pos Pred Value : 0.21290
Neg Pred Value : 0.95980
Prevalence : 0.06348
Detection Rate : 0.02870
Detection Prevalence : 0.13478
Balanced Accuracy : 0.66939

Trained on 2682 pts, tested on 1150 pts
1. Children with HTN have a higher risk of CHD compared to NT
2. Patients classified by ESH have a higher CV risk than those classified by AAP?
Risk of CHD increases progressively with the stage of HTN. Patients classified per AAP at lower risk for CHD?
Patients classified per AAP and FR are at a lower risk for developing CHD compared to pts classified by ESH (higher risk)
Risk of CHD increases progressively with the severity and type of HTN.
BP classification

- Adults
  - Based on CV risk

- Children
  - Based on statistical distribution of BP

Can we classify BP in children based on CV risk predicted by adult database?

Quartiles of the estimated risk:
- Group 1 (NT) = 0-0.068
- Group 2 (HN) = 0.068-0.145
- Group 3 (HTN1) = 0.145-0.293
- Group 4 (HTN2) => 0.293
Systolic and diastolic BP per CHD risk (quartiles)

**Medians**
- Systolic BP: 121, 133, 130, 145
- Diastolic BP: 72, 76, 72, 71
Systolic and diastolic 24h BP per CHD risk

**Systolic 24h BP per CHD risk**

- Medians: 124, 128, 127, 134
- Significant differences:
  - CHD risk quartiles 1 vs 4: ****
  - CHD risk quartiles 2 vs 4: **
  - CHD risk quartiles 3 vs 4: *

**Diastolic 24h BP per CHD risk**

- Medians: 72, 71, 68, 72
- Significant differences:
  - CHD risk quartiles 1 vs 2: ns
  - CHD risk quartiles 1 vs 3: ns
  - CHD risk quartiles 2 vs 4: *
  - CHD risk quartiles 3 vs 4: ns

Kruskal-Wallis tests:
- Systolic: p = 5.4e-08
- Diastolic: p = 0.04
Classification of adolescents’ BP based on cardiovascular (CHD) risk estimated from adult database using big data / machine learning technology

CV risk-based BP thresholds remarkably close to current guidelines for office and ambulatory (based on BP distribution)

CV risk is elevated in a range of BP levels (e.g. 120-140 systolic)

Can we use CV estimates for BP management in children?

BP 135/80 + CV risk >0.3 = treatment
BP 135/80 + CV risk <0.3 = monitoring
Thank you for your attention!
Fuzzy logic and artificial neural network

• Allow for an uncommon view on a common problem (BP)
  – Fuzzy threshold, fuzzy range
  – Non-linear, multi-variate, multi-layered machine learning techniques

• Use of vast amount of data from adult population studies for predictions in pediatric population?

Artificial intelligence is coming to pediatric hypertension!
ML algorithm predicts heart attacks with 90% accuracy

By Ryan Daws
Editor of AI News. A gadget lover, music purveyor, and ex-host of a consumer technology show.

Posted on May 14, 2019
Justification for fuzziness

• Variations of BP by 5-15 mgHg due to:
  – BP measurement accuracy
  – BP device selection (auscultatory / oscillometric)
  – BP device algorithm
  – BP method (attended, unattended)
  – BP variability subsequent measurements
  – BP normative data
  – Use / non-use of normative data
  – Age/height related normative data
  – Seasonal, temperature, stress related variations
Fuzzy BP thresholds in children?

Upper fuzzy limit for age:
- 130 mmHg for 13 yr old
- 134 mmHg for 15 yr old
- 138 mmHg for 17 yr old

Fuzzy range for height:
- 120-130 mmHg for boys 160 cm
- 130-140 mmHg > 180 cm height